Factors influencing ovarian cancer survival worldwide

Lisa Melissa Matz

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
University of London

January 2017

Department of Non-Communicable Disease Epidemiology

Faculty of Epidemiology and Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

No funding received
Research group affiliation: Cancer Survival Group

Declaration

I, Lisa Melissa Matz, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date: 11 January 2017

Dedication

This thesis is dedicated to my mom, who taught me the true meanings of courage and strength

Acknowledgements

First and foremost, I would like to thank sincerely my supervisors, Professor Michel Coleman and Dr. Claudia Allemani, for their continued guidance and encouragement. It has been an honour and inspiration to work with them throughout these past three years.

Additionally, I would like to thank Professor Martin Gore, who bravely stepped in at the last minute to be my clinical advisor. Our discussions on ovarian cancer were insightful and an invaluable contribution to this thesis.

This thesis would not have been possible without the hard work of the CONCORD Central Analytic Team in cleaning the massive data set from the cancer registries that was used in the analyses. I cannot thank them enough for preparing these data; they all deserve medals for their incredible efforts.

I would also like to thank the various members of the Cancer Survival Group at the London School of Hygiene and Tropical Medicine who welcomed me warmly to the group over three years ago, and have been a constant source of support and encouragement throughout my PhD. I would especially like to thank Yuki, Natalia and Lisa for their help with scheduling meetings with my supervisors – it was quite a difficult task at times!

My family, though thousands of miles away, have supported me throughout these past few years. I could not have done it without their unwavering support and belief that I could do anything (even if I kept telling them I could not, in fact, be two places at once).

I would also like to thank endlessly my friends who have encouraged me when I doubted myself, laughed with me when things were rough, distracted me when things were stressful and listened to me talk relentlessly about work while at the pub– I could not have done this without any of you.

I would especially like to thank Anjali, Eileen, Gui, Joy and Lily: you ladies have been a consistent source of support, despite all of us being scattered across several time zones and continents. I have always felt I could run to you when I needed to. Friends do not get any better than you.

To all of my officemates – thank you for understanding how stressful and intense working on a PhD can be. I wish those of you still working on your degrees the best of luck.

Finally, I would like to thank my mom, Linda, to whom this thesis is dedicated. She taught me that courage is facing your greatest fears head on, without hesitation; and that strength is facing those fears day after day. I am the person I am today, and doing something I enjoy immensely, because of her endless strength and courage. And for that, I will never be able to thank her enough.

Abstract

Ovarian cancer survival varies widely worldwide. This variation may be explained by several factors, including international variation in the histological subtypes of ovarian cancer, stage at diagnosis and race/ethnicity.

Data used for this thesis were extracted from the CONCORD-2 study. The CONCORD-2 study collected data for 793,098 adult women (aged 15-99 years) in 61 countries who were diagnosed during the 15-year period 1995-2009 with a cancer of the ovary. Ovarian cancer was defined broadly to include tumours of the fallopian tube, uterine ligaments and adnexa, other specified and unspecified female genital organs, peritoneum or retroperitoneum. Age-standardised net survival was the main outcome for each analysis.

The worldwide distribution of and international variation in histological groups of ovarian cancer was examined, as an approach to understanding international differences in overall ovarian cancer survival. International comparisons of ovarian cancer survival have traditionally analysed ovarian cancer as a single homogenous group. However, ovarian cancer comprises several histologically distinct subtypes, which have very different survival outcomes. Survival from the most common histology, type II epithelial, was much lower than that for other histological groups in most countries.

International differences in stage-specific net survival were also explored, where adequate data were available, in order to understand the impact of stage at diagnosis on survival. Survival from localised tumours was much higher overall, and for each histological group, than for advanced-stage disease in all countries.

Net survival by race was estimated for Israel, New Zealand and the United States. Survival was consistently higher for the majority racial group than for the minority group.

The results presented in this thesis provide a valuable contribution to the understanding of variations in ovarian cancer survival, which may thus be used to inform health care policies and plans to reduce disparities in survival.

Table of Contents

DECLARATION **2**

DEDICATION **3**

ACKNOWLEDGEMENTS **4**

ABSTRACT **6**

LIST OF TABLES **11**

LIST OF FIGURES **13**

CHAPTER 1: INTRODUCTION **14**

1.1 ANATOMY AND BIOLOGY OF THE OVARY AND FALLOPIAN TUBES **14**
1.1.1 OVARIES 14
1.1.2 FALLOPIAN TUBES 16
1.1.3 THE MENSTRUAL CYCLE 16
1.2 OVARIAN CANCER **18**
1.2.1 EPITHELIAL OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CANCER 18
1.2.2 GERM CELL 28
1.2.3 SEX CORD-STROMAL 30
1.3 DEFINITION OF OVARIAN CANCER **31**
1.4 CLASSIFICATION SYSTEMS FOR STAGE OF DISEASE AT DIAGNOSIS **32**
1.4.1 FÉDÉRATION INTERNATIONALE DE GYNÉCOLOGIE ET D'OBSTÉTRIQUE (FIGO) 33
1.4.2 TUMOUR NODE METASTASIS (TNM) 33
1.4.3 SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) SUMMARY STAGE 2000 33
1.5 SCREENING FOR OVARIAN CANCER **33**
1.6 AIMS AND OBJECTIVES **41**

CHAPTER 2: LITERATURE REVIEW **42**

2.1 METHODS **42**
2.2 SURVIVAL AND HISTOLOGY **42**
2.3 SURVIVAL AND STAGE AT DIAGNOSIS **45**
2.4 SURVIVAL AND RACE/ETHNICITY **47**
2.4.1 UNITED STATES 47
2.4.2 NEW ZEALAND 50
2.5 SURVIVAL AND PLACE OF RESIDENCE **51**
2.5.1 NATIONAL-LEVEL DIFFERENCES 51

2.5.2 INTERNATIONAL DIFFERENCES 51
2.6 SURVIVAL AND SOCIOECONOMIC STATUS 52
2.7 SURVIVAL AND TREATMENT 56
2.8 OTHER INFLUENCES ON OVARIAN CANCER SURVIVAL 59

CHAPTER 3: MATERIAL AND METHODS 61

3.1 METHODS TO ACHIEVE THE AIM AND OBJECTIVES OF THE PHD 61
3.2 THE CONCORD PROGRAMME 61
3.2.1 POPULATION-BASED CANCER REGISTRY DATA 62
3.3 INCIDENCE, PREVALENCE AND MORTALITY 74
3.3.1 INCIDENCE 74
3.3.2 PREVALENCE 75
3.3.3 MORTALITY 75
3.4 NET SURVIVAL 76
3.5 COHORT, PERIOD AND COMPLETE APPROACHES 79
3.6 AGE-STANDARDISATION 82
3.7 STATISTICAL ANALYSES 83

CHAPTER 4: HISTOLOGICAL GROUPS OF OVARIAN CANCER: WORLDWIDE DISTRIBUTION 85

4.1 INTRODUCTION 85
4.2 MATERIAL AND METHODS 86
4.3 RESULTS 91
4.3.1 TOPOGRAPHICAL SUB-SITE 91
4.3.2 OVARIAN CANCER HISTOLOGY 93
4.4 DISCUSSION 136

CHAPTER 5: OVARIAN CANCER SURVIVAL BY HISTOLOGICAL GROUP 144

5.1 INTRODUCTION 144
5.2 MATERIAL AND METHODS 144
5.3 RESULTS 151
5.3.1 HISTOLOGICAL GROUP BY COUNTRY AND CALENDAR PERIOD 151
5.3.2 HISTOLOGICAL GROUP BY SUB-SITE 199
5.3.3 SURVIVAL FOR HISTOLOGICAL SUBTYPES 203
5.4 DISCUSSION 205

CHAPTER 6: OVARIAN CANCER SURVIVAL BY STAGE AT DIAGNOSIS 211

6.1 INTRODUCTION 211
6.2 MATERIAL AND METHODS 211
6.3 RESULTS 216

6.3.1 STAGE AT DIAGNOSIS 216
6.3.2 STAGE AT DIAGNOSIS AND HISTOLOGY 232
6.4 DISCUSSION 237

CHAPTER 7: OVARIAN CANCER SURVIVAL BY RACE/ETHNICITY 241

7.1 INTRODUCTION 241
7.2 MATERIAL AND METHODS 241
7.3 RESULTS 244
7.4 DISCUSSION 250

CHAPTER 8: STRENGTHS AND LIMITATIONS 252

8.1 STRENGTHS 252
8.2 LIMITATIONS 252

CHAPTER 9: CONCLUSION 256

9.1 DISTRIBUTION OF HISTOLOGY 256
9.2 SURVIVAL BY HISTOLOGICAL GROUP 257
9.3 SURVIVAL BY STAGE AT DIAGNOSIS 258
9.4 SURVIVAL BY RACE/ETHNICITY 258
9.5 FUTURE DIRECTIONS 259
9.6 CONCLUSION 260

REFERENCES 264

APPENDIX A: CONCORD-2 DATA SPECIFICATION 275

APPENDIX B: ETHICAL APPROVALS 325

APPENDIX C: SENSITIVITY ANALYSIS 327

List of tables

TABLE 1.1 COMPATIBILITY OF FIGO AND TNM STAGING SYSTEMS 34
TABLE 1.2 SEER SUMMARY STAGE 2000 CLASSIFICATION 35
TABLE 2.1 KEY TOPICS AND SEARCH TERMS FOR LITERATURE REVIEW 43
TABLE 3.1 MAIN VARIABLES FOR ANALYSIS 72
TABLE 4.1 OVARIAN CANCER HISTOLOGICAL GROUPS AND SUBTYPES 87
TABLE 4.2 DISTRIBUTION (%) OF TOPOGRAPHY (SUB-SITE) BY CONTINENT AND CALENDAR PERIOD OF DIAGNOSIS, 1995-2009, 51 COUNTRIES 92
TABLE 4.3 DISTRIBUTION (%) OF TOPOGRAPHY (SUB-SITE) BY OVARIAN CANCER HISTOLOGICAL GROUP, CALENDAR PERIOD AND CONTINENT, 1995-2009, 51 COUNTRIES 95
TABLE 4.4 WORLDWIDE DISTRIBUTION (%) OF OVARIAN CANCER BY HISTOLOGICAL GROUP AND CALENDAR PERIOD, 1995-2009, 51 COUNTRIES 100
TABLE 4.5 DISTRIBUTION (%) OF HISTOLOGICAL GROUPS BY CONTINENT AND CALENDAR PERIOD OF DIAGNOSIS, 1995-2009 104
TABLE 4.6 DISTRIBUTION (%) OF HISTOLOGICAL GROUPS BY COUNTRY AND CALENDAR PERIOD OF DIAGNOSIS, 1995-2009 105
TABLE 4.7 EPITHELIAL OVARIAN CANCER SUBTYPES: WORLDWIDE DISTRIBUTION (%) BY CALENDAR PERIOD, 1995-2009, 51 COUNTRIES 121
TABLE 4.8 EPITHELIAL OVARIAN CANCER SUBTYPES: DISTRIBUTION (%) BY CONTINENT AND CALENDAR PERIOD, 1995-2009 123
TABLE 4.9 EPITHELIAL OVARIAN CANCER SUBTYPES: DISTRIBUTION (%) BY COUNTRY AND CALENDAR PERIOD, 1995-2009 125
TABLE 5.1 OVARIAN CANCER HISTOLOGICAL GROUPS AND SUBTYPES 148
TABLE 5.2 WORLDWIDE DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGY AND MEAN AGE AT DIAGNOSIS, 1995-2009, 60 COUNTRIES 152
TABLE 5.3 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY HISTOLOGICAL GROUP (EPITHELIAL TUMOURS), COUNTRY AND CALENDAR PERIOD, 1995-2009, 60 COUNTRIES 156
TABLE 5.4 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY HISTOLOGICAL GROUP (NON-EPITHELIAL TUMOURS), COUNTRY AND CALENDAR PERIOD, 1995-2009, 60 COUNTRIES 168
TABLE 5.5 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY COUNTRY AND CALENDAR PERIOD FOR ALL TUMOURS, TUMOURS OF SPECIFIC MORPHOLOGY, TUMOURS OF NON-SPECIFIC MORPHOLOGY AND TUMOURS WITH MISSING MORPHOLOGY, 1995-2009, 60 COUNTRIES 184
TABLE 5.6 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY SUB-SITE, HISTOLOGICAL GROUP, COUNTRY AND CALENDAR PERIOD, UNITED KINGDOM AND UNITED STATES, 1995-2009 200
TABLE 5.7 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY HISTOLOGICAL SUBTYPE, COUNTRY AND CALENDAR PERIOD, UNITED KINGDOM AND UNITED STATES, 1995-2009 204
TABLE 6.1 WORLDWIDE DISTRIBUTION (%) OF STAGE AT DIAGNOSIS AND MEAN AGE AT DIAGNOSIS, 2001-2009, 25 COUNTRIES 217
TABLE 6.2 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) (95% CI) BY COUNTRY, REGISTRY, CALENDAR PERIOD AND STAGE AT DIAGNOSIS, 1995-2009, 25 COUNTRIES 222
TABLE 6.3 DISTRIBUTION (%) OF STAGE AT DIAGNOSIS BY HISTOLOGICAL GROUP AND CALENDAR PERIOD, UNITED STATES, 2001-2009 234
TABLE 6.4 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) BY HISTOLOGICAL GROUP, STAGE AT DIAGNOSIS AND CALENDAR PERIOD, UNITED STATES, 2001-2009 235
TABLE 7.1 OVARIAN CANCER HISTOLOGICAL GROUPS AND SUBTYPES 243
TABLE 7.2 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) BY RACE, COUNTRY AND CALENDAR PERIOD, 1995-2009 246

TABLE 7.3 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) BY RACE, HISTOLOGICAL GROUP AND PERIOD OF DIAGNOSIS, UNITED STATES, 1995-2009 247
TABLE 7.4 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (NS, %) FOR EPITHELIAL OVARIAN CANCER BY RACE AND HISTOLOGICAL GROUP, NEW ZEALAND, 1995-2009..... 249

List of figures

FIGURE 1.1 THE FEMALE REPRODUCTIVE SYSTEM 15
FIGURE 1.2 THE MENSTRUAL CYCLE 17
FIGURE 1.3 THE HISTOLOGICAL SUBTYPES OF OVARIAN CANCER, INCLUDING FALLOPIAN TUBE AND PRIMARY PERITONEAL TUMOURS 19
FIGURE 1.4 WILSON AND JUNGNER CLASSIC SCREENING CRITERIA 36
FIGURE 1.5 UPDATES TO THE CLASSIC SCREENING CRITERIA 38
FIGURE 3.1 METHODS OF CANCER PATIENT REGISTRATION AND CRITERIA FOR INCLUSION IN SURVIVAL ANALYSES 67
FIGURE 4.1 DATA EXCLUSION FLOW CHART FOR THE WORLDWIDE DISTRIBUTION OF OVARIAN CANCER HISTOLOGY, 1995-2009 88
FIGURE 4.2 ANATOMIC SUB-SITE DISTRIBUTION WITHIN HISTOLOGICAL GROUP BY CONTINENT, 1995-2009 94
FIGURE 4.3 WORLDWIDE DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGY: 51 COUNTRIES, 1995-2009 101
FIGURE 4.4 DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGICAL GROUPS BY CONTINENT, 2005-2009 103
FIGURE 4.5 DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGICAL GROUPS BY COUNTRY (CENTRAL AND SOUTH AMERICA AND NORTH AMERICA), 2005-2009 116
FIGURE 4.6 DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGICAL GROUPS BY COUNTRY (ASIA AND OCEANIA), 2005-2009 117
FIGURE 4.7 DISTRIBUTION (%) OF OVARIAN CANCER HISTOLOGICAL GROUPS BY COUNTRY (EUROPE), 2005-2009 118
FIGURE 5.1 DATA EXCLUSION FLOW CHART FOR NET SURVIVAL ANALYSIS BY OVARIAN CANCER HISTOLOGICAL GROUP, 1995-2009 146
FIGURE 5.2 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR TYPE I EPITHELIAL TUMOURS, 1995-1999 153
FIGURE 5.3 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR TYPE I EPITHELIAL TUMOURS, 2000-2004 154
FIGURE 5.4 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR TYPE I EPITHELIAL TUMOURS, 2005-2009 155
FIGURE 5.5 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR TYPE II EPITHELIAL TUMOURS, 1995-1999 ... 164
FIGURE 5.6 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FROM TYPE II EPITHELIAL TUMOURS, 2000-2004 165
FIGURE 5.7 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FROM TYPE II EPITHELIAL TUMOURS, 2005-2009 166
FIGURE 6.1 DATA EXCLUSION FLOW CHART FOR NET SURVIVAL ANALYSIS BY STAGE AT DIAGNOSIS, 2001-2009 ... 213
FIGURE 6.2 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR LOCALISED TUMOURS, 2004-2009 219
FIGURE 6.3 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR ADVANCED TUMOURS, 2004-2009 220
FIGURE 6.4 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR TUMOURS WITH MISSING STAGE, 2004-2009221
FIGURE 6.5 FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (%) FOR OVARIAN CANCER BY STAGE AT DIAGNOSIS AND HISTOLOGICAL GROUP, UNITED STATES, 2004-2009 236

Chapter 1: Introduction

Ovarian cancer ranks 7th in both incidence and mortality among women worldwide. In 2012, an estimated 238,000 women were diagnosed with and 151,000 women died from ovarian cancer, representing 4% of all new cancer diagnoses and 4% of cancer deaths among women[1]. Early symptoms, such as persistent abdominal pain, bloating or decreased appetite, are vague[2], and most women present with disease at an advanced stage[3].

1.1 Anatomy and biology of the ovary and fallopian tubes

1.1.1 Ovaries

The ovary is the primary endocrine gland of the female reproductive system. It has two main functions: to produce the eggs and to secrete the female sex hormones, oestrogen and progesterone[4,5]. Suspended within the peritoneal cavity by the broad ligament, the ovaries are paired organs that are attached to either side of the body of uterus by the ovarian ligaments [Figure 1.1]. The ovarian ligaments extend from the posterior side of the uterus as the round ligament. The tubal extremity of the ovary is attached to the broad ligament by the suspensory ligament of the ovary. The tubal extremity is the area of the ovary closest to the fimbriated end of the fallopian tube[5]. Recent evidence suggests that the fimbriated end of the fallopian tube may be the primary site of origin for most pelvic high-grade serous tumours among women[6].

The ovary has three main components: surface, cortex and medulla. The surface is made up of epithelial cells, one of the three main types of cell found in the ovaries. The cortex is located just below the ovarian surface epithelium and contains the outer supporting stroma and the follicles, which produce the eggs. Stromal cells form the supporting structural tissue of the cortex and produce oestrogen and progesterone, and germ cells are found in the follicles. The medulla is the central part of the ovary: it contains the inner

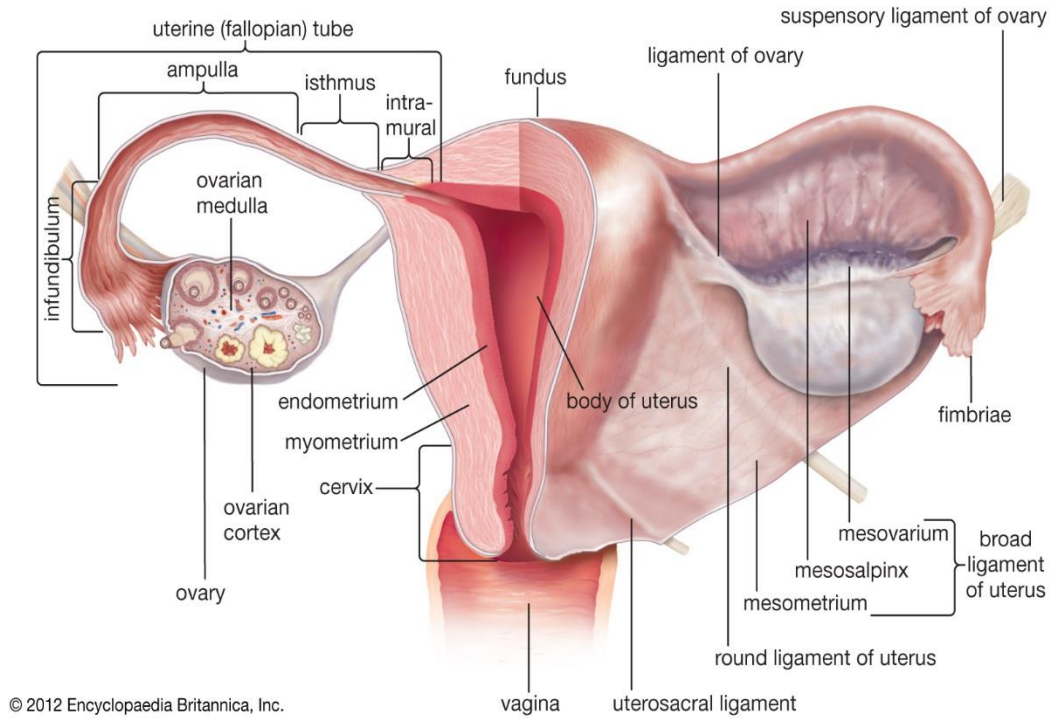


Figure 1.1 The female reproductive system

Source: Editors of Encyclopædia Britannica. Fallopian tube: anatomy - uterus [illustration]. 2012. [cited 12 September 2016]. Available from: https://www.britannica.com/science/fallopian-tube/images-videos/uterus/138859.

supporting stroma and a rich neurovascular network providing blood to the ovary from the ovarian arteries[7].

1.1.2 Fallopian tubes

The fallopian tubes comprise the fimbriae, infundibulum, ampulla and isthmus [Figure 1.1]. The infundibulum is the end of the tube closest to the ovary into which the finger-like fimbriae help gather the ovulated egg(s) into the fallopian tube. The ampulla is the longest part of the tube and the most common site of fertilisation of the egg by a sperm. The fallopian tube narrows at the uterine end to form the isthmus which enters into the body of the uterus[5].

1.1.3 The menstrual cycle

The ovaries are involved in the regulation of the menstrual cycle as part of the endocrine system, through a complex feedback loop [Figure 1.2]. The cycle begins with the follicular phase when the hypothalamus recognises low levels of oestrogen and progesterone in the bloodstream and secretes gonadotropin-releasing hormone (GnRH). The pituitary gland responds to the release of GnRH by producing and releasing luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH signal the ovaries to produce oestrogen and progesterone, which stimulate growth of the follicles and prepare the uterus for pregnancy. During the follicular phase, one dominant egg-producing follicle develops from a primordial follicle to a matured egg. Once the follicle has completely matured, ovulation occurs. During ovulation, the ovarian surface epithelium ruptures to release the egg into the fimbriated end of the fallopian tube where it then travels to the uterus[4].

The second half of the menstrual cycle is called the luteal phase and occurs immediately after ovulation. During the luteal phase, the lining of the dominant follicle grows to form a corpus luteum [Figure 1.2]. The corpus luteum temporarily secretes oestrogen and

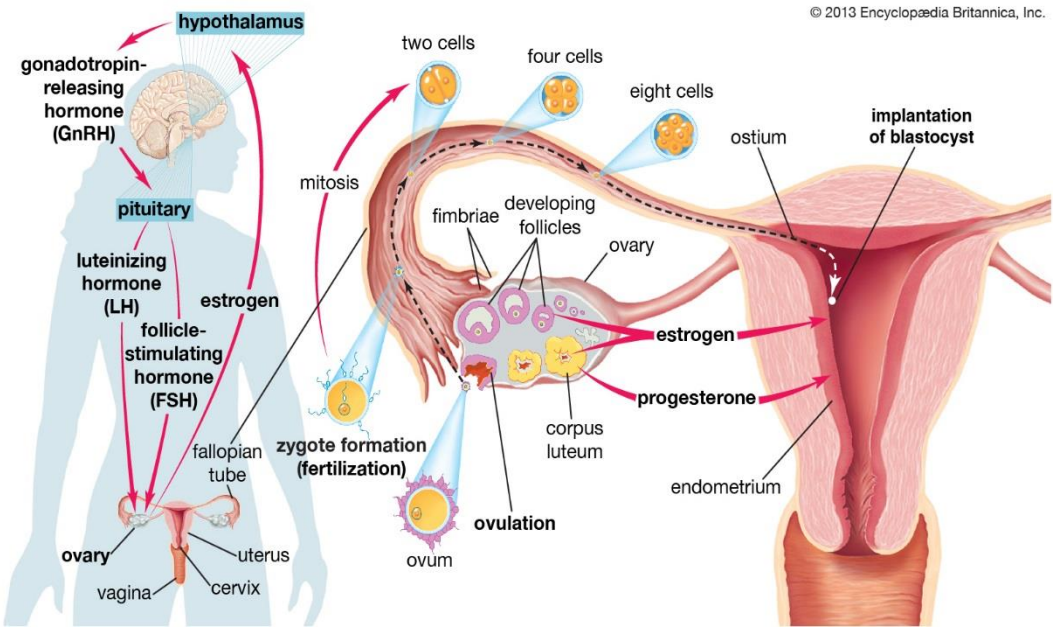


Figure 1.2 The menstrual cycle

Source: Editors of Encyclopædia Britannica. Fallopian tube: anatomy - pituitary gland: secretion and function of gonadotropins [illustration]. 2013. [cited 12 September 2016]. Available from: https://www.britannica.com/science/fallopian-tube/images-videos/The-hypothalamus-and-pituitary-gland-control-the-secretion-of-gonadotropins/102076.

progesterone to thicken the lining of the uterus for pregnancy and prevent further ovulation. If pregnancy does not occur, the corpus luteum stops producing hormones and degenerates. This reduction in oestrogen and progesterone will be recognised by the hypothalamus and a new cycle will begin[4].

1.2 Ovarian cancer

Since the early part of the 20th century, it has been recognised that ovarian cancer is not a single disease, but comprised of various histologically different tumour types[8]. Ovarian cancers have generally been divided into epithelial and non-epithelial groups for many years. Epithelial, germ cell and sex cord-stromal tumours are the commonest types of ovarian cancer. They can be further subdivided into distinct histological subtypes [Figure 1.3]. The developmental pathway and clinical prognosis for a particular ovarian tumour depends upon the histological subtype[2].

1.2.1 Epithelial ovarian, fallopian tube and primary peritoneal cancer

Epithelial ovarian cancer is the most common type of ovarian tumour, making up 90% of all primary malignant ovarian cancers[9]. Histological subtypes of epithelial tumours primarily include: clear cell, endometrioid, mucinous, serous, squamous, transitional cell (Brenner) and undifferentiated carcinoma[2,10]. Recent work has enabled finer subdivision of epithelial ovarian cancers into different groups according to a combination of morphological, molecular and clinical characteristics[10-14]. Each histological subtype has distinct molecular pathways that influence chemosensitivity, the pattern of metastasis and the probability of survival[11,15].

Under one proposed classification scheme, “type I” epithelial tumours include low-grade serous, endometrioid, clear cell, mucinous, squamous and transitional cell (Brenner) carcinomas. They often present at an early stage, may arise from borderline ovarian tumours or endometriosis, and typically have a good prognosis[10-12,16].

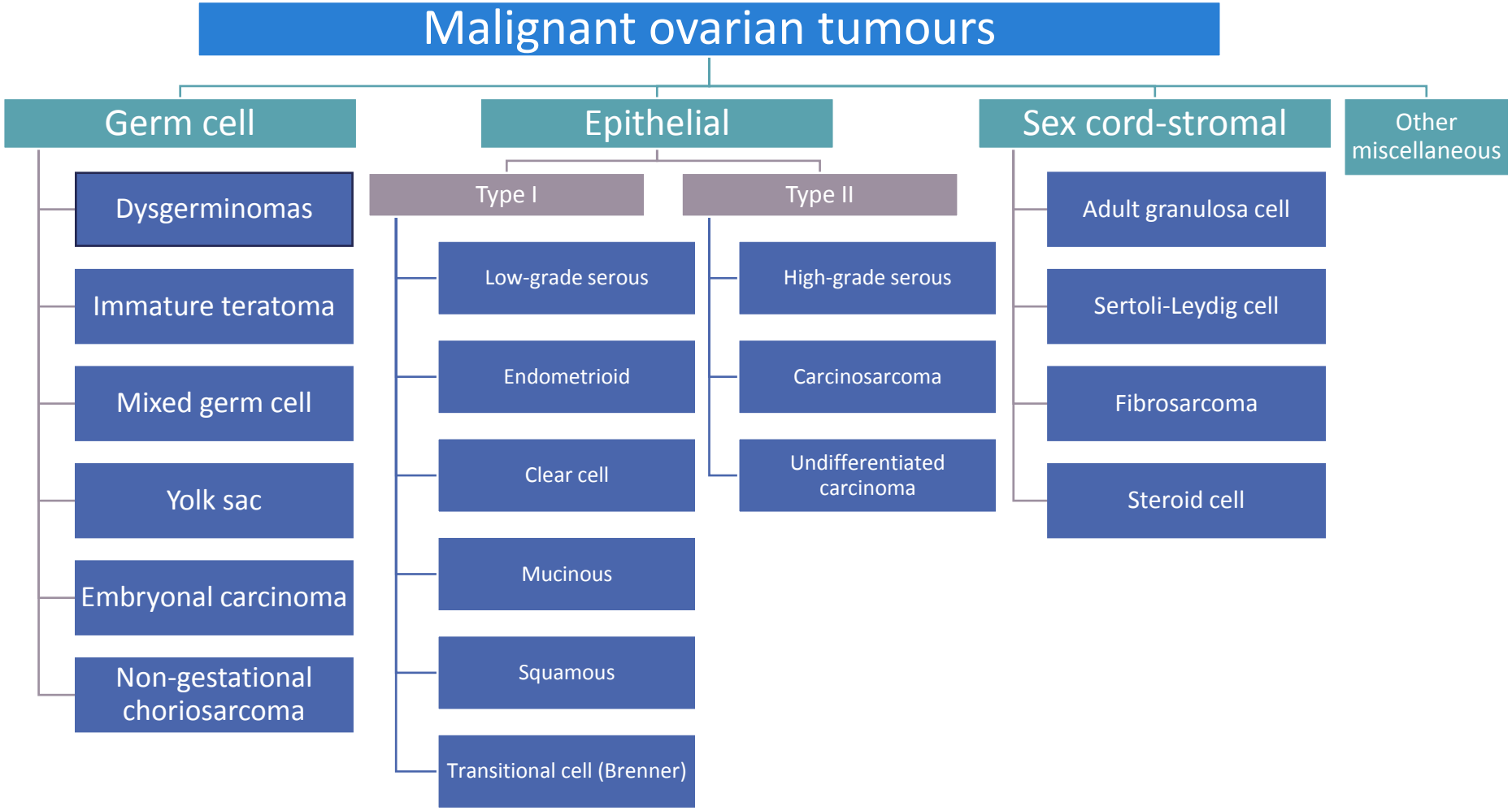


Figure 1.3 The histological subtypes of ovarian cancer, including fallopian tube and primary peritoneal tumours

Using the same classification scheme, “type II” epithelial tumours comprise high-grade serous carcinoma, undifferentiated carcinomas and malignant mixed mesodermal tumours (carcinosarcoma). They account for around 75% of epithelial ovarian cancers, typically present at an advanced stage and have a poor prognosis[10-12,16].

Fallopian tube and primary peritoneal carcinoma arise outside the anatomical ovary, but most tumours at these sites are now considered to be part of the spectrum of ovarian malignancies.

Primary fallopian tube carcinoma is a rare cancer that presents clinically in a similar manner to epithelial ovarian cancer and is treated clinically in the same way[17]. Malignant subtypes of fallopian tube carcinoma include clear cell, endometrioid, mucinous, serous, transitional cell and undifferentiated epithelial carcinomas[2]. Non-epithelial fallopian tube tumours are extremely rare, accounting for only around 7% of malignant fallopian tube cancers, and can include leiomyosarcoma and germ cell tumours[2,18].

Primary peritoneal carcinoma in women is also extremely rare. Macroscopically, primary peritoneal carcinoma may look like an epithelial ovarian carcinoma that has spread to the abdomen, and microscopically, the cells often resemble those of epithelial ovarian carcinoma[19]. Primary peritoneal carcinomas are also managed in the same way as advanced-stage epithelial ovarian cancer[10,17]. Non-epithelial types of primary peritoneal cancer do occur, such as malignant mesothelioma, desmoplastic small round cell tumours and solitary fibrous tumours, but these types account for only one-third of primary peritoneal cancers[2,18].

Due to the anatomical location of the three sites, primary fallopian tube and peritoneal carcinomas may be diagnosed as primary epithelial ovarian cancer[12,17]. Around 15% of tumours diagnosed as primary ovarian have been found to actually be primary peritoneal tumours[2]. During 1995-2004, age-adjusted annual incidence of primary ovarian

carcinoma in the US was much higher (119.9 per million) than for primary peritoneal (6.78 per million) or fallopian tube (3.72 per million) carcinomas[18]. The incidence of ovarian carcinoma fell over the 33-year period from 1973 to 2005, and the incidence of peritoneal and fallopian tube carcinomas increased. The decrease in incidence in ovarian cancer over time may be partially artificial and attributable to the establishment of guidelines in 1993 to define primary peritoneal carcinoma[18,20].

The guidelines for diagnosis of primary fallopian tube cancer are more restrictive than those for primary ovarian cancer. In order for a tumour to be considered a primary fallopian tube carcinoma, the majority of the tumour has to be within the fallopian tube rather than the ovary, and there must be evidence of an intraepithelial tubal carcinoma. Additionally, there must be a clear transition from benign to malignant epithelium[21].

A diagnosis of primary peritoneal cancer is rare because the guidelines for diagnosis are also very restrictive. Regardless of whether there is extensive tumour involvement of the peritoneum or other abdominal organs, if the tumour within the ovary is greater than 5mm, the cancer is, nevertheless, considered to be primary ovarian rather than primary peritoneal carcinoma[12,20].

Subtypes of epithelial ovarian, fallopian tube and primary peritoneal cancer

Serous

Serous carcinoma is the most common histological subtype at all three primary sites[2,18]. Around 40-50% of ovarian cancers and around 66-90% of fallopian tube carcinomas are serous tumours[2,22]. Non-serous peritoneal carcinoma is extremely uncommon[2].

Serous tumours of ovarian, tubal and peritoneal origin are divided into low-grade and high-grade serous carcinoma depending upon the degree of differentiation[2]. Low-grade serous carcinoma (LGSC) is distinct from high-grade serous carcinoma (HGSC); progression from low-grade to high-grade only occurs rarely[10]. Low-grade serous ovarian carcinomas

are relatively rare, accounting for only 5% of serous ovarian carcinomas. Low-grade serous fallopian tube carcinoma is also very rare[2].

High-grade serous ovarian carcinoma is the most common subtype of epithelial ovarian cancer, and women with high-grade serous ovarian tumours typically present at older ages than women with low-grade tumours. Most serous peritoneal tumours are high-grade and resemble high-grade serous ovarian tumours[2].

Endometrioid carcinoma

Endometrioid tumours are the second most common type of ovarian and fallopian tube carcinoma[18]. Around 20-33% of women diagnosed with endometrioid tumours also have primary endometrial cancer or hyperplasia[9]. Most endometrioid tumours are early-stage and are confined to the ovary at diagnosis, with only 17% of women diagnosed with bilateral tumours. Endometrioid tumours are generally well-differentiated and low-grade, and women with low-grade tumours have higher survival than women diagnosed with high-grade tumours[2].

Clear cell carcinoma

Clear cell tumours are generally large (around 15 cm in diameter), but unilateral[2]. Around 85% of clear cell tumours are stage I or II at diagnosis[9]. Survival from early-stage disease is high, but advanced-stage disease does not respond well to chemotherapy and thus, survival is lower[2].

Mucinous carcinoma

Mucinous tumours account for around 3-4% of all ovarian tumours[2]. Mucinous ovarian tumours are usually stage I at diagnosis and are well-differentiated or moderately-differentiated. Survival from early-stage mucinous tumours is generally high, but advanced-stage disease, though rare, is often aggressive and does not respond well to chemotherapy. Metastatic tumours from other sites, such as the gastrointestinal tract, often mimic a primary ovarian mucinous tumour. Thus, identifying a mucinous tumour as

a primary ovarian tumour is often difficult. Primary ovarian tumours are more frequently unilateral and larger than mucinous tumours at other primary sites[23].

Transitional cell (Brenner) carcinoma

Transitional cell tumours are large (16-20 cm in diameter) and usually confined to the ovary at diagnosis. Around 80% of these tumours are stage I at diagnosis and only 12% are bilateral. Women diagnosed with stage I disease have high 5-year survival, while women diagnosed with tumours that have spread outside the ovaries have similar survival to other advanced epithelial tumours[2].

Squamous carcinoma

Squamous carcinomas are an extremely rare form of malignant epithelial ovarian tumour comprised of squamous cells that do not originate from germ cells. Squamous tumours are primarily high-grade and survival from these tumours is poor[19]. Around 34% of women diagnosed with squamous carcinoma have stage I disease, while 21% and 25% have stage III and stage IV, respectively. Survival varies by stage and can be as high as 86% for early stage tumours, but as low as 3% for stage IV tumours[24].

Carcinosarcoma

Carcinosarcomas can also be referred to as malignant mixed mesodermal or malignant mixed Müllerian tumours. These tumours are rare, accounting for only 2% of ovarian tumours. Most women are diagnosed at advanced stages with high-grade large tumours (14 cm)[2].

Undifferentiated carcinoma

An undifferentiated carcinoma is an epithelial tumour without differentiation, thus identifying a specific cell type is impossible. Most women diagnosed with undifferentiated carcinoma have advanced-stage disease and poor survival[2].

Epidemiology of epithelial tumours

A strong family history of either breast or ovarian cancer in a first degree relative at an early age is a primary risk factor for epithelial ovarian cancer[17]. Older age of the woman is another important risk factor, and the median age at diagnosis for epithelial ovarian cancer is 60 years[25]. In a recent study from the US, peritoneal carcinomas were generally diagnosed at older ages (mean age at diagnosis of 67 years) than fallopian tube (mean age at diagnosis of 64 years) and ovarian (mean age at diagnosis of 63 years) carcinomas[18].

While only 10% of epithelial ovarian cancers are due to genetic abnormalities, women with BRCA1 mutations have a 35-50% increased risk of disease, and women with BRCA2 mutations have a 10-30% increased risk[26]. Lynch syndrome can also increase a woman's risk of ovarian cancer by 3-33%[27]. Women with BRCA mutations are more likely to develop type II tumours[12]. BRCA mutations are also more common in women with fallopian tube and peritoneal cancer than women in the general population[2]. Additional risk factors include endometriosis, nulliparity, early menarche, late menopause and lack of oral contraceptive use[9,26].

Biological mechanisms of epithelial tumours

The pathogenesis of ovarian cancer is not fully understood. There are two conventional theories regarding the development of epithelial ovarian cancer. The first theory refers to incessant ovulation, or the repeated wounding and repair of the surface epithelium of the ovary during ovulation[28]. This repetition increases epithelial proliferation for repair and, therefore, the frequency of DNA mutations and the formation of ovarian cortical inclusion cysts[25]. Ovarian inclusion cysts form through invagination of the ovarian surface epithelium into the surrounding ovarian stroma[12]. The second theory involves the increase of gonadotropic hormones (LH and FSH) during ovulation, which also increase proliferation, potentially leading to malignant transformation of the epithelium of ovarian inclusion cysts[25,26,29]. Most risk factors traditionally associated with epithelial ovarian

cancer, such as older age, nulliparity, early menarche, late menopause and lack of oral contraceptive use, can be used to support both theories of the development of ovarian cancer because they are all associated with an increased lifetime number of ovulations. Additionally, BRCA mutations result in a decreased ability to repair genetic damage, which increases risk of disease.

The primary critique of the theory of incessant ovulation is that the ovarian surface epithelium does not resemble the main histologic types of epithelial ovarian tumours (serous, endometrioid, mucinous, clear cell or transitional cell). The second theory, involving gonadotropic hormones, attempts to mitigate this weakness by assuming that, prior to malignant transformation, ovarian inclusion cysts undergo metaplastic change. The cysts, which comprise the mesothelium (the cell type of the ovarian surface epithelium), undergo metaplasia and are converted to cell types representing the primary histological subtypes of epithelial ovarian cancer[12,25].

Epithelial ovarian cancer has conventionally been defined as cancer that begins in the ovaries and this idea is central to both traditional theories of epithelial ovarian cancer development. However, while some epithelial ovarian tumours may start in the ovaries, given the lack of evidence of a precursor lesion arising from or in the ovary, it is possible that some epithelial ovarian tumours may originate outside the ovaries and only involve the ovaries secondarily[12].

LGSC is thought to develop in a step-wise manner from a serous cystadenoma or adenofibroma to an atypical proliferative serous tumour (APST). APSTs are serous borderline tumours which then progress to non-invasive micropapillary serous borderline tumours (MPSC). Once an MPSC becomes invasive, it is considered an LGSC[30].

The pathogenesis of HGSC is less clear than that of LGSC[30]. Most high-grade serous ovarian tumours are now thought to originate in the fallopian tubes rather than the ovary[31-33].

Recent studies examining the fallopian tubes of high-risk women with BRCA mutations have found that early-stage invasive tubal carcinomas are present in up to 70% of women with high-grade serous ovarian carcinoma, and serous tubal intraepithelial carcinoma (STIC) is now considered to be a precursor lesion for this particular histological subtype of epithelial ovarian cancer. Malignant cells from a STIC may shed and implant on the ovarian surface during ovulation when the fimbriated end of the fallopian tube is in close contact with the ovary. Additionally, normal, non-malignant tubal epithelial cells may shed from the fimbria and implant on the ovary to form an inclusion cyst. Once implanted, the cyst may then undergo malignant transformation[12].

The aetiology of fallopian tube cancer is unknown, but some studies show a protective effect of oral contraceptive use and parity, similar to the pattern observed for serous ovarian carcinoma[22]. Similarly, the aetiology for primary peritoneal carcinoma is unknown and difficult to establish because this type of cancer is so rare. There is some evidence that primary peritoneal carcinomas develop along the same pathway as ovarian carcinoma, particularly high-grade serous ovarian carcinoma[18]. However, while contraceptive use may decrease the risk of primary peritoneal carcinoma, increasing parity may not be as protective as for ovarian cancer[22].

Endometrioid and clear cell tumours are known to develop from endometriotic cysts, which are said to be the result of endometrial tissue implanted on the ovary[26] or passing through the fallopian tube[12] due to endometriosis. Endometriosis is a disease that primarily affects women of reproductive age, and around 10% of women of reproductive age have endometriosis. Endometriosis is when cells similar to the ones lining the uterus are found outside the womb; these cells are linked to the menstrual cycle, growing and bleeding along with the cells lining the uterus. However, unlike the cells lining the uterus, the cells are not shed from the body during menstruation. This can cause inflammation,

pain and the formation of scar tissue[34]. Endometriosis is an established risk factor for ovarian cancer[26].

The molecular development of transitional cell and mucinous tumours is not well established, but these tumours may develop from transitional cell nests at the tubal-mesothelial junction. Transitional cell nests are clusters of benign epithelial cells, usually located in the connective tissue of the fallopian tubes. Transitional cell and mucinous tumours may develop from these cell nests located in the transitional epithelium between the fallopian tubes and peritoneum. Further, it is believed that mucinous and transitional cell tumours develop along the same molecular pathway and may develop simultaneously, although transitional cell tumours tend to be small and slow-growing, while mucinous tumours tend to be large and fast-growing[12].

Treatment guidelines for epithelial tumours

Staging of ovarian cancer requires a surgical procedure to examine the spread of disease. During an exploratory laparotomy, samples of tissue from the ovary, fallopian tube, pelvic lymph nodes, omentum and diaphragm are biopsied and examined microscopically for malignant cells. The stage of disease is then based on the size, extent and location of the tumour (see section 1.4). Treatment for ovarian cancer depends on the stage of disease, therefore accurate staging of disease is critical for receipt appropriate treatment[17].

Standard treatment for early-stage epithelial ovarian cancer includes surgery, usually consisting of hysterectomy, bilateral salpingo-oophorectomy and omentectomy, and platinum-based chemotherapy. Early-stage tumours are generally confined to the ovary and are well-differentiated. For those tumours, salpingo-oophorectomy (unilateral or bilateral) may be adequate on its own. Women with early-stage and well-differentiated tumours may receive unilateral salpingo-oophorectomy to preserve fertility. Adjuvant

chemotherapy with cisplatin, carboplatin and paclitaxel is recommended for all early-stage patients, except those with stage IA well-differentiated tumours[17].

Treatment for advanced-stage tumours includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and other procedures to remove the tumour, such as debulking, followed by combination chemotherapy[17]. Optimal cytoreduction – where the residual tumour is less than 1cm – has been shown to improve survival significantly. Systemic chemotherapy is recommended for women who have residual disease of 1cm or more after surgery. Around 80% of advanced-stage tumours will relapse and should then be treated with either platinum-based treatment if the tumour was platinum-sensitive (i.e. the disease relapsed six months or more after cessation of initial treatment), or alternative options for platinum-resistant disease (i.e. the disease recurred within six months of stopping initial treatment or progressed during induction therapy)[17].

Advanced-stage epithelial tumours may also be treated with intraperitoneal (IP) chemotherapy after surgery. Clinical trials have shown favourable outcomes for IP chemotherapy for women with platinum-sensitive, small residual tumours. Hyperthermic peritoneal chemotherapy (HIPEC) is another treatment option that has been only recently used to treat ovarian cancer. Exploratory trials are in progress to examine the most effective drug combination and time at target temperatures for drug delivery, in addition to defining which women will benefit the most from HIPEC[17].

Treatment for fallopian tube and peritoneal carcinomas is the same as for epithelial ovarian tumours[17,18].

1.2.2 Germ cell

Germ cell tumours are responsible for 3% of invasive ovarian tumours worldwide, though they can account for up to 20% of ovarian tumours in some East Asian countries[19]. Germ cell tumours include several histologically distinct tumour subtypes[2]. The majority (95%)

of germ cell tumours are benign mature cystic teratomas[19,35]. Dysgerminomas are the most frequent subtype of malignant germ cell tumour, but only make up 1-2% of all malignant ovarian tumours. Immature teratomas are the second most common subtype of malignant germ cell tumours. Mixed germ cell tumours represent about 8% of malignant germ cell tumours and are a mixture of two or more malignant germ cell tumours. The most common mixed germ cell tumour is a mixed dysgerminoma and yolk sac tumour. Pure yolk sac tumours, non-gestational choriocarcinomas and embryonal carcinomas are extremely rare subtypes of malignant germ cell tumours[2].

Epidemiology of germ cell tumours

Germ cell tumours represent 60% of all malignant ovarian tumours among women aged 21 years or younger[19]. The average age at diagnosis for dysgerminoma is 22 years, immature teratomas are most common among women aged 30 or younger and the mean age at diagnosis is 16 years for mixed germ cell tumours[2]. While most risk factors for germ cell tumours are unknown, congenital malformations of the genital tract, Turner's syndrome and gonadoblastomas are possible risk factors for dysgerminoma[9].

The majority (60-70%) of malignant germ cell tumours are stage I or II at diagnosis, while only 20-30% are stage III. Stage IV tumours are extremely rare[36].

Biological mechanisms of germ cell tumours

Germ cell tumours develop from benign germ cells, which are the egg-producing cells within the ovary. However, the pathway to malignant transformation of these cells is not clearly understood[19,37]. The duration of symptoms prior to diagnosis is generally only two to four weeks; therefore, germ cell tumours are thought to develop rapidly[36].

Treatment guidelines for germ cell tumours

As germ cell tumours are primarily unilateral, standard surgery may be more conservative than for epithelial tumours[38]. Standard treatment typically involves unilateral salpingo-oophorectomy or total abdominal hysterectomy and bilateral salpingo-oophorectomy,

plus platinum-based adjuvant combination chemotherapy. If the cancer is early-stage, unilateral salpingo-oophorectomy may be performed to preserve fertility in young women, and chemotherapy may not be required. For advanced-stage disease, unilateral salpingo-oophorectomy if followed by chemotherapy may be performed instead of bilateral salpingo-oophorectomy and hysterectomy, in order to preserve fertility[39]. Germ cell tumours generally respond well to chemotherapy[38].

1.2.3 Sex cord-stromal

Sex cord-stromal tumours are a diverse group of rare ovarian tumours that can involve a variety of different cell types[40]. Subtypes of malignant sex cord-stromal tumours primarily include fibrosarcoma, steroid cell, adult granulosa cell and Sertoli-Leydig cell tumours[2,19]. The diversity of cell types and the fact that the tumours may be composed of one or more cell type leads to difficulty in correctly identifying the tumour subtype[40]. Adult granulosa cell tumours, the most common subtype, only comprise 1% of all malignant ovarian tumours and steroid cell tumours only account for 0.1% of ovarian tumours[2].

Adult granulosa cell tumours are generally low-grade, unilateral and confined to the ovary at diagnosis[2]. Though adult granulosa cell tumours are slow-growing, these tumours have been known to recur up to 20 years after the initial diagnosis[2]. Sertoli-Leydig cell tumours are usually confined to the ovaries at diagnosis, and are well-differentiated[40]. A recent study found that 86% of Sertoli-Leydig cell tumours were stage I at diagnosis[41].

Epidemiology of sex cord-stromal tumours

While the incidence of sex cord-stromal tumours is highest among women in their fifties[26], these tumours can occur throughout the reproductive years and after menopause[19,42]. The average age of adult granulosa cell patients is 53 years, but the mean age for Sertoli-Leydig cell tumours is 25 years[2]. Risk factors for sex cord-stromal tumours are not well known, but may include race/ethnicity, obesity, family history of breast or ovarian cancer,

lack of oral contraceptive use and nulliparity, particularly for granulosa cell tumours[43]. BRCA mutations do not increase the risk of granulosa cell tumours[44].

Biological mechanisms of sex cord-stromal tumours

The aetiology of sex cord-stromal tumours is unknown; however, the development of granulosa cell tumours may be associated with infertility and the use of ovulation-stimulating drugs[19,44,45]. There are two proposed pathways for development of granulosa cell tumours due to ovulation-stimulating drugs: the granulosa cell tumour may already exist within the ovary and the hormonal drugs trigger growth, or increased amounts of follicle-stimulating hormone may be carcinogenic to granulosa cells[44,45]. Granulosa cell tumours may also be associated with endometrial hyperplasia due to stimulation of the endometrium in response to the increase in oestrogen, which is secreted by granulosa cell tumours. Around 13% of women diagnosed with granulosa cell tumours also develop well-differentiated endometrial adenocarcinoma[44].

Treatment guidelines for sex cord stromal tumours

The treatment for sex cord-stromal tumours is similar to that for epithelial ovarian tumours. Early-stage disease may be treated with conservative surgery, consisting of only unilateral salpingo-oophorectomy[44]. Adjuvant chemotherapy may be used to treat early-stage disease, but the benefits of such treatment are not yet confirmed[42,46,47]. For advanced disease, total abdominal hysterectomy, bilateral salpingo-oophorectomy and debulking surgery may be performed along with administration of platinum-based combination chemotherapy[42,44,47]. Accurate staging of the tumour is of particular importance because of the higher tendency for advanced-stage disease to relapse many years later. All patients should be observed indefinitely after initial treatment[42].

1.3 Definition of ovarian cancer

Given the newly proposed theories of development for serous ovarian carcinoma involving the fallopian tubes, and the extra-ovarian nature of the development of

endometrioid, clear cell, mucinous and transitional cell tumours, it seems likely that the majority of epithelial ovarian tumours may actually originate outside the ovary[10,12]. Additionally, the restrictive guidelines for primary fallopian tube and peritoneal carcinoma lead to a bias in diagnosing pelvic tumours as "ovarian" carcinoma. Since 2000, fallopian tube and primary peritoneal carcinomas have been included in ovarian cancer trials[17]. Therefore, for the purposes of this thesis, the definition of ovarian cancer will include primary fallopian tube and peritoneal cancer as well as tumours of the uterine ligaments and adnexa, and other specified and unspecified female genital organs (International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes C48.0-C48.2, C56.9, C57.0-C57.4 and C57.7-C57.9)[48].

1.4 Classification systems for stage of disease at diagnosis

The stage of disease is important for accurate treatment of ovarian, tubal and peritoneal cancer. When examining cancer survival, stage at diagnosis is key, and the staging system should not allow for changes in stage after biopsy or initial treatment. The stage of the disease describes the extent of the spread of disease and is based on location of the primary tumour, tumour size, lymph node involvement and metastasis at diagnosis. Unless the disease is advanced at diagnosis, ovarian cancer is generally staged through surgery and pathological analysis of tissue samples of the tumour[49]. Three main staging systems for ovarian cancer are used: the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) system, the Union for International Cancer Control's (UICC) Tumour Node Metastasis (TNM) system and the Surveillance, Epidemiology and End Results (SEER) programme's Summary Stage 2000. Agreement between FIGO, UICC and the American Joint Committee for Cancer ensures that the different staging systems for ovarian cancer are compatible and comparable between countries.

1.4.1 Fédération Internationale de Gynécologie et d'Obstétrique (FIGO)

The FIGO staging classification system for is unique to gynaecological tumours [Table 1.1][49]. The staging guidelines are applicable to all histological subtypes of ovarian cancer, as well as primary fallopian tube and primary peritoneal carcinoma.

1.4.2 Tumour node metastasis (TNM)

Ovarian cancer can also be staged using the TNM system[50]. Tumours are classified on the basis of the size and extent of the primary tumour (T), involvement of regional lymph nodes (N) and the presence or absence of metastasis (M). Individual TNM values can be combined to create a grouped variable representing stages I-IV, which are compatible with FIGO stages I-IV. T, N and M may be determined through pathological or clinical examination, or both. Clinical examination for staging can include physical examination or imaging, while pathological examination involves microscopic examination of the tumour.

1.4.3 Surveillance, Epidemiology, and End Results (SEER) Summary Stage 2000

SEER Summary Stage 2000 is primarily used by the North American Association of Central Cancer Registries[51]. It was developed by the US National Cancer Institute's SEER programme. SEER Summary Stage 2000 is compatible with TNM and the stages and definitions of each stage are listed in Table 1.2. Previous work has shown that for ovarian cancer there is very little misclassification when converting SEER Summary Stage 2000 to TNM[52].

1.5 Screening for ovarian cancer

Successful screening techniques for ovarian cancer have been difficult to develop. Screening tests should follow the classic guidelines proposed by Wilson and Jungner in 1968 [Figure 1.4][53]. These guidelines have been updated over the past few decades, and new criteria build upon the guidelines originally proposed by Wilson and Jungner

Continued on page 37

Table 1.1 Compatibility of FIGO and TNM staging systems

FIGO	T	N[a]	M[b]	Definition
I	T1	N0	M0	Tumour limited to the ovaries or fallopian tubes
IA	T1a	N0	M0	Tumour limited to one ovary, capsule intact, or fallopian tube, no tumour on surface, no malignant cells in ascites or peritoneal washings
IB	T1b	N0	M0	Tumour limited to both ovaries, capsules intact, or fallopian tubes, no tumour on surface, no malignant cells in ascites or peritoneal washings
IC	T1c1-3	N0	M0	Tumour limited to one or both ovaries or fallopian tubes with any of the following: surgical spill, capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings
II	T2	N0	M0	Tumour involves one or both ovaries or fallopian tubes with pelvic extension or primary peritoneal cancer
IIA	T2a	N0	M0	Extension and/or implants on the uterus and/or tubes and/or ovaries
IIB	T2b	N0	M0	Extension to other pelvic tissues
III	T1/T2	N1	M0	Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal spread outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	T3a2	N0/N1	M0	Positive retroperitoneal lymph nodes only or microscopic peritoneal metastasis beyond the pelvis
IIIB	T3b	N0/N1	M0	Macroscopic peritoneal metastasis beyond the pelvis $\leq$ 2cm
IIIC	Any T	N0/N1	M0	Macroscopic peritoneal metastasis beyond the pelvis $\geq$ 2cm
IV	Any T	Any N	M1	Distant metastasis excluding peritoneal metastases
IVA	Any T	Any N	M1	Pleural effusion with positive cytology
IVB	Any T	Any N	M1	Parenchymal metastases and metastases to extra-abdominal organs

[a] N0 indicates no regional lymph node involvement and N1 indicates regional lymph node involvement. [b] M0 indicates no metastasis and MI indicates metastasis.

Table 1.2 SEER Summary Stage 2000 Classification

Stage	Definition
0	*In situ*
1	Localised only
2	Regional spread by direct extension only
3	Regional lymph nodes involved only
4	Regional spread by both direct extension and lymph node involvement
5	Regional, NOS (not otherwise specified)
7	Distant site(s) or lymph node(s) are involved
9	Unknown if there is extension or metastasis

Wilson and Jungner classic criteria for screening

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all”

Figure 1.4 Wilson and Jungner classic screening criteria

[Figure 1.5][54]. As ovarian cancer is a leading cause of death from gynaecological malignancy worldwide, it meets the first criterion for screening. Standard treatment guidelines for most types of ovarian cancer exist and access to treatment is generally available, which satisfy the second and third criteria.

Screening tests will only be useful in reducing mortality if a precursor lesion can be detected and the rate of tumour growth is slow enough to allow for early disease detection. Mathematical modelling using data from risk-reducing salpingo-oophorectomies among women with BRCA1 mutations suggests that serous tumours may be in situ, stage I or stage II for more than four years, and stage III or stage IV for an additional year, before they present clinically[55]. While it appears there may be a lengthy latent period for serous ovarian cancer, the latent period is not easily recognisable and there is no early symptomatic stage for most ovarian tumours, which is required for the fourth criterion.

Serous tumours tend to be small and slow-growing during this occult phase of development, remaining only 1 cm in diameter for the majority of the time before increasing to only 3 cm as the tumour progresses to stage III or IV[55]. Once the disease is stage III or IV, tumours grow rapidly, doubling in size every 2-3 months[56]. This evidence suggests that in order for a screening test to achieve 50% sensitivity, an annual screening test would need to be able to detect tumours as small as 1.3 cm in diameter. For 80% sensitivity, the screening test would need to detect tumours less than 0.4 cm in diameter, and for a 50% reduction in mortality from serous tumours, the annual screening test would need to detect tumours 0.5 cm in diameter[55]. Previous work has shown that in order to achieve a positive predictive value of 10% for a screening test for epithelial ovarian cancer (meaning that 10% of women who screen positive for epithelial ovarian

Updates to the classic screening criteria

1. The screening programme should respond to a recognised need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The programme should ensure informed choice, confidentiality and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

Figure 1.5 Updates to the classic screening criteria

cancer actually have the disease), the screening test should have a sensitivity of greater than 75% and a specificity of at least 99.6%[25].

Screening methods previously assessed in trials may not be able to detect such small tumours required to achieve a mortality benefit from annual screening. Lead-time bias will occur if a screening test detects disease earlier than it would have been if it had been diagnosed without screening, but does not result in a delay of death. With lead-time bias, the perceived survival time is longer with screening but this "improvement" in survival is due only to the earlier detection of disease through screening rather than an impact of the screening test on mortality. Screening techniques for ovarian cancer include pelvic examination, measurement of serum cancer antigen 125 (CA125) and transvaginal sonography, and used separately these tests have not been successful in reducing ovarian cancer mortality[57]. However, there is some evidence that when used in combination, ovarian cancer may be detected at an earlier stage. Recent results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) show that multimodal screening consisting of transvaginal ultrasound and CA125 assessment using the risk of ovarian cancer algorithm is more likely to lead to earlier diagnosis of ovarian or primary peritoneal cancer than no screening. The UKCTOCS also showed that multimodal screening could prevent up to 20% of ovarian cancer deaths. Women eligible for the trial were post-menopausal and did not have an increased risk of ovarian cancer[57]. Results from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the US showed no evidence of a mortality benefit from screening[58] and more research is needed to confirm the results from the UKCTOCS.

Further, given the histologically distinct subtypes of ovarian cancer, one screening test is unlikely to be sufficient for detecting all ovarian tumours. Therefore, screening techniques such as the multimodal screening method used in UKCTOCS would be difficult to

implement at the population level[25]. For type I tumours that grow slowly and tend to reach a large size while still confined to the ovary, pelvic examination and transvaginal ultrasound may be effective tools for early diagnosis. However, type I tumours are much less common and less aggressive than type II tumours, thus a mass screening programme for these tumours may not be appropriate. Requiring that screening tests for ovarian cancer focus on detecting tumours while still confined to the ovary is unlikely to be effective for type II tumours, which appear to develop outside the ovary. Effective screening tools for type II tumours might focus on detection while the tumour is small, rather than early stage, and would need to include examination of the fallopian tubes and transvaginal ultrasound[12].

The target population for ovarian cancer screening tests may change based on the specific subtype of ovarian tumour for which the test is aiming to detect. Additionally, screening techniques may need to be tailored further for different risk groups because the effect of annual screening on ovarian cancer mortality may vary between low-risk women and high-risk women. High-risk women, particularly those with Lynch syndrome or BRCA mutations, may benefit from more frequent screening, such as 4-monthly CA125 assessment as implemented in Phase II of the UK Familial Ovarian Cancer Screening Study[27,56]. While risk stratification for screening for ovarian cancer may be necessary, it must also be cost-effective.

While there is some evidence of a mortality benefit from screening as shown in the UKCTOCS, more research is needed to confirm this result in the general population, and to achieve similar results in high-risk groups. Additionally, screening tests for other ovarian cancer subtypes need to be explored. Thus, the majority of the Wilson and Jungner screening criteria have yet to be satisfied for ovarian cancer.

1.6 Aims and objectives

The aim of this thesis is to examine various factors that may help to explain how and why ovarian cancer survival differs between and within countries.

- Objective 1: Does the distribution of histology vary by country or geographic region, or over time?
- Objective 2: Does survival vary between histological groups?
- Objective 3: Does survival vary by stage at diagnosis?
- Objective 4: Does survival vary by race/ethnicity?

Chapter 2: Literature review

2.1 Methods

The aim of this literature review is to synthesise current knowledge on the factors that influence ovarian cancer survival. These factors include histology, stage at diagnosis, place of residence, race/ethnicity, treatment, socioeconomic status and health insurance status.

The Medline, EMBASE and Global Health databases were searched using the keywords detailed in Table 2.1 for articles published between January 1970 and August 2016. The review was limited to articles in English.

Additional articles for the literature review were found by hand-searching the references of articles included in the review.

2.2 Survival and histology

The different histological subtypes of ovarian cancer differ in aetiology and developmental pathways, risk factors, prognosis and survival outcome[10,12]. The majority of women are diagnosed with epithelial ovarian cancer, which confers the lowest survival of the three main types of ovarian cancer. In particular, survival for women with high-grade serous carcinoma is much lower than for other types of ovarian cancer. For women diagnosed between 1988 and 2001 with epithelial ovarian cancer in the US, 5-year disease-specific survival was highest for those with endometrioid tumours (71.5%) and lowest for those with serous tumours (38.6%). Women with mucinous (67.1%) and clear cell (64.6%) carcinoma also had relatively high survival compared to those with serous tumours[59].

Table 2.1 Key topics and search terms for literature review

Key topics	*Search terms*
Disease of interest	(ovar* OR gynecol* or gynaecol*) AND (neoplasm* OR oncol* OR cancer* OR tumour* OR tumor*)
Factor of interest	
histology	morphology OR histology OR type* OR subtype*
stage at diagnosis	stage at diagnosis OR (cancer staging AND diagnosis)
race/ethnicity	rac* OR ethnicit*
place of residence	geography OR region* OR residence
socioeconomic status	socioeconomic status OR SES OR social class OR socioeconomic factor* OR socioeconomic difference* OR socioeconomic inequal* OR socioeconomic inequit* OR disparit* OR income OR education OR employment OR occupation* OR poverty OR deprivation
treatment	treatment OR surgery OR chemotherapy
insurance status	insurance OR insurance coverage OR insurance status
Outcome	survival analysis OR survival

There is some evidence, however, that histology may not impact risk of death from ovarian cancer. Among women receiving treatment for ovarian cancer, particularly primary debulking surgery, at a tertiary care centre in Germany from 2000 to 2010, histological subtype did not influence mortality for women diagnosed with advanced-stage disease[60]. The results from this analysis suggest that differences in survival between histological subtypes may be due to differences in the distribution of stage at diagnosis within each subtype.

Survival from borderline ovarian tumours is extremely high. In a study of long-term survival from borderline tumours among women diagnosed from 2000 to 2007 in Sweden, 5-year relative survival from borderline tumours was 97%. Survival for women diagnosed from 1980 to 1989 was as high as 94% 10 years after diagnosis and 91% 15 years after diagnosis[61].

The incidence of the various ovarian cancer histological subtypes varies with age[62], and they may respond differently to standard treatment. In a prospective study conducted in India, younger women were more likely to be diagnosed with germ cell tumours while sex cord-stromal tumours were more common among older women, and epithelial tumours were diagnosed in women of all ages. The peak age of incidence ranged from 21 to 30 years for germ cell tumours, 51 to 60 years for sex cord-stromal tumours and 21 to 50 years for epithelial tumours[63]. A study in Iran in 2004 found that young women aged 20-29 and older women aged 70-79 had higher incidence of germ cell tumours than women of other ages. The median age of diagnosis overall was 49 years. While this age at diagnosis is much younger than in more developed countries, the age structure of cancer patient populations in less developed regions is generally younger[64].

Some studies have examined the differences of the histological subtypes of ovarian cancer, but the literature focuses primarily on incidence rather than survival. Articles are

limited by small numbers of patients and restricted to only a few countries. The majority of the literature focuses on epithelial ovarian cancer; very few studies include or focus on women with germ cell or sex cord-stromal tumours.

Survival from a specific histological subtype may vary by topographical sub-site. Women diagnosed with primary peritoneal serous tumours have been shown to have poorer survival than women diagnosed with serous tumours of the ovary or fallopian tube. No differences in survival from serous tumours were seen between women diagnosed with fallopian tube or ovarian topography[65,66].

2.3 Survival and stage at diagnosis

For most cancers, patients with the most advanced-stage have the lowest survival and this is also true for women with ovarian cancer. Though there is no traditional stepwise prognosis from the earliest stage to the most advanced stage with ovarian cancer, women diagnosed at an earlier stage do tend to survive much longer than women diagnosed at a later stage of disease[67]. Differences in survival between groups defined by stage at diagnosis may be partly explained by the differences in the histological subtypes of ovarian cancer, or the socioeconomic status, race/ethnicity, residence, treatment or insurance status of the patient[3,68].

Women with unstaged disease are of particular interest, since understanding why these women are unstaged should inform and help improve efforts to diagnose ovarian cancer earlier. In the US, women diagnosed from 2000-2007 with unstaged disease were identified from the SEER database. Unstaged disease was higher among older women, black women, unmarried women and those living in rural Appalachia in the south-eastern part of the US. Over time, however, the overall percentage of patients with unstaged disease has fallen[69], signifying that efforts to adequately stage all patients have been successful.

International differences in survival have also been observed at each stage of disease. Using population-based cancer registry data from Australia, Canada, Denmark, Norway, and the UK, 20,073 women diagnosed with ovarian cancer from 2004-2007 were analysed. Overall 1-year survival was the lowest for the UK (69% vs. 72-75% elsewhere) and women with advanced disease also had lower survival in the UK than in four of the other countries. Survival differences within each stage suggest that distribution of stage at diagnosis does not fully explain the international differences in overall survival, and that other factors such as tumour biology, diagnostic delay, staging procedures or treatment are likely to be relevant[3]. In order to compare stage-specific survival in different countries, staging guidelines must be specific and used accurately in all regions[52].

The symptoms of ovarian cancer vary for each stage, with early-stage cancer having little or no obvious symptoms. Therefore, early-stage ovarian cancer may be diagnosed more by accident than through early presentation with symptoms. Women (n=2,371) diagnosed with one of 15 different cancers, including ovarian cancer, were interviewed as part of a study on the duration of symptoms before diagnosis. Symptoms that are typically associated with ovarian cancer, such as urinary problems, changes in bowel habits and difficulty in eating were all associated with delay in presentation[70]. Health insurance claims data may be used to indicate whether a woman has ovarian cancer, and therefore, diagnose women earlier than relying upon self-presentation[71,72]. Non-recognition of the seriousness of symptoms has been shown to be the main cause of patient-mediated delay in presentation[73,74] and evidence shows that women are less aware of either the symptoms of ovarian cancer symptoms or the lethality[75,76] especially when compared to that with breast cancer[77].

2.4 Survival and race/ethnicity

2.4.1 United States

Research in the US focuses primarily on the disparities in survival between white and black women. While white women may have a higher incidence of ovarian cancer, black women have higher mortality[78]. Additionally, 5-year survival has increased from 1974 to 2001 from 37% to 44% for white women, but has decreased from 41% to 38% for black women[79]. Evidence from previous studies suggests that racial disparities first appeared in the 1980s with the emergence of debulking surgery, thus implying a lack of access to optimal treatment for black women. In a recent study of women diagnosed from 1973-2007 with follow-up until 2008, black women were more likely to die from ovarian cancer than white women, even when controlling for age, stage, marital status, year of diagnosis and surgery. The study, however, did not control for any socioeconomic factors[80]. In a similar study of women in the US diagnosed during 1994-1998, black women were more likely to die from ovarian cancer than white women, even after controlling for age, stage at diagnosis, tumour grade, family history of ovarian cancer and parity, as well as socioeconomic factors such as the percentage of households below the federal poverty line, the percentage of households enrolled in Medicaid, and years of education[81]. The results from this study suggest that access to treatment and differences in quality of treatment may explain much of the variation in survival between white and black women.

Socioeconomic status (SES) and race/ethnicity have been shown to be interconnected, and race/ethnicity has been used as a proxy measure for SES for studies based in the United States. However, studies have shown inconsistent results regarding the impact of SES on racial disparities in cancer survival and mortality. Though ovarian cancer survival tends to be lower for black women than white women (e.g., for women diagnosed between 1988 to 2001, 5-year disease-specific survival was 40.1% for black women compared to 44.1% for white women[59]), this differential is not always evident after

adjustment for factors that are usually correlated with SES, such as education, income and insurance status[82-84]. Additionally, while there is some evidence that racial disparities in survival may persist after controlling for SES, these differences may be minimised if white and black women have equal access to standard care and treatment[85,86].

Among women enrolled in Medicare in the US and diagnosed with advanced-stage epithelial ovarian cancer during 1995-2007, black women were less likely to receive guideline-adherent care than white women (54% vs. 68%) and differences in rates of treatment were associated with differences in survival[87]. However, clinical trial results[85] and data on women treated in the same hospital[88] show that when black and white women diagnosed with advanced-stage epithelial ovarian cancer received similar treatment, there were no survival differences. Furthermore, when the likelihood of receiving treatment is controlled for, differences in survival across racial groups are eliminated[89].

Providing equal access to optimal treatment may not be all that is required to eliminate racial disparities, however, because some studies have shown that some racial disparities in outcome persist even with equal access to treatment[90,91]. Evidence from the Southwest Gynaecologic Oncology Group phase III clinical trials showed that the risk of mortality was 48% higher for black women than for white women. However, this analysis did not control for the likely differences in background mortality between black and white women, and the higher risk of death could be explained by differences in the risk of dying from causes other than ovarian cancer.

Black women may also be more likely to be diagnosed with advanced-stage cancer than white women[92,93], even after adjustment for socioeconomic factors[94], suggesting that stage at diagnosis may partly explain racial differences in overall survival. In a study of women diagnosed with advanced-stage disease, race was not associated with mortality

when controlling for age and tumour characteristics. Women included in the analysis were treated at the same tertiary care centre, thus, the results suggest that differences in survival between white and black women at each stage at diagnosis may be due to differences in treatment[83].

In addition to differential access to treatment[95-97], lower socioeconomic status and differences in histological subtype, racial differences in survival may be explained by differences in comorbidities and other modifiable risk factors between white and black women in the US[98].

American Indian and Alaskan Native (AI/AN) populations in the United States have the lowest 5-year survival of all ethnic groups for several cancers, including ovarian cancer. The primary explanation for this difference is sub-optimal treatment. AI/AN women are less likely to receive surgery and standard care than all other racial and ethnic groups[99]. AI/AN women may be less likely to receive optimal care because they are not accessing available treatment through Medicaid. Women with ovarian cancer did not enrol in Medicaid any sooner than women without ovarian cancer, signalling that there may be other barriers to access to optimal care than insurance status for AI/AN women[100].

Histological subtype is an important predictor of survival, thus, if there are racial differences in the incidence of specific subtypes of ovarian cancer, this could contribute to the differentials seen between ethnic groups in survival from all ovarian cancers combined. In the US, white women are more likely to present with low-risk histological subtypes than black women[101], and in one study, after adjustment for histology, survival differences between black and white women were eliminated[102], suggesting that histology may partly explain racial differences in survival. Thus, the higher survival seen for white women may be partly explained by a higher proportion of white women diagnosed with tumours with favourable outcomes. This study, however, was limited to

germ cell tumours of the ovary, for which survival is generally high for both white and black women, and a more recent study showed contrasting results. For white and black women diagnosed with germ cell tumours from 2003 to 2011, black women had lower survival than white women, even after controlling for stage and treatment[103].

Asian Americans have higher survival from ovarian cancer than white women. Data from the SEER programme for women diagnosed during 1988 to 2009 showed that Asian women were younger at diagnosis (56 vs 64 years), more likely to undergo primary surgery, have earlier stage disease, have non-serous histology and have lower tumour grade. The 5-year disease-specific survival was 59.1% for Asian Americans compared to 47.3% for white women. Better survival for this population may be explained by the higher proportion of women diagnosed with non-aggressive tumour histology[104].

2.4.2 New Zealand

Studies from New Zealand have explored survival differences between racial and ethnic groups. Ovarian cancer incidence is higher for Pacific (17.6 per 100,000) and Māori (13.8 per 100,000) women in New Zealand than non-Māori, non-Pacific women (12.3 per 100,000)[105]. When comparing 5-year age-adjusted relative survival, Māori women had higher survival than Pacific Islander women and non-Māori/non-Pacific women. When the results were adjusted for stage at diagnosis, the survival differences were eliminated[106]. While Māori people are generally more deprived and utilise health services less frequently than non-Māori/non-Pacific women, they tend to present at earlier stages and have more well-differentiated tumours than non-Māori/non-Pacific women. This evidence may suggest that Māori women are more likely to be diagnosed with histological subtypes that are less aggressive[106,107].

2.5 Survival and place of residence

2.5.1 National-level differences

Access to high-quality care is key to ensuring optimal survival, and access may be influenced by where a woman lives. Women in living rural areas of a given country are less likely to access optimal and timely care, and may therefore have a disadvantage compared to women living in more urban areas[108-113]. In a recent study of epithelial ovarian cancer survival in Australia, mortality was higher for women living in rural areas than women living in urban areas. Higher mortality persisted even after adjustment for FIGO stage, treatment, socioeconomic status, histology and age[114].

The influence of residence on stage at diagnosis is varies by population. There were no differences in stage at diagnosis for women diagnosed with ovarian cancer between 2004 and 2011 and living in large cities, small towns or rural areas of Poland. Tumour grade and morphology also did not differ between the three groups. However, this study only included women who were treated at a large urban medical centre, and thus all women had access to the same quality of care[115]. In northern England, distance to hospital was found to predict diagnosis of ovarian cancer at death, suggesting that distance to care may be an important barrier to receiving optimal care[116]. However, earlier studies found that time to hospital or care did not impact stage at diagnosis, receipt of treatment or survival[117,118], and in the US the variation in treatment is primarily explained by age, stage at diagnosis and comorbidities rather than area of residence[119].

2.5.2 International differences

International differences in cancer survival are also of particular interest to gauge how well a country is faring in its cancer control programmes. Data from the EUROCARE-4 database on over 97,000 women with ovarian cancer diagnosed between 1995 and 2002 with follow-up until 2003 were used to measure differences in ovarian cancer survival between European countries. Overall survival increased moderately from 32.4% in 1991-

1993 to 36.3% in 2000-2003, but there were still marked differences between countries. One-year survival for women in 2000-2003 was highest for Sweden (79.3%) and lowest for Slovakia (56.1%). There were also wide differences in five-year survival. Five-year survival was highest in Austria (45.1%) and lowest in Slovakia (25.3%). Differences in the distribution of histological subtypes may account for some of the variation in survival between countries, because Sweden and Austria have a lower percentage of serous tumours, which are thought to be more aggressive than other histological subtypes, than Slovakia. Differences in stage at diagnosis and treatment may also contribute[120,121]. EUROCARE-5 provided updated results to the EUROCARE-4 study, though the patterns for ovarian cancer are similar. The study included women diagnosed with ovarian cancer between 1995 and 2007 with follow-up until 2008. For Europe as a whole, 5-year relative survival was 38.2% in 2005-2007 and there was no significant change in relative survival over time from 1999 to 2007. Regionally, the UK and Ireland had the lowest 5-year relative survival of 31.0% and northern Europe had the highest (41.1%). The greatest improvements in survival were seen in eastern Europe[122].

2.6 Survival and socioeconomic status

Since the 1950s, studies have shown that socioeconomic status (SES) is an important factor in cancer survival for various populations. SES differences in cancer survival have been observed for many different types of cancer. The differences tend to be wider for cancers that are generally diagnosed at a localised stage (breast, uterine, bladder, colon cancers) than for those more often diagnosed at an advanced stage. Conceptually, socioeconomic differences in cancer survival could be explained by factors related either to the tumour (e.g., stage at diagnosis and biological characteristics), or to the patient (host factors, susceptibility to treatment, psychosocial factors) or to the health care system (treatment received, medical expertise and screening)[3,123,124].

Socioeconomic differentials in stage at diagnosis may be an important contributing factor to socioeconomic inequalities in overall cancer survival. Given the potential for higher survival with earlier diagnosis, if affluent patients are more likely to be diagnosed at a localised stage than deprived patients, then they will experience higher survival than deprived patients. When differences in stage at diagnosis do not contribute meaningfully to inequalities in survival, residual confounding by stage may still occur if deprived patients are more likely than affluent patients to be misclassified as having localised disease rather than advanced disease due to inadequate diagnostic investigation.

Stage migration bias occurs when one group of patients "migrates" from one stage to another solely due to differences in diagnostic techniques. With the development of improved diagnostic techniques, some patients who would previously have been incorrectly staged with localised disease will now be correctly staged with advanced disease. This "migration" from localised to more advanced disease will result in higher stage-specific survival for both localised-stage patients and advanced-stage patients. The newly diagnosed advanced-stage patients have higher survival than the original advanced-stage patients because their disease is not as advanced as the original group of advanced-stage patients, thus, the stage-specific survival for the group will increase. Further, the stage-specific survival for localised-stage patients will also increase because the patients incorrectly staged as localised-stage had lower survival than the true localised-stage patients, and moving the misclassified patients to the advanced-stage group will improve the stage-specific survival of the localised-stage group. Because affluent patients tend to have access to better quality care, they may be more likely to be accurately stages with improved techniques than deprived patients. Therefore, the lower stage-specific survival for deprived patients than affluent patients may be a consequence of inadequate staging of deprived patients resulting in inaccurate staging[123,125].

Studies of the impact of SES on ovarian cancer survival have shown that inequalities in survival between SES groups remain after controlling for age and stage, and are evident regardless of which socioeconomic indicator is used, suggesting that there are other underlying causes than stage for differences in survival between socioeconomic groups[123].

Women living with epithelial ovarian cancer in economically deprived areas of New South Wales (Australia) had higher excess mortality than women living in affluent areas. Women living in poorer areas had a 21% higher risk of death from ovarian cancer than affluent women, and poorer survival persisted even after adjustment for FIGO stage and age[114]. Stage, however, may not completely explain socioeconomic differences in survival. For women living in England and diagnosed between 2006 and 2010, SES was not associated with stage at diagnosis[126].

Socioeconomic status is intricately linked with occupation. In a review of 48 studies on environmental and occupational risk factors for ovarian cancer published from 1970 to 1997, there was evidence that women working as hairdressers or beauticians or working in the printing industry may be at an increased risk of disease. However, these studies did not assess whether the increased risk of disease was confounded by income[127]. A study in Sweden found contrasting results, showing that incidence of ovarian cancer from 1961 to 1979 did not differ between blue collar workers, white collar workers and self-employed non-agricultural workers[128]. Occupational data on middle-aged women living in France in 1975 was used to classify women with ovarian cancer into seven occupational classes: professional and managerial, routine non-manual workers, self-employed, farmers, skilled manual workers, unskilled manual workers and agricultural workers. Occupational class was not found to be associated with ovarian cancer mortality[129].

Socioeconomic status may indirectly influence awareness of ovarian cancer symptoms, thus resulting in a delay of diagnosis[70,130,131]. Women living in Wales who were included in

the International Cancer Benchmarking Partnership were interviewed regarding their awareness of ovarian cancer symptoms and how long they would wait to see their doctor if they experienced certain symptoms. Women were asked about key ovarian cancer symptoms, including post-menopausal bleeding, pelvic and abdominal pain, eating difficulties and changes in bladder and/or bowel movements. Lower symptom awareness was more common in women who were less educated, single or older, or who did not have a family history of ovarian cancer. A long delay in presentation (longer than 3 weeks after symptom onset) was more common among women who reported more practical and emotional barriers to seeing their doctor. While presentation delay was not more common in those with lower symptom awareness, women who are less educated may also face more practical barriers to seeing their doctor within three weeks. Increasing awareness of symptoms may lead to a shortening of the delay in presentation to the health care system and, thus, may lead to better survival[130].

Biological characteristics of the tumour, such as histology, may also vary by socioeconomic group or may be influenced by lifestyle factors that are impacted by SES. However, further research is needed to quantify the impact of socioeconomic differentials in tumour biology on cancer survival[123].

Early studies of data from the 1960s and 1970s show that ovarian cancer incidence and mortality were highest for the most affluent women in some countries in Europe and South America, though this gradient was not evident in North America or other European countries[132]. A more recent study from Iran shows similar results, with higher incidence of ovarian cancer in the most affluent provinces than in deprived areas[133]. In more developed countries, recent studies show that while incidence of ovarian cancer is still highest for the most affluent women, mortality from ovarian cancer is lowest[134,135].

The relationship between SES and ovarian cancer survival varies by country and population. A study of 635 Swedish women diagnosed with epithelial ovarian cancer between 1993 and 1995 and followed until December 2007 found no association between SES and survival after adjustment for tumour stage and grade[136]. A similar study in Norway found that differences in survival between highly educated women and those with only 7-9 years of education were eliminated after controlling for age, stage at diagnosis and smoking status[137]. Results from the ELDCARE project showed that for European women who were older (aged 65-84), affluence was not correlated with relative survival from ovarian cancer[138]. In a Canadian study of the effect of macro-level SES indicators, community income was found to have no impact on the risk of dying from ovarian cancer[139]. For women diagnosed with ovarian cancer from 1980-1989 in England, deprivation did not influence relative survival[140].

2.7 Survival and treatment

Differences in access to or the quality of treatment are likely to be a primary reason for differences in ovarian cancer survival. Treatment differentials may explain some of the survival inequalities between SES groups, and in the US may even explain much of the variation in survival for different racial and ethnic groups. Differences in the expertise of the physician or type of treatment centre may contribute to treatment differentials[123]. Factors associated with the quality of treatment a woman receives include hospital characteristics (public vs. private, low- vs. high-case load or non-teaching vs. teaching) and physician characteristics (low- vs. high-case load or subspecialty). Women treated at private, high-case load or teaching hospitals are more likely to receive standard and complete treatment[97,141-149]. Additionally, women who are attended by a gynaecological oncologist or high-case load surgeons tend to receive better care than those attended by general physicians or low case load surgeons[97,141,143,145,147,150-154]. The impact of receiving specialised, guideline-adherent care may not be equal for women diagnosed at different

stages. Women with advanced-stage disease may be less likely to have better survival after receiving specialised treatment than women with early-stage disease[148,155]. Additionally, when the likelihood of receiving treatment is controlled for, there were no differences in survival between women treated by specialists and those treated by non-specialists[156,157].

Differences in treatment guidelines may lead to inaccurate staging. In the UK, systematic lymphadenectomy is not required as part of the standard surgical treatment for women who are thought to have stage I disease, and this may lead to some women with advanced-stage disease being incorrectly diagnosed with early-stage disease. Thus, if stage-specific survival is lower in the UK, this may be explained, at least partially, by inaccurate staging of tumours in women with advanced-stage disease[158].

Disparities in surgical treatment may also impact survival. Optimal cytoreduction, where residual disease is less than 1cm, has been shown to improve survival significantly for women with advanced-stage epithelial ovarian cancer. Differences between countries in the proportion of women whose tumours are optimally debulked may therefore partly explain variation in stage-specific survival. Fewer women in the UK have their tumours optimally surgically debulked than women in the US and other European countries. This lower rate of optimal cytoreduction could explain lower 1-year survival estimates seen in the UK for advanced-stage women compared to women in other European countries[3,158].

Disparities in surgical treatment may also partially explain differences in survival between white and black women in the US. Data from the National Cancer Data Base in the US for 47,160 women diagnosed from 1998 to 2002 showed that black women were less likely than white women to receive surgical treatment than white women. For black women who did receive treatment, they were less likely than white women to receive guideline-adherent care as recommended by the National Comprehensive Cancer Network[159]. Thus,

variation in stage-specific survival between racial groups may be partially explained by disparities and differences in treatment.

Receipt of standard and complete treatment is a key factor in improving survival[160]. Studies in the US have shown that women who are non-white, publicly insured or uninsured, older, have comorbidities or lower income are less likely to receive standard treatment[141,142,159,161-167] and may be more likely to be treated by physicians who do not follow standard treatment guidelines[141,145,146,164,168]. These women are obviously at a disadvantage compared to their white, privately insured, younger or more affluent counterparts. Women who are enrolled in Medicare may also receive sub-optimal treatment[169]. Improvements in survival over time are similar across age groups for ovarian cancer. For women diagnosed with ovarian cancer from 1988 to 1999 in England there was not much improvement in survival over time for both middle-aged (55-69 years) women and older (70-84 years) women, suggesting that while age may impact receipt of treatment, the overall survival benefit for new treatments is equal for all age groups[170].

Access to treatment may be influenced by SES and access to optimal care important in survival. Even with a national healthcare programme and cancer plan, disparities in treatment persist[171,172]. Women diagnosed from 1995-2006 in England deprived patients were less likely to receive full hysterectomies including omentectomies compared to more affluent patients. Therefore, there may be other factors beyond insurance status that influence access to treatment, particularly for women with lower SES[171]. Socioeconomic status was also shown to be a significant factor in ovarian cancer survival in Japan, where there is also a universal health care system, for women diagnosed during 1993 to 2004. Deprivation gaps in 1-year survival were narrower than for 5-year and conditional 5-year survival[173].

In two clinical trials, survival differences between socioeconomic groups in England and Wales were eliminated when women received high-quality treatment and standard care for ovarian cancer. The International Collaborative Ovarian Neoplasm (ICON2 and ICON3) trials included 1,408 women diagnosed with ovarian cancer from 1991-1998. Women diagnosed during 1991-1996 were included in the ICON2 trial and received either cyclophosphamide, doxorubicin and cisplatin combination chemotherapy or single-agent carboplatin. Women diagnosed from 1995-1998 received either of the two treatments from the ICON2 trial, or paclitaxel plus carboplatin. The results from the clinical trial showed that all treatments had a similar impact on survival, therefore further analysis could be done using the entire trial group. After adjusting for age, calendar period of diagnosis, duration of follow-up and stage, deprived women did not have higher excess mortality from ovarian cancer than affluent women. The results from these trials suggest that the socioeconomic differences in ovarian cancer survival in England and Wales may be due to barriers to receiving high-quality treatment and standard care[174].

Insurance status may also be a significant predictor of ovarian cancer survival. Evidence from both the USA and Switzerland suggests that women with private insurance are more likely to receive better treatment and to have higher survival than underinsured or uninsured women[175,176], and when results from the US were stratified by insurance status, racial disparities in survival between white and black women were eliminated[177].

2.8 Other influences on ovarian cancer survival

Social support may positively influence survival, particularly for younger women and those diagnosed with early-stage disease. Deprived patients are less likely to have access to social support, and this differential may also contribute to survival inequalities. Other patient characteristics such as nutrition, health-seeking behaviours and comorbidities may also influence SES differences in survival, but further research is needed to quantify the impact of these factors[123,178,179].

Marital status can be an indicator of social support. Though marital status may be related to SES, there is evidence that married women are more likely to be diagnosed at an earlier stage, to receive standard treatment, and to be less likely to die from their cancer, even after controlling for age, histology, treatment, race/ethnicity, education and median household income[180-182]. The impact of marriage may not be the same worldwide or for widows. In India, single women had higher survival from ovarian cancer than married women[183], which contrasts with previous results from the US and Norway[180-182]. In Norway, while married women had better survival than single and divorced women, they had similar survival outcomes as widows[184].

Comorbidities may influence stage of disease, treatment and survival, and may also be associated with older age, which is also associated with lower survival. Women with lower SES tend to have more comorbidities than women with a higher SES[185]. Women with comorbidities had a significantly higher 30-day mortality than women without any comorbidities[186]. Women in the US diagnosed with ovarian cancer from 1998 to 2000 were less likely to receive aggressive treatment if they had comorbidities, and women with comorbidities had lower survival than women without comorbidities across all stages[187].

Chapter 3: Material and methods

3.1 Methods to achieve the aim and objectives of the PhD

The aim of this thesis is to examine differences in ovarian cancer survival between countries and over time, with the ultimate purpose of explaining variations in survival to stimulate and guide the development of cancer control policies.

In order to compare accurately survival estimates from different regions or populations, the data used for analysis must be population-based and adhere to a strict, centralised protocol. Standardised quality control indicators should be used to evaluate the quality and completeness of the data. Population-based cancer survival is usually estimated as net survival in a relative survival framework, where the cause of death is either unknown or cannot be used because it is unavailable or unreliable. Net survival is the survival of cancer patients up to a specified time after diagnosis of cancer after controlling for other causes of death. To account for differences in competing risks of death – background mortality – between countries or over time within a specific country, life tables that accurately represent the mortality experience of the populations from which the cancer patients come are required to estimate net survival in a relative survival framework. To ensure that any survival differences seen are not due to differences in the age structure of the cancer populations, survival estimates that will be compared between countries or over time should also be age-standardised, to minimise any remaining effect age may have on survival.

3.2 The CONCORD programme

The CONCORD programme for the global surveillance of cancer survival, led by the Cancer Survival Group at the London School of Hygiene & Tropical Medicine, currently includes data from 279 population-based cancer registries in 67 countries, 38 of which have 100% national coverage for adult cancers. Patients diagnosed with a cancer of the breast

(women), cervix, colon, liver, lung, ovary, prostate, rectum or stomach, or leukaemia (adults and children) during the 15-year period from 1995 to 2009 were included in the second cycle of the CONCORD programme, which included data for over 25 million cancer patients worldwide[188].

3.2.1 Population-based cancer registry data

Population-based cancer registries aim to collect systematically a limited set of data on every cancer patient resident within a defined geographic area. Population-based registries can be general, collecting data on all cancer types, or specific, focusing on one type of cancer. Sources of data for population-based cancer registries include medical records from hospitals, oncology clinics, screening programmes, radiology and pathology laboratories, and clinical trials, as well as death registries.

By contrast, hospital-based registries collect information from patients seen at or receiving treatment at a specific hospital. The catchment area for a hospital is often hard to define. Hospitals may receive patients living nearby or far away; thus, it is difficult to define the geographic area from which the patients visiting the hospital come. While the data collected by a hospital-based registry can be used to monitor clinical performance of a particular hospital, these data cannot be used to understand the burden of cancer in a defined population.

The primary responsibility of a population-based cancer registry is to measure and monitor the burden of cancer within a specific region. The data collected by population-based registries may be used to measure the incidence, prevalence or survival for a particular malignancy. Incidence rates and trends are used to plan and monitor strategies for prevention, while prevalence data may be used to establish priorities for cancer care. Survival data are used to measure the effectiveness of health systems in dealing with cancer in order to guide cancer control policies. Since population-based registries collect

data on all cancer patients within a defined population, and the survival estimates obtained using data from population-based cancer registries account for the fact that cancer patients may die from other causes than their cancer, survival patterns and trends derived from population-based cancer registry data can be used for regional and international comparisons.

The data collected by registries include information on the patient (date of birth, sex, address or postcode), the tumour (date of diagnosis, topography, histology, behaviour), the treatment (chemotherapy, radiation, surgery) and the outcome (vital status, date of vital status).

Specific rules for defining the date of diagnosis for a tumour are recommended by the International Agency for Research on Cancer (IARC), the European Network of Cancer Registries (ENCR) and the US National Cancer Institute's SEER programme[189-191]. Generally, the date of diagnosis will be the date of first histological or cytological confirmation of malignancy. If that date is unknown, then the date of first hospital admission where the patient is treated for the malignancy of interest may be used. Finally, the date of first outpatient consultation may be used if the first two dates are not available.

In order to be able to use cancer registry data for survival analysis, the vital status of the patient (alive, dead, emigrated, lost to follow-up) and the date of the last known vital status are required. Cancer registries may follow up their registered patients for vital status either actively or passively.

Passive follow-up is the term used when cancer registries routinely receive notification of deaths from a vital statistics office, or they link cancer patient registrations to vital statistics records at routine intervals. Deaths are usually registered in the jurisdiction where the patient died and then forwarded, if necessary, to the vital statistics office in the region where the patient lived. Deaths among patients who are diagnosed when living

in a different location than the location at the time of their death will be missed by registries with linkages to only local vital statistics records. Linkages with a national death database can capture deaths among cancer patients who have moved within the country between the time of diagnosis and death, but will not capture deaths among patients who have moved to another country[192]. Computerised linkages with other databases, such as social security systems, health insurance, driver's licence records or electoral registers, may also be used to obtain the date on which a patient was last known to have been alive, to have moved within a country, or to have emigrated. Patients are matched to vital statistics records with their national identification number and/or demographic variables, such as name, sex and date of birth. Patients whose cancer registration record does not match with a death record are then considered as alive at the date of the linkage. Thus, patients who are lost to follow-up are presumed to be still alive at the date of the linkage or the end of study, because it is impossible to distinguish them from patients whose registration record cannot be matched to a death record because they are in fact still alive. There is an assumption, therefore, that patients who are lost to follow-up are similar, with respect to their survival, to patients who are alive at the date of linkage or end of the study period. If patients who are lost to follow-up are different from those who are alive, however, the survival estimates may be biased, particularly if the reason for the patient being lost to follow-up is associated with a patient's risk of dying[193].

Due to the reliance on vital statistics, passive follow-up requires high-quality death registration within the region covered by the population-based cancer registry. Problems with the record linkage between the registry data and the vital statistics data may lead to "immortals", or cancer patients who are assumed to be alive but who have actually died.

Active follow-up is the term used when the registry actively and routinely obtains the vital status of each patient by contacting hospitals, clinics or patients' families. Active follow-

up is more expensive and time-consuming than passive follow-up, but may result in fewer patients being lost to follow-up than passive follow-up. With passive follow-up, patients who are lost are assumed to be alive, and thus, identical to patients who are still in the population and actually alive. Therefore, it is impossible to quantify the number of patients lost to follow-up when using passive follow-up. However, given the direct contact active follow-up requires, it can be assumed that this may lead to fewer patients being lost to follow-up. Active follow-up is often used when vital registration systems are not reliable, but it may also be used to complement passive follow-up.

Of the 279 registries included in the CONCORD-2 study, 60% followed-up their registered patients passively, 2% actively and 38% used both active and passive follow-up[188]. Survival estimates derived from data collected by population-based cancer registries using different methods of follow-up are comparable if death ascertainment is complete, because missing deaths can inflate survival estimates[192,193], and all patients whose records were not matched to death records are presumed to be alive at the end of the study[192,193].

Protocol for inclusion

In order for their data to be included in the CONCORD programme, population-based cancer registries must have recorded incident cancers at some point during 1995-2009, and have follow-up data on the vital status of all those patients until at least 31 December 2009. Cancer registries were required to code their data on topography, histology and behaviour according to the ICD-O-3 classification[48]. Women aged 15-99 years diagnosed with a malignant primary neoplasm of the ovary (ICD-O-3 topography code C56.9) were included in the analyses reported here. Tumours of the peritoneum and retroperitoneum (C48.0-C48.2), fallopian tube, uterine ligaments and adnexa (C57.0-C57.4), other specified and unspecified female genital organs (C57.7-C57.9) were also included, because these tumours are treated clinically in the same manner as ovarian neoplasms, and high-grade serous carcinomas (the most common subtype of tumours of the ovary) are often found

at these sites. Tumours of in situ, benign or uncertain behaviour, or metastatic from another primary site, were excluded from survival analyses. Records that were incomplete or contained invalid data were also excluded.

Death-certificate and autopsy-only registrations

Women whose cancer was detected only at autopsy or registered only through a death certificate were not included in the analyses. Survival time is calculated from the date of diagnosis until the date of death, date of last known vital status or last date of the study; therefore, cancers detected at autopsy or registered only through a death certificate would appear to have zero survival time. In reality, the survival time of autopsy only and death-certificate-only (DCO) patients is not zero, but unknown. Therefore, in order to avoid biasing the results, women registered through DCO or autopsy only were excluded from the analysis.

Attempts are made by each registry to trace back death-certificate-initiated (DCI) registrations, to see if the date of diagnosis can be obtained. If the registry is successful in obtaining the date of diagnosis for a DCI registration, then the actual survival time for that patient can be calculated and they are included in survival analyses with patients registered while alive [Figure 3.1]. Patients with DCI records that can be traced back by the registry tend to have lower survival than patients registered while alive[194]. Thus, it is important for registries to attempt to trace back all DCI registrations, or the survival estimates for that population may be overestimated. If the date of diagnosis for a DCI registration remains unknown after efforts to trace back the record, then the date of diagnosis is set as the date of registration, and these DCO patients are not included in analysis.

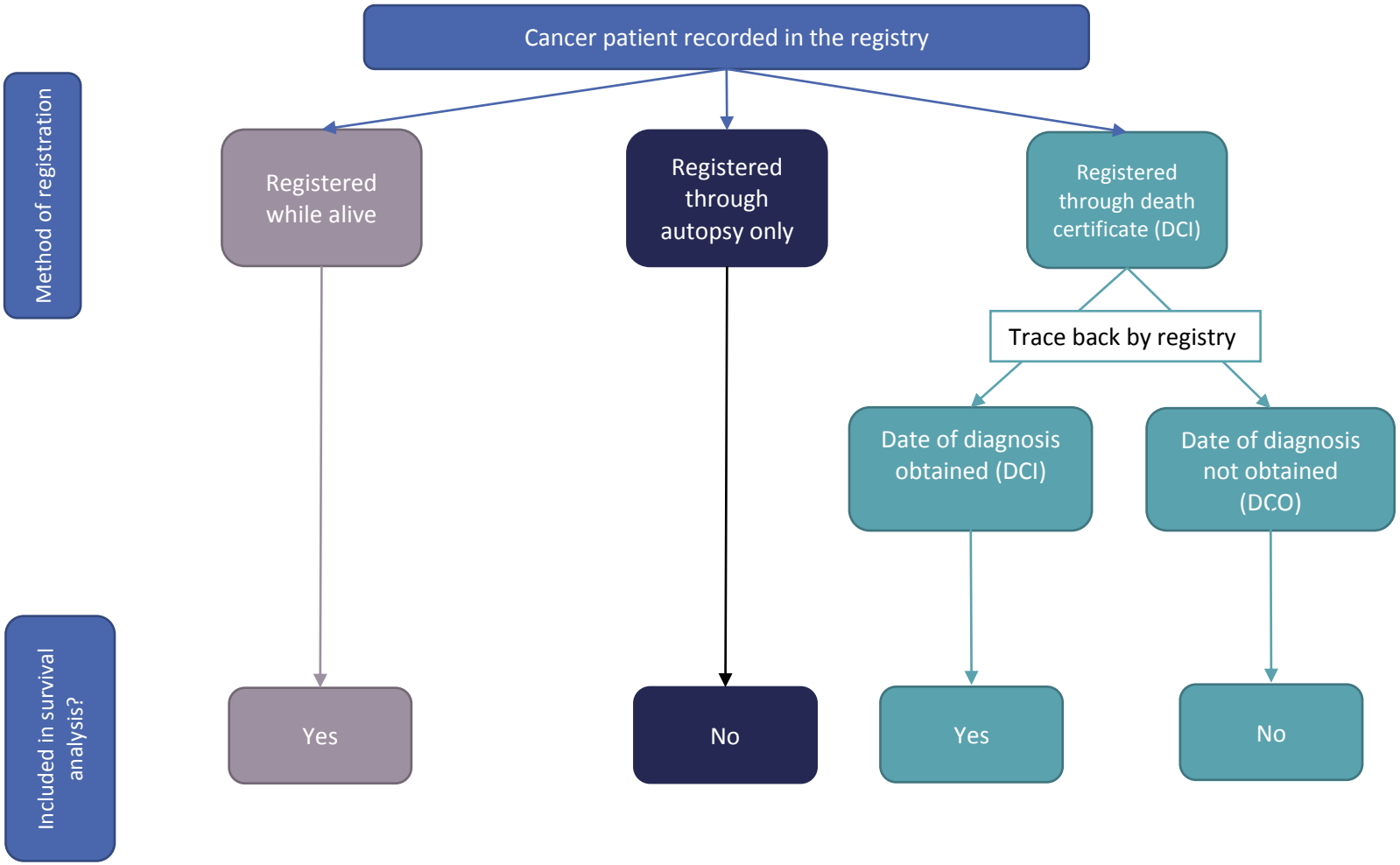


Figure 3.1 Methods of cancer patient registration and criteria for inclusion in survival analyses

Second or higher-order tumours

Second or higher-order tumours are primary tumours diagnosed in the same person. A woman with a second or higher-order primary ovarian tumour may have lower survival than a woman who has been diagnosed with a first primary ovarian cancer, because the prior cancer may inhibit adequate treatment of the ovarian tumour[195,196]. The detection of second or higher-order primary by a cancer registry depends on how long the cancer registry has been active. Longer-established cancer registries are more likely to identify subsequent tumours as second or higher-order cancers because they have had more time to collect data on first primaries than newly-established cancer registries. Newer registries may not have any data on a first primary tumour that was diagnosed prior to the operation of the registry and may thus wrongly assume that the second or higher-order cancer is in fact a first primary tumour. If survival analysis were restricted to patients with first primary tumours, then the proportion of patients excluded for analysis with second or higher order cancers will depend on how long a registry has been active and will result in cancer patient populations from longer-established and newly-established registries that will not be directly comparable. Data from the longer-established cancer registry will comprise a group of patients who are more likely to have true first primary tumours and consequently higher survival than patients with subsequent tumours, while data from the newly-established cancer registry will include not only patients with true first primaries, but also patients with second or higher-order primaries and will, consequently, have lower survival[195,197,198].

Differences in the implementation of screening programmes may also influence the proportion of cancer patients diagnosed with a second or higher-order cancer. Patients who are diagnosed with their first primary cancer through screening tests that detect slow-growing tumours that may not result in death from that cancer, such as the prostate specific antigen (PSA) test for prostate cancer or liquid based cytology for cervical cancer,

and who are then later diagnosed with a second primary cancer, would be excluded from analyses for the second primary if survival analyses were restricted to first primaries. Differences in the intensity of screening programmes between countries and within countries may thus lead to differences in the prevalence of patients with multiple primaries and the proportion of patients excluded from analyses.

Improvements in diagnostic tests and treatment for some malignancies will lead to increases in survival. Thus, the number of cancer survivors remaining at risk of being diagnosed with a second primary cancer will also increase. As the prevalence of patients with multiple primaries increases, the proportion of patients excluded from analyses restricted to first primaries would also increase.

Inclusion of second or higher-order tumours may impact survival estimates only slightly, particularly for cancers with poor prognosis[195,196]. However, these tumours should still be included in analysis, to ensure comparison of the same groups of patients in different countries or regions, which may follow different rules to define multiple primary tumours[196].

Women diagnosed with an ovarian cancer that was their second or higher-order primary tumour were included in the analysis, using the rules to define multiple primary tumours proposed by the International Association of Cancer Registries (IACR) and ENCR[199]. Different coding rules, which are less restrictive, are used by the US National Cancer Institute's SEER programme[200]; however, data collected by registries using the SEER guidelines were recoded according to the IACR rules before extraction of datasets. If a woman was diagnosed with two or more ovarian cancers, only the first tumour was included in the analysis.

Quality control

The CONCORD Analytic Team assessed the quality and completeness of the cancer registry data. The CONCORD programme quality control procedures are performed in three phases, designated as protocol adherence, exclusions and editorial checks.

In “protocol adherence”, each variable is checked to ensure that it is correctly coded according to the CONCORD protocol [appendix A]. The CONCORD protocol specified a range of valid values for each variable. Any value outside the range of valid values is considered non-compliant. A detailed protocol adherence report is then created sent to each registry, and the registry is given the opportunity to correct any mistakes.

In the “exclusions” phase, the logical coherence between variables in each record is assessed, and incomplete or inaccurate records are assigned to one or more error categories. These include errors such as inconsistency in date sequences, and inconsistencies between sex and site, site and morphology, and age and site. Records with incomplete or inaccurate data are excluded during this phase. Duplicate registrations – records with the same site, person identifier and tumour identifier – are excluded, with the most complete record being retained. Synchronous tumours are designated as tumours diagnosed in the same person, at the same site and with the same date of diagnosis: only the most complete record for these tumours is retained. For multiple tumours diagnosed in the same person at the same topographic site but with different dates of diagnosis, the record with the earliest date of diagnosis is retained. A detailed report on all exclusions is sent to each registry. The report includes exclusion tables for each cancer that show the number and proportion of patients excluded in each error category for 1995-1999, 2000-2004 and 2005-2009.

During the “editorial” phase, the plausibility of the distributions of the main quality indicators is assessed. A detailed report is sent to each registry, including editorial tables

that show the distribution of histologically verified tumours, tumours of non-specific morphology, the proportion of patients lost to follow-up, the proportion of patients censored within five years of diagnosis and the proportion of deaths occurring within 30 days of diagnosis, for each cancer. The distributions of the day and the month of the date of birth, the date of diagnosis and the date of last known vital status should be constant across all months and days, since one would expect an even distribution of diagnoses across all months and days of the year, except for days 28-31. Spikes in the distributions indicate where registries may have imputed data when these dates were missing.

Variables

A cleaned dataset containing only registrations of women diagnosed with tumours of the ovary, fallopian tube, peritoneum, uterine ligaments and adnexa was provided by the CONCORD Central Analytic Team [Table 3.1]. Age at diagnosis, date of diagnosis, vital status and date of vital status are required variables for calculating the time survived since diagnosis for each woman. The variables for continent, country, registry and region were used to identify the place of residence for each woman for international comparisons of survival. The basis of diagnosis, ICD-O-3 topography and ICD-O-3 morphology were used in analyses examining the distribution of and survival from different histological subtypes of ovarian cancer. The CONCORD protocol offered several options to submit information on stage: T, N and M (pathological and clinical), condensed TNM, SEER Summary Stage 2000 and FIGO were the most relevant stage classification systems for ovarian cancer. A complex algorithm was developed to optimise the availability of the stage information (i.e., to reduce the proportion of missing information). Several grouped variables were created in order to obtain a broader (localised vs. advanced) and, when possible, a more detailed stage distribution (TNM stage, SEER Summary Stage 2000). Survival by stage at diagnosis was examined using the grouped (localised vs. advanced) stage variable.

Table 3.1 Main variables for analysis

Variable	Description
Continent	Continent
Country	Country of residence of the patient
Registry	Cancer registry in which the patient is registered
Person code	Unique patient identifier
Tumour code	Assigned to each tumour to identify first, second or higher-order tumours
Sex	Sex of cancer patient
Region	Smaller geographic regions (province, state, county, etc.) within each registry coverage area
Race/ethnicity	Race/ethnicity of patient
Date of diagnosis	Date of cancer diagnosis
Age	Age at diagnosis
Vital status	Alive, dead, lost to follow-up, not known
Date of vital status	Date of last known vital status
Basis of diagnosis	Indicates method of the cancer diagnosis (clinical, microscopically verified, death certificate only, autopsy only)
ICD-O-3 topography	Four-character ICD-O-3 code indicating anatomic site of tumour
ICD-O-3 morphology	Four-digit ICD-O-3 code indicating morphology of tumour
Behaviour	Indicates whether the tumour is benign, in situ, invasive or uncertain whether benign or malignant
SEER Summary stage 2000	Stage of disease (in situ, localised, regional, distant, unknown) based on the North American Association of Central Cancer Registries' guidelines
Pathological T	First component of the TNM classification of stage indicating tumour size based on pathological examination
Pathological N	Second component of the TNM classification of stage indicating extent of regional lymph node involvement based on pathological examination
Pathological M	Third component of the TNM classification of stage indicating presence or absence of distant metastases based on pathological examination
Clinical T	First component of the TNM classification of stage indicating tumour size based on clinical examination
Clinical N	Second component of the TNM classification of stage indicating extent of regional lymph node involvement based on clinical examination
Clinical M	Third component of the TNM classification of stage indicating presence or absence of distant metastases based on clinical examination
Condensed T	Indicates localised or advanced disease based on European Network of Cancer Registries' guidelines
Condensed N	Indicator of regional lymph node involvement
Condensed M	Indicator of metastasis

Variable	Description
FIGO stage	Specialised classification of tumour stage for gynaecological cancers
Tumour size	Maximum tumour diameter in millimetres
Number of lymph nodes examined	Exact number of lymph nodes examined
Number of lymph nodes involved	Exact number of lymph nodes containing tumour cells

Ethical approval

Ethical approval for the CONCORD programme was obtained from the London School of Hygiene and Tropical Medicine's Observational/Interventions Research Ethics Committee (LSHTM Ethics Reference No. 6396) [appendix B]. Ethical approval was also obtained from the Ethics and Confidentiality Committee of the UK's National Information Governance Board (now the Health Research Authority; ECC 3-04(i)/2011) and the National Health Service's Research Ethics Service (Southeast; 11/LO/0331). Separate statutory or ethical approval was obtained in more than 40 other jurisdictions before data were released.

3.3 Incidence, prevalence and mortality

Cancer incidence, prevalence and mortality are important population-based measures of the cancer burden. Incidence can be used to understand better the causes of cancer and to plan prevention programmes. The prevalence of a cancer is useful for planning the allocation of cancer services, and mortality may be used to assess the effectiveness of cancer care.

3.3.1 Incidence

The cancer incidence rate refers to the number of new cancer patients per unit of population over a defined period of time, typically, per year. It is defined as the number of new cancers per 100,000 (or 10,000 or 1,000,000) person-years at risk over a specified time period – usually one year. The incidence rate is an important measure to identify populations at higher risk for a particular cancer, for cancer prevention and control. The number of new cases in a defined population, the numerator of the incidence rate, can be obtained from cancer registry data. The denominator is the person-years at risk, and is usually defined as the total person-time at risk during a given time period[201]. The mid-year population can be used to approximate the number of person-years lived by persons in the defined population during the year of interest.

$$Incidence\ rate\ = \frac{No.of\ new\ cancer\ cases\ in\ 1\ year}{No.of\ persons\ comprising\ mid\text{-}year\ population}\ x\ 10^5$$

$$= rate\ per\ 10^5\ person\text{-}years$$

The incidence rate of a particular cancer will influence the mortality rate from that malignancy, but is not influenced by events after diagnosis, such as treatment or survival. Incidence is, however, influenced by events that occur before diagnosis, such as screening, as well as changed in the definition and coding of malignancies. International differences in incidence rates may be partly due to varying levels of ascertainment of cases as well as actual differences in the incidence. Trends in incidence over time may be useful, but these can be affected by changes in the definition of the cancer, improved diagnostic techniques, screening programmes and the completeness of registration[201].

3.3.2 Prevalence

Total, or complete, point prevalence is defined as the current number of people alive with a particular disease in a given population at a specified point in time. Partial prevalence limit total prevalence to patients diagnosed during a certain time period. Prevalence can be used by health care providers to allocate resources for cancer treatment and care within a population.

Unlike incidence, prevalence is affected by survival, because the pattern of survival determines the number of people alive with a particular cancer at a given time, which is the numerator of the prevalence.

$$Prevalence\ = \frac{No.of\ cancer\ survivors\ in\ defined\ population}{No.of\ people\ in\ defined\ population}\ x\ 10^5$$

$$= prevalence\ per\ 10^5\ persons$$

3.3.3 Mortality

A cancer mortality rate is the number of deaths attributed to that specific cancer per unit of population in a defined period of time, typically a year, usually expressed per 100,000

person-years. It is defined as the number of deaths, the numerator, available from national statistics agencies, divided by the denominator, the person-years at risk, approximated by the mid-year general population estimate[201].

$$Mortality\ rate = \frac{No.of\ deaths\ in\ population\ in\ 1\ year}{No.of\ persons\ comprising\ mid\text{-}year\ population}\ x\ 10^5$$

$$= rate\ per 10^5\ person\text{-}years$$

Mortality is affected by both incidence and survival. In order to die from a certain cancer, a patient must first be diagnosed with and then fail to survive from that cancer, and the patient's death must be accurately recorded as due to that cancer. In order for the death to be attributable to that cancer, the death must be medically certified and the underlying cause of death on the death certificate must be recorded as that cancer. The mortality rate can be affected by changes in coding of death and differing practices in selecting the underlying cause of death. The mortality rate for a particular time period is thus a combination of the incidence and survival from earlier years for cancers with good prognosis and the incidence and survival for cancers with poorer prognosis for the recent time period[201]. The mortality rate, therefore, is a delayed evaluation of progress, or lack thereof, in the effectiveness of cancer care. Mortality may not be the best evaluative measure of changes in diagnosis or treatment, because the mortality rate is derived from deaths of patients diagnosed in several different years, particularly for cancers with good prognosis, who may not have had the same treatment.

3.4 Net survival

Population-based cancer survival (net survival) can be used as a measure of the overall effectiveness of cancer care and management in a given health system for earlier periods of diagnosis. It can evaluate the utilisation of and access to cancer care and stimulate and guide the development of cancer control policies. Survival can be affected by changes in diagnostic techniques, and the intensity of screening or early diagnostic activity, as well

as the efficacy of treatment. Screening programmes may result in an increase in survival that is not necessarily due to improvements in treatment or care. This increase may occur if smaller, slower-growing tumours are detected by a new screening programme, resulting in a group of longer-surviving patients who previously would have not been diagnosed. An increase in survival may also occur if tumours are detected during the pre-clinical asymptomatic phase, but there is no delay in death for the cancer patients – the increase in survival in this case is solely due to the earlier detection of the tumour[201].

Monitoring survival over time is important for helping guide health policy and cancer control plans. Improvements in survival can reflect progress in diagnosing patients earlier or the efficacy of treatment. Survival data can be more accurate than mortality data for evaluating progress in diagnosis and cancer care, because survival data from population-based registries undergo several quality control checks while mortality data comes from a single source – the death certificate. Death certificates are very rarely validated with clinical or pathological information.

Unlike incidence, prevalence and mortality, survival is not a simple ratio calculation. The outcome of survival analysis is the time to a particular event; therefore, some element of time must be included in the calculation of survival. For cancer survival analysis, survival time is usually measured from the date of diagnosis until the date of death, date of last known vital status or the end of the study. Full dates, including the day, month and year of the patient's birth, diagnosis and death should be used in cancer survival analysis to obtain the most precise estimates[202]. Using partial dates with just the month and year, can create bias in the estimation of survival. If a patient is diagnosed and dies in the same month, the survival time for that patient will be zero while the true survival time can be up to 31 days. Using partial dates may also make it impossible to distinguish DCO registrations from patients where the survival is known but appears to be zero because

the patient was diagnosed and died within the same month. Given that the first few months after diagnosis is when the probability of death changes the most rapidly and the widest differences in survival are most often seen during this time period, using partial dates makes it impossible to determine the precise differences in survival between countries.

The outcome of survival analysis – the distribution of the time to an event – can be expressed as the survival function *S(t)* or the hazard function *h(t)*. The survival function gives the probability that a person survives longer than some specified time *t* since diagnosis. The hazard function is defined as the rate at which the event of interest, usually death from any cause, occurs at a specified time since diagnosis. The hazard function is also known as the force of mortality. The hazard will usually change over time, often substantially. While the population at risk was the general population for incidence and mortality, the population at risk for survival analyses is the cancer patient population.

The objective of population-based cancer survival analyses is to obtain an estimate for net survival. Net survival is formally defined as the survival of cancer patients in the hypothetical world where the only cause of death is cancer. It more readily interpretable to describe it as estimating the survival of cancer patients up to a specified time after diagnosis after controlling for competing risks of death.

Net survival can be estimated in two general contexts: cause-specific, where the exact cause of death is known, or relative survival where the exact cause of death is unknown, unreliable or inaccessible. Population-based cancer survival is usually estimated in a relative survival framework because the cause of death available from cancer registries may not be reliable, particularly when comparing survival from different countries. Estimating cancer survival within a relative survival framework also eliminates any issues

with differences or inaccuracies in cause of death coding, because the cause of death is not required for analysis.

Cancer patients may die from causes other than their cancer, and because of the lack of cause of death data in the relative survival setting, it is impossible to identify which cancer patients have died from their cancer and which have died from other causes. Therefore, the relative survival setting requires that the background mortality, or mortality in the general population, is accounted for to ensure that excess deaths in the cancer patient population are due to cancer and not other causes. Deaths from causes other than cancer are assumed to be conditionally independent of deaths due to cancer and deaths due to cancer are assumed to be small. Life tables are used to account for the background mortality in a population when estimating survival, assuming that the mortality from other causes within the cancer patient population is similar to the mortality of the general population. Life tables are required when comparing population-based cancer survival in populations with differing levels of background mortality, because the net survival estimates then provide a true representation of differences in cancer survival after adjusting for differences in background mortality. Life tables should be specific to a given sex, country or region of residence, race and level of deprivation, to control for differing levels of background mortality between these groups.

Pohar Perme recently proposed a non-parametric method to estimate net survival that takes into account competing risks of death and the fact that competing risks are higher in the oldest age groups[203]. This method is considered as an unbiased estimator of net survival.

3.5 Cohort, period and complete approaches

In survival analysis, patients are generally followed for a specified amount of time to observe whether the event of interest, usually death, occurs. If all patients can be

followed for a specified time (e.g., 5 years), then survival can be estimated using the cohort approach. For cancer survival analysis, a cohort of patients will usually be a group of patients diagnosed within the same year or calendar period. All patients who are included in the analysis have had the potential to be followed-up for the specified amount of time. The cohort approach to survival estimation is the gold standard, because all patients are diagnosed within the same period, are likely to have receive the similar treatment, and are observed and followed through time for at least the specified amount of time [Figure 3.2]. Five-year survival can be estimated using the cohort approach for patients diagnosed between 1995 and 2004, because at least five years of follow-up are available for patients diagnosed in each of those years. However, 5-year survival cannot be estimated using the cohort approach for patients diagnosed between 2005 and 2009 because five years of follow-up are not available for all patients.

The period approach can be used to estimate five-year survival for patients diagnosed between 2005 and 2009 with follow-up until 31 December 2009. The period approach enables prediction of 5-year survival for patients diagnosed in 2005-2009 by using the survival experience of patients who were diagnosed in earlier years and who were alive at some point during 2005-2009. It is assumed when using the period approach that the survival probabilities for the patients diagnosed in each year of the analysis will remain identical to the actual survival experience of the patients diagnosed in the year for which survival is being estimated. Thus, in Figure 3.1 it is assumed that the survival probabilities seen in 2009 will remain the same as the probabilities that will be seen in later years. This assumption is likely true for estimates of short-term survival, but may be problematic when estimating long-term survival. In the period approach, different parts of the survival function are contributed by patients diagnosed during different years, and period survival can then be interpreted as the predicted short-term survival for a specified number of years after diagnosis for patients diagnosed in a recent year or period for which complete

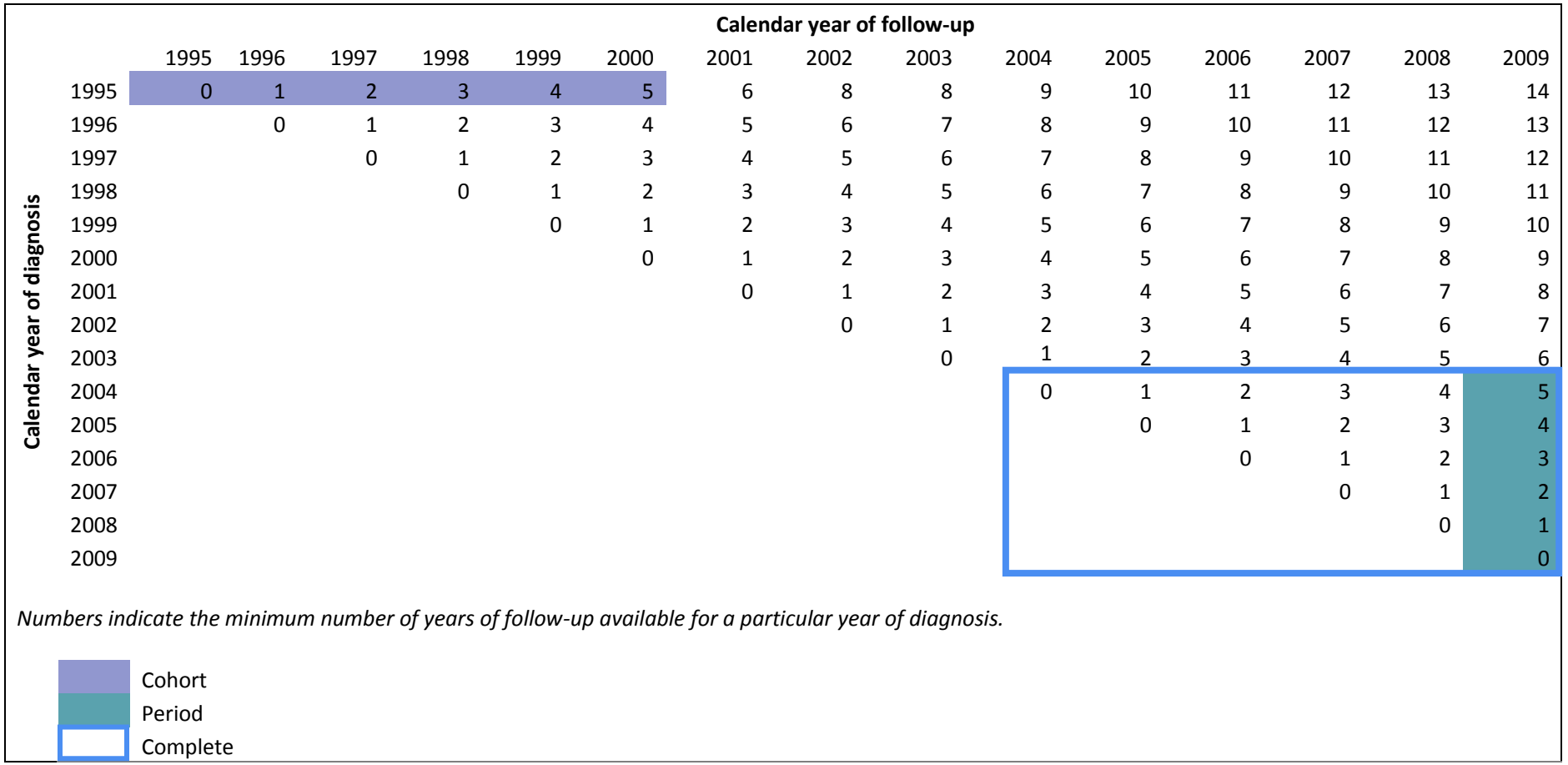


Figure 3.2 Cohort, period and complete approaches to survival estimation

follow-up of all patients is not yet available[204]. The period approach allows for survival to be estimated for more recent years of diagnosis, rather than having to wait for the full follow-up time to pass (for example, five years) as with the cohort approach.

The complete approach can also be used. The complete approach uses all relevant data available, i.e., for patients diagnosed more recently than those available for the cohort approach, but without requiring full follow-up data for all patients diagnosed during the years of interest. If there is at least one diagnosis year with full follow-up time available, then the complete approach can be used. For example, for estimating survival for five years after diagnosis for patients diagnosed between 2004 and 2009, a complete approach can be used because there is five years of follow-up available for the patients who were diagnosed during 2004. Patients who do not have full five-years of follow up are then censored at the end of the study (31 December 2009) if they have not died or been lost to follow-up[205].

3.6 Age-standardisation

Age-standardisation is important for appropriate comparison of cancer survival estimates for all ages combined. The excess risk of death from cancer increases with age; therefore, differences in the age distribution of cancer patients can confound comparisons of survival for all ages combined between countries or within the same country over time. While using life tables and net survival to control for the fact that competing risks increase with age, a residual effect of age on survival estimates for all ages combined may still occur. Age-standardisation removes most or all of the remaining effect of age on survival estimates. In order to produce an age-standardised survival estimate, age-specific survival estimates for each age group must first be calculated. The age-specific survival estimates are multiplied by the corresponding age-specific weights, which represent the proportion of cancer patients in each specific age group. The recommended set of age-specific weights for cancer survival is the International Cancer Survival Standard (ICSS)[206]. ICSS

weights for cancers for which incidence increased with age, were used in this thesis when age standardisation was possible. Using the same age-specific weights for all groups being compared will ensure that the differences in the age distributions of the cancer patients, by country and over time, will not affect the comparison of the survival estimates. A summation of the weighted age-specific survival estimates provides the age-standardised survival estimate for all age groups combined, which is a weighted average of the age-specific estimates.

3.7 Statistical analyses

All statistical analyses were conducted using Stata version 14[207]. Net survival was estimated up to five years after diagnosis using the Pohar Perme estimator implemented in Stata using *stns*[208]. Survival was analysed by calendar period of diagnosis (1995-1999, 2000-2004 and 2005-2009), histological group, stage at diagnosis and race/ethnicity. Cumulative probabilities of survival are reported as percentages, truncated to 0-100%. Standard errors were derived using the Greenwood[209] method and 95% confidence intervals are reported. Life tables for single year of age (0-99 years), calendar year, sex, country and, where possible, race were used to account for the background mortality of the populations. Age-standardisation was attempted using ICSS weights. Age at diagnosis was categorised into five age groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. If an age-specific estimate could not be produced, or fewer than 10 women were available for analysis in an age group, data for adjacent age groups were pooled and the re-estimated survival used for both of the original age groups. If two or more age-specific estimates could not be produced, or fewer than 10 women were available for analysis in two or more age groups, then only the unstandardised estimate is reported. Survival was estimated using the cohort approach for women diagnosed during 1995-1999 and 2000-2004 and the period approach for women diagnosed during 2005-2009 for the analysis by histological group and race/ethnicity. The periods of diagnosis were slightly different for

the analysis by stage at diagnosis: 2001-2003 and 2004-2009. The cohort approach was used to estimate survival for the first calendar period, while the complete approach was used to estimate survival for the later calendar period. More detailed descriptions of the methods used for each analysis are provided in each chapter.

Chapter 4: Histological groups of ovarian cancer: worldwide distribution

4.1 Introduction

International comparisons of cancer incidence, mortality and survival are crucial to inform and plan health policy and cancer control programmes. Low survival has been a stimulus for cancer plans and strategies in many countries, such as the United Kingdom and Denmark[3]. Comparisons of lung cancer survival have routinely been divided into small-cell and non-small cell subtypes due to their different prognosis, clinical behaviour and treatment.

Ovarian cancer is arguably an even more heterogeneous group of diseases than lung cancer, and histology should thus be considered in the interpretation of international variation in ovarian cancer survival, particularly the distribution of type I and type II epithelial tumours. This is because type I epithelial tumours are generally associated with higher survival than type II tumours, so the proportion of type I epithelial tumours may influence survival estimates for all ovarian cancers combined. Differences in the distribution of histology may thus contribute to international variations in survival from all ovarian cancers combined, in addition to international differences in stage at diagnosis and treatment.

The CONCORD-2 study on the global surveillance of cancer survival has shown the extent to which ovarian cancer survival varies worldwide when comparing estimates for ovarian cancer with all histological types combined[188]. It remains unclear how much of the variation in ovarian cancer survival could be attributed to international variation in the distribution of histological groups in each country. The international distribution of ovarian cancer histology was examined using population-based data from the CONCORD-2 study. The aim was to describe the worldwide variation of ovarian cancer histological

groups, and then to examine whether this variation may influence international comparisons of population-based cancer survival.

4.2 Material and methods

The CONCORD-2 study[188] collected data for 779,302 adult women (aged 15-99 years) in 61 countries who were diagnosed during the 15-year period 1995-2009 with a cancer of the ovary. Ovarian cancer was defined broadly to include tumours of the fallopian tube, uterine ligaments and adnexa, other specified and unspecified female genital organs, peritoneum or retroperitoneum (International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes C56.9, C57.0-C57.4, C57.7-C57.9, C48.0-C48.2)[48]. The CONCORD-2 protocol, the ethical approvals and the quality control procedures have been described elsewhere[188] and in Chapter 3[a].

Six "histological groups" were defined based on ICD-O-3 morphology codes, the literature[210] and clinical advice [Table 4.1]. Based on the categorisation proposed by Kurman and Shih in 2004[16], recently updated in 2016[10], type I epithelial tumours included clear cell, endometrioid, mucinous, squamous and transitional cell carcinomas, and type II epithelial tumours included serous carcinoma, mixed epithelial and stromal carcinoma and undifferentiated and other epithelial carcinoma. Throughout this chapter, "histological group" refers to the broader categories of tumours, each comprising one or more of the "histological subtypes".

Individual patient data were available for 793,098 women diagnosed with ovarian cancer from 1995 to 2009 [Figure 4.1]. This number is slightly larger than the number of women included in the analysis for the main CONCORD-2 article, because of a data submission

[a] The material in Chapters 4-7 is based on examination of the distribution of and survival from ovarian cancer histology, stage at diagnosis and race/ethnicity. A few paragraphs of material and methods are repeated in each of these chapters for ease of reference and to ensure consistency of the descriptions. A detailed definition and description of the data and methods can be found in Chapter 3.

Table 4.1 Ovarian cancer histological groups and subtypes

Histological group[a]	Histological subtype	ICD-O-3 morphology code
Type I epithelial	Clear cell carcinoma	8005, 8310, 8443, 9110
	Endometrioid carcinoma[b]	8380, 8382-8383, 8560, 8570
	Mucinous carcinoma	8470-8471, 8480-8482, 8490
	Squamous carcinoma	8051-8084
	Transitional cell or Brenner carcinoma	8120-8131, 9000
Type II epithelial	Serous carcinoma[c]	8050, 8441, 8450, 8460-8461
	Mixed epithelial-stromal carcinoma	8313, 8323, 8381, 8930-8991, 9010-9030
	Undifferentiated or other epithelial	8010-8015, 8020-8046, 8090-8110, 8140-8231, 8246-8300, 8311-8312, 8314-8322, 8324-8325, 8336-8337, 8341-8375, 8384-8440, 8452-8454, 8500-8551, 8561-8562, 8571-8589
Germ cell	Germ cell	8240-8245, 8330-8335, 8340, 9060-9105, 9380-9523
Sex cord-stromal	Sex cord-stromal	8590-8671, 8810
Other specific non-epithelial	Other specific non-epithelial	8680-8806, 8811-8921, 9040-9055, 9120-9373, 9530-9589
Non-specific	Non-specific	8000-8004

[a] Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of histological groups and topographical sub-sites (see text). [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial.

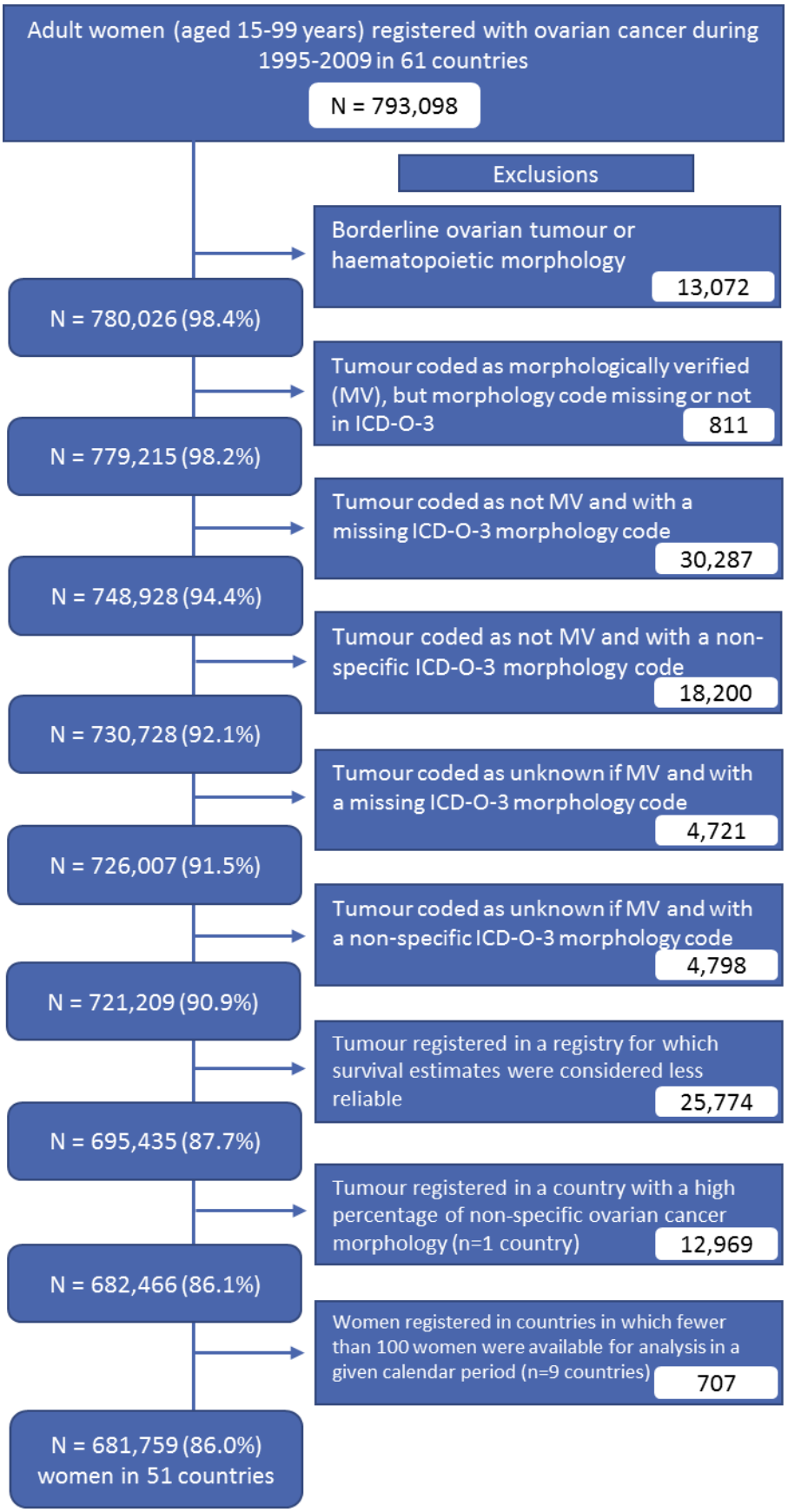


Figure 4.1 Data exclusion flow chart for the worldwide distribution of ovarian cancer histology, 1995-2009

error that was corrected after the analysis for the main article had been completed. Data submitted by Ontario for women diagnosed from 1995 to 2007 did not initially include tumours of the ovary, but included only tumours of the fallopian tube and peritoneum. The registry resubmitted data including all sub-sites for the entire 15-year period, resulting in an increase of 13,796 women.

Recent evidence suggests that high-grade serous carcinoma, the most common type of ovarian cancer, originates in the fallopian tube. Therefore, cancers of the fallopian tube and other specified and unspecified female genital organs were included in a broader definition of ovarian cancer. Similarly, primary peritoneal and retroperitoneal carcinomas are managed in the same way as advanced-stage epithelial ovarian cancer, and they are also included[12]. The term "ovarian" in this chapter refers to tumours at all sub-sites, unless the context makes clear that it refers to tumours of the anatomic ovary.

Ovarian cystadenomas were reclassified from invasive (behaviour code 3) in ICD-O-2 to borderline (uncertain whether benign or malignant with a behaviour code 0 or 1) in ICD-O-3, which was introduced in 2000. Due to this change in coding, some women diagnosed with borderline tumours were included in the data submissions to the CONCORD-2 study.

Women diagnosed with borderline tumours or haematological malignancies were excluded (n=13,072). Of the remaining 780,026 women, 90.6% (706,808) had tumours that were coded by the registry as having been morphologically verified, while 7.5% (58,682) were not coded as morphologically verified and 1.9% (14,536) were coded as unknown whether morphologically verified or not. For tumours coded as morphologically verified, 705,997 (99.9%) had a valid ICD-O-3 morphology code, but no morphology code or only an invalid code (codes not included in either ICD-O-2 or ICD-O-3) was available for 811 (0.1%), and these tumours were excluded. Tumours coded as not morphologically verified were primarily those with morphology coded as missing (CONCORD-2 assigned

code of 9999; 30,287, 51.6% of non-morphologically verified tumours); these tumours were excluded. A further 18,200 non-morphologically verified tumours with non-specific morphology were excluded.

The remaining 10,195 tumours that had been coded as not having been morphologically verified were included, because a specific ICD-O-3 morphology code was nevertheless available, implying that morphological verification had in fact been performed. Tumours for which it was unknown whether morphological verification had been performed or not were evenly distributed across specific (n=5,017), non-specific (n=4,798) and missing morphology (n=4,721). Of these tumours, those with non-specific morphology and missing morphology were excluded. The remaining 5,017 tumours coded as unknown whether morphologically verified were included, because a specific morphology was also recorded, again implying that morphological verification had been completed.

In total, 721,209 women (98.3% with specific ICD-O-3 morphology codes and a further 1.7% with non-specific morphology codes 8000-8004) were available for analysis after the first round of exclusions.

The distribution of ovarian cancer histology was examined for all countries in each calendar period (1995-1999, 2000-2004 and 2005-2009) for which data were available for at least 100 women. Records from registries from which the survival estimates in the main CONCORD-2[188] analysis were considered less reliable were also excluded, because the results from this analysis will be used to inform the results of survival analyses of ovarian cancer. Survival estimates were flagged as less reliable if a higher than usual proportion of patients was excluded from analyses because the cancer was registered only through a death certificate, or the date of last vital status was not known. The focus of this analysis was the distribution of specific histological groups, so women diagnosed in Sweden had

to be excluded, because 97.5% of tumours were coded by the registry as undifferentiated or other epithelial carcinoma, or as non-specific morphology (ICD-O-3 codes 8000-8004).

The distribution of the three main topographical sites (fallopian tube, peritoneum and ovary) was also examined for all continents for each calendar period. The distribution of topography was also examined within histological groups for each continent. Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9).

After all exclusions, 681,759 women (86.0% of the 793,098 women for whom data were available for analysis) were included in the analysis of the histological and topographical distributions (192,080 in 1995-1999; 240,397 in 2000-2004; 249,282 in 2005-2009) [Table 4.2].

4.3 Results

4.3.1 Topographical sub-site

Of the 681,759 women whose data were available for analysis, 615,681 (90.3%) were diagnosed with a tumour of the ovary, 40,905 (6.0%) were diagnosed with peritoneal cancer and 25,713 (3.7%) with fallopian tube cancer [Table 4.2]. From 1995 to 2009, the proportion of tumours assigned to the ovary decreased from 91.9% to 88.9% for all countries combined, while the proportion of peritoneal and fallopian tube tumours increased from 4.6% to 7.0% and 3.5% to 4.1%, respectively.

The distribution of sub-sites varied somewhat by continent, though tumours of the ovary was by far the most common sub-site in all continents [Table 4.2]. During 1995-1999, the

Table 4.2 Distribution (%) of topography (sub-site) by continent and calendar period of diagnosis, 1995-2009, 51 countries

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
ALL COUNTRIES[d]							
Total	**25,173**	**3.7**	**40,905**	**6.0**	**615,681**	**90.3**	**681,759**
1995-99	6,635	3.5	8,926	4.6	176,519	91.9	192,080
2000-04	8,280	3.4	14,448	6.0	217,669	90.5	240,397
2005-09	10,258	4.1	17,531	7.0	221,493	88.9	249,282
AMERICA (CENTRAL AND SOUTH)							
Total	**143**	**2.0**	**554**	**7.8**	**6,393**	**90.2**	**7,090**
1995-99	21	1.9	102	9.2	990	88.9	1,113
2000-04	65	2.0	300	9.2	2,913	88.9	3,278
2005-09	57	2.1	152	5.6	2,490	92.3	2,699
AMERICA (NORTH)							
Total	**11,500**	**3.9**	**23,504**	**7.9**	**261,127**	**88.2**	**296,131**
1995-99	2,950	3.4	5,117	5.9	79,392	90.8	87,459
2000-04	3,638	3.6	8,277	8.1	89,859	88.3	101,774
2005-09	4,912	4.6	10,110	9.5	91,876	85.9	106,898
ASIA							
Total	**1,785**	**3.1**	**1,959**	**3.5**	**53,021**	**93.4**	**56,765**
1995-99	381	2.9	397	3.1	12,142	94.0	12,920
2000-04	566	2.9	734	3.8	18,012	93.3	19,312
2005-09	838	3.4	828	3.4	22,867	93.2	24,533
EUROPE							
Total	**10,934**	**3.6**	**13,347**	**4.4**	**277,432**	**92.0**	**301,713**
1995-99	3,062	3.6	2,899	3.4	78,095	92.9	84,056
2000-04	3,723	3.4	4,559	4.2	100,609	92.4	108,891
2005-09	4,149	3.8	5,889	5.4	98,728	90.8	108,766
OCEANIA							
Total	**811**	**4.0**	**1,541**	**7.7**	**17,708**	**88.3**	**20,060**
1995-99	221	3.4	411	6.3	5,900	90.3	6,532
2000-04	288	4.0	578	8.1	6,276	87.9	7,142
2005-09	302	4.7	552	8.6	5,532	86.6	6,386

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

proportion of primary peritoneal cancer was highest in Central and South America (9.2%) and lowest in Asia (3.1%). Correspondingly, the lowest proportion of ovarian cancer was in Central and South America (88.9%) while the highest proportion was in Asia (94.0%). A similar distribution was seen for women diagnosed between 2000 and 2004, but for women diagnosed between 2005 and 2009, the highest proportion of peritoneal cancer (9.5%) and the lowest proportion of ovarian cancer (85.9%) were seen in North America.

Tumours assigned to the ovary were the most common sub-site within each histological group except for other specific non-epithelial tumours [Figure 4.2]. The majority (84.8%) of other specific non-epithelial tumours were coded as primary peritoneal cancers, while only 11.5% of ovarian tumours and 3.7% of fallopian tube cancers were other specific non-epithelial tumours [Table 4.3]. The distribution of topography by histological group was generally constant over time and similar for each continent.

Given the similarities in biological origin and development of tumours of the fallopian tube, peritoneum and ovary, as well as their treatment and survival[10,12,17], the remainder of the analysis focuses on the distribution of histological groups for all sub-sites combined.

4.3.2 Ovarian cancer histology

Type II epithelial tumours were the most common histological group worldwide (476,461; 69.9%), followed by type I epithelial (152,874; 22.4%) [Table 4.4]. Germ cell, sex cord-stromal, other specific non-epithelial and non-specific tumours were all rare: they only comprised 8% of tumours worldwide; the distribution of these groups remained relatively stable over the 15-year period 1995 to 2009 [Figure 4.3]. The proportion of type II epithelial tumours increased slightly from 68.6% to 71.1% from 1995 to 2009, and there was a corresponding decrease in type I epithelial tumours (from 23.8% to 21.2%: Table 4.4).

Continued on page 102

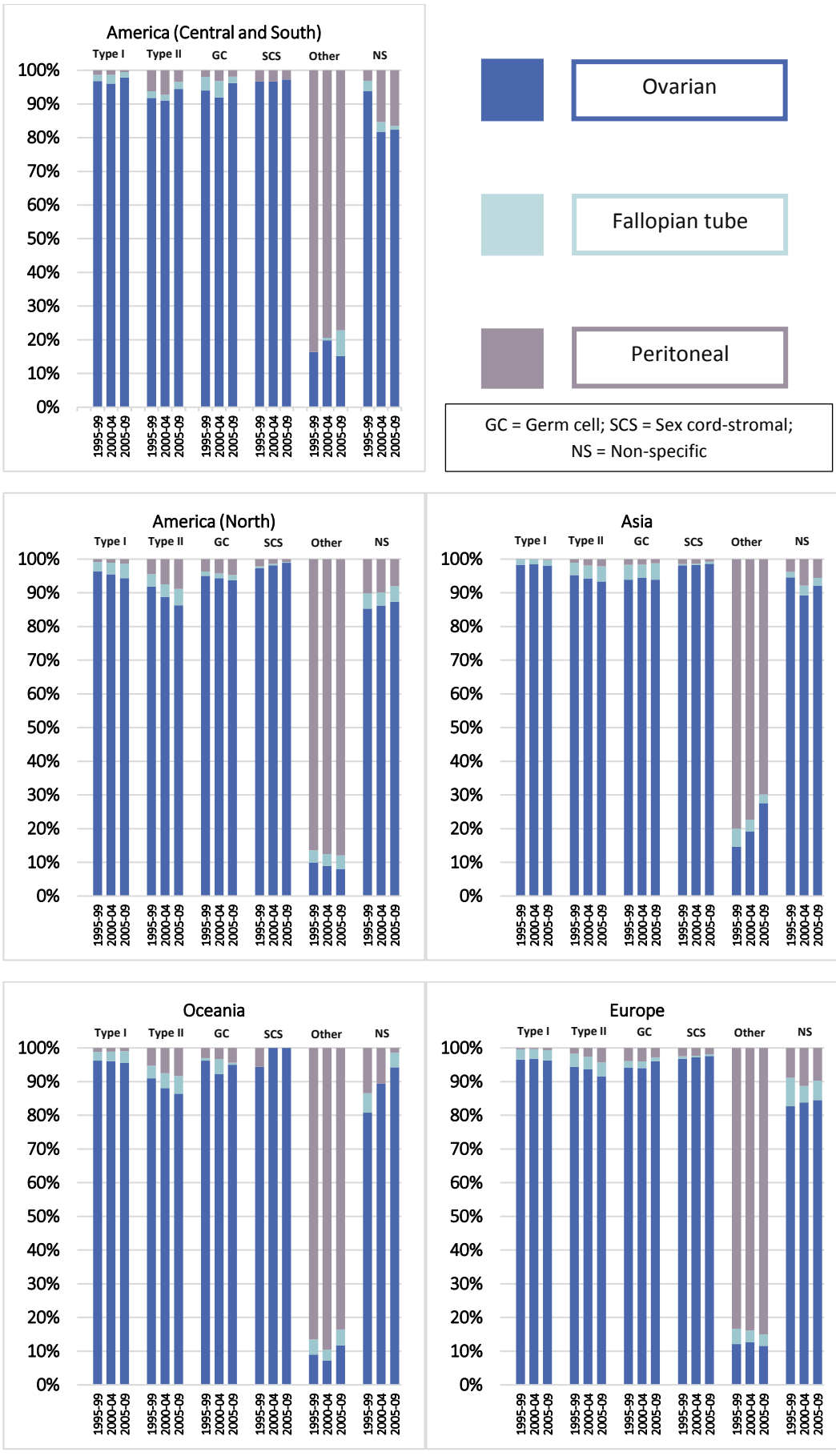


Figure 4.2 Anatomic sub-site distribution within histological group by continent, 1995-2009

Table 4.3 Distribution (%) of topography (sub-site) by ovarian cancer histological group, calendar period and continent, 1995-2009, 51 countries

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
TOTAL							
Type I	**4,566**	**3.0**	**1,124**	**0.7**	**147,184**	**96.3**	**152,874**
1995-99	1,248	2.7	288	0.6	44,234	96.6	45,770
2000-04	1,582	2.9	355	0.7	52,336	96.4	54,273
2005-09	1,736	3.3	481	0.9	50,614	95.8	52,831
Type II	**19,121**	**4.0**	**23,286**	**4.9**	**434,054**	**91.1**	**476,461**
1995-99	4,928	3.7	4,071	3.1	122,704	93.2	131,703
2000-04	6,207	3.7	8,205	4.9	153,096	91.4	167,508
2005-09	7,986	4.5	11,010	6.2	158,254	89.3	177,250
Germ cell	**291**	**2.2**	**456**	**3.4**	**12,562**	**94.4**	**13,309**
1995-99	80	2.2	122	3.3	3,491	94.5	3,693
2000-04	107	2.3	169	3.6	4,412	94.1	4,688
2005-09	104	2.1	165	3.3	4,659	94.5	4,928
Sex cord-stromal	**54**	**0.5**	**207**	**1.8**	**11,183**	**97.7**	**11,444**
1995-99	21	0.6	79	2.3	3,280	97.0	3,380
2000-04	17	0.4	74	1.9	3,906	97.7	3,997
2005-09	16	0.4	54	1.3	3,997	98.3	4,067
Other non-epithelial	**654**	**3.7**	**14,896**	**84.8**	**2,019**	**11.5**	**17,569**
1995-99	201	4.1	4,141	84.7	546	11.2	4,888
2000-04	212	3.4	5,250	84.9	720	11.6	6,182
2005-09	241	3.7	5,505	84.7	753	11.6	6,499
Non-specific	**487**	**4.8**	**936**	**9.3**	**8,679**	**85.9**	**10,102**
1995-99	157	5.9	225	8.5	2,264	85.6	2,646
2000-04	155	4.1	395	10.5	3,199	85.3	3,749
2005-09	175	4.7	316	8.5	3,216	86.8	3,707
AMERICA (CENTRAL AND SOUTH)							
Type I	**28**	**2.0**	**14**	**1.0**	**1,335**	**96.9**	**1,377**
1995-99	4	1.8	3	1.4	213	96.8	220
2000-04	15	2.6	8	1.4	564	96.1	587
2005-09	9	1.6	3	0.5	558	97.9	570
Type II	**91**	**1.9**	**265**	**5.6**	**4,345**	**92.4**	**4,701**
1995-99	14	1.9	45	6.3	661	91.8	720
2000-04	39	1.8	160	7.2	2,010	91.0	2,209
2005-09	38	2.1	60	3.4	1,674	94.5	1,772

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site and histological group (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
Germ cell	**10**	**3.6**	**7**	**2.5**	**263**	**93.9**	**280**
1995-99	2	4.0	1	2.0	47	94.0	50
2000-04	6	4.8	4	3.2	114	91.9	124
2005-09	2	1.9	2	1.9	102	96.2	106
Sex cord-stromal	**0**	**0.0**	**6**	**3.1**	**188**	**96.9**	**194**
1995-99	0	0.0	1	3.3	29	96.7	30
2000-04	0	0.0	3	3.3	87	96.7	90
2005-09	0	0.0	2	2.7	72	97.3	74
Other non-epithelial	**8**	**2.8**	**226**	**79.6**	**50**	**17.6**	**284**
1995-99	0	0.0	51	83.6	10	16.4	61
2000-04	1	0.8	104	79.4	26	19.8	131
2005-09	7	7.6	71	77.2	14	15.2	92
Non-specific	**6**	**2.4**	**36**	**14.2**	**212**	**83.5**	**254**
1995-99	1	3.1	1	3.1	30	93.8	32
2000-04	4	2.9	21	15.3	112	81.8	137
2005-09	1	1.2	14	16.5	70	82.4	85
AMERICA (NORTH)							
Type I	**2,195**	**3.5**	**706**	**1.1**	**60,599**	**95.4**	**63,500**
1995-99	563	2.7	178	0.9	20,042	96.4	20,783
2000-04	759	3.4	233	1.1	21,015	95.5	22,007
2005-09	873	4.2	295	1.4	19,542	94.4	20,710
Type II	**8,758**	**4.2**	**15,000**	**7.1**	**187,230**	**88.7**	**210,988**
1995-99	2,232	3.7	2,676	4.4	55,525	91.9	60,433
2000-04	2,704	3.7	5,431	7.5	64,345	88.8	72,480
2005-09	3,822	4.9	6,893	8.8	67,360	86.3	78,075
Germ cell	**79**	**1.4**	**244**	**4.3**	**5,342**	**94.3**	**5,665**
1995-99	20	1.3	59	3.7	1,512	95.0	1,591
2000-04	26	1.4	82	4.3	1,799	94.3	1,907
2005-09	33	1.5	103	4.8	2,031	93.7	2,167
Sex cord-stromal	**18**	**0.4**	**63**	**1.4**	**4,389**	**98.2**	**4,470**
1995-99	7	0.5	29	2.1	1,324	97.4	1,360
2000-04	7	0.5	20	1.4	1,427	98.1	1,454
2005-09	4	0.2	14	0.8	1,638	98.9	1,656
Other non-epithelial	**308**	**3.7**	**7,187**	**87.4**	**731**	**8.9**	**8,226**
1995-99	88	3.6	2,086	86.4	239	9.9	2,413
2000-04	96	3.5	2,393	87.5	245	9.0	2,734
2005-09	124	4.0	2,708	88.0	247	8.0	3,079

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site and histological group (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
Non-specific	**142**	**4.3**	**304**	**9.3**	**2,836**	**86.4**	**3,282**
1995-99	40	4.6	89	10.1	750	85.3	879
2000-04	46	3.9	118	9.9	1,028	86.2	1,192
2005-09	56	4.6	97	8.0	1,058	87.4	1,211
ASIA							
Type I	**303**	**1.6**	**28**	**0.1**	**18,560**	**98.2**	**18,891**
1995-99	71	1.6	2	0.0	4,251	98.3	4,324
2000-04	96	1.5	8	0.1	6,484	98.4	6,588
2005-09	136	1.7	18	0.2	7,825	98.1	7,979
Type II	**1,263**	**4.1**	**562**	**1.8**	**28,967**	**94.1**	**30,792**
1995-99	249	3.7	73	1.1	6,453	95.2	6,775
2000-04	396	3.9	194	1.9	9,652	94.2	10,242
2005-09	618	4.5	295	2.1	12,862	93.4	13,775
Germ cell	**122**	**4.4**	**41**	**1.5**	**2,589**	**94.1**	**2,752**
1995-99	34	4.4	13	1.7	723	93.9	770
2000-04	37	3.9	15	1.6	888	94.5	940
2005-09	51	4.9	13	1.2	978	93.9	1,042
Sex cord-stromal	**5**	**0.4**	**14**	**1.2**	**1,168**	**98.4**	**1,187**
1995-99	1	0.4	4	1.5	263	98.1	268
2000-04	1	0.2	6	1.4	415	98.3	422
2005-09	3	0.6	4	0.8	490	98.6	497
Other non-epithelial	**57**	**3.5**	**1,226**	**74.9**	**354**	**21.6**	**1,637**
1995-99	19	5.3	289	80.1	53	14.7	361
2000-04	21	3.4	471	77.3	117	19.2	609
2005-09	17	2.5	466	69.9	184	27.6	667
Non-specific	**35**	**2.3**	**88**	**5.8**	**1,383**	**91.8**	**1,506**
1995-99	7	1.7	16	3.8	399	94.5	422
2000-04	15	2.9	40	7.8	456	89.2	511
2005-09	13	2.3	32	5.6	528	92.1	573
EUROPE							
Type I	**1,914**	**3.0**	**329**	**0.5**	**62,582**	**96.5**	**64,825**
1995-99	570	3.0	86	0.5	18,231	96.5	18,887
2000-04	670	2.8	90	0.4	22,865	96.8	23,625
2005-09	674	3.0	153	0.7	21,486	96.3	22,313
Type II	**8,361**	**3.9**	**6,440**	**3.0**	**200,761**	**93.1**	**215,562**
1995-99	2,263	3.8	1,036	1.7	55,930	94.4	59,229
2000-04	2,836	3.7	2,032	2.6	72,508	93.7	77,376
2005-09	3,262	4.1	3,372	4.3	72,323	91.6	78,957

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site and histological group (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
Germ cell	**70**	**1.7**	**147**	**3.6**	**3,922**	**94.8**	**4,139**
1995-99	23	2.0	45	3.9	1,081	94.1	1,149
2000-04	30	2.0	62	4.0	1,445	94.0	1,537
2005-09	17	1.2	40	2.8	1,396	96.1	1,453
Sex cord-stromal	**31**	**0.6**	**119**	**2.2**	**5,232**	**97.2**	**5,382**
1995-99	13	0.8	40	2.4	1,580	96.8	1,633
2000-04	9	0.5	45	2.3	1,911	97.3	1,965
2005-09	9	0.5	34	1.9	1,741	97.6	1,784
Other non-epithelial	**260**	**3.8**	**5,817**	**84.1**	**837**	**12.1**	**6,914**
1995-99	87	4.6	1,580	83.3	230	12.1	1,897
2000-04	88	3.5	2,119	83.9	319	12.6	2,526
2005-09	85	3.4	2,118	85.0	288	11.6	2,491
Non-specific	**298**	**6.1**	**495**	**10.1**	**4,098**	**83.8**	**4,891**
1995-99	106	8.4	112	8.9	1,043	82.7	1,261
2000-04	90	4.8	211	11.3	1,561	83.8	1,862
2005-09	102	5.8	172	9.7	1,494	84.5	1,768
OCEANIA							
Type I	**126**	**2.9**	**47**	**1.1**	**4,108**	**96.0**	**4,281**
1995-99	40	2.6	19	1.2	1,497	96.2	1,556
2000-04	42	2.9	16	1.1	1,408	96.0	1,466
2005-09	44	3.5	12	1.0	1,203	95.6	1,259
Type II	**648**	**4.5**	**1,019**	**7.1**	**12,751**	**88.4**	**14,418**
1995-99	170	3.7	241	5.3	4,135	91.0	4,546
2000-04	232	4.5	388	7.5	4,581	88.1	5,201
2005-09	246	5.3	390	8.3	4,035	86.4	4,671
Germ cell	**10**	**2.1**	**17**	**3.6**	**446**	**94.3**	**473**
1995-99	1	0.8	4	3.0	128	96.2	133
2000-04	8	4.4	6	3.3	166	92.2	180
2005-09	1	0.6	7	4.4	152	95.0	160
Sex cord-stromal	**0**	**0.0**	**5**	**5.6**	**206**	**231.5**	**89**
1995-99	0	0.0	5	5.6	84	94.4	89
2000-04	0	0.0	0	0.0	66	100.0	0
2005-09	0	0.0	0	0.0	56	100.0	0
Other non-epithelial	**21**	**4.1**	**440**	**86.6**	**47**	**9.3**	**508**
1995-99	7	4.5	135	86.5	14	9.0	156
2000-04	6	3.3	163	89.6	13	7.1	182
2005-09	8	4.7	142	83.5	20	11.8	170

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site and histological group (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

	Fallopian tube[a]		Peritoneal[b]		Ovarian[c]		Total
	N	%	N	%	N	%	N
Non-specific	**6**	**3.6**	**13**	**7.7**	**150**	**88.8**	**169**
1995-99	3	5.8	7	13.5	42	80.8	52
2000-04	0	0.0	5	10.6	42	89.4	47
2005-09	3	4.3	1	1.4	66	94.3	70

Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology codes were excluded from the analysis of distribution of topographical sub-site and histological group (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [a] Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. [b] Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. [c] Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). [d] African countries were not included because fewer than 100 women were available for each calendar period.

Table 4.4 Worldwide distribution (%) of ovarian cancer by histological group and calendar period, 1995-2009, 51 countries

Period of diagnosis	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific non-epithelial		Non-specific[d]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
1995-99	192,080	45,770	**23.8**	131,703	**68.6**	3,693	**1.9**	3,380	**1.8**	4,888	**2.5**	2,646	**1.4**
2000-04	240,397	54,273	**22.6**	167,508	**69.7**	4,688	**2.0**	3,997	**1.7**	6,182	**2.6**	3,749	**1.6**
2005-09	249,282	52,831	**21.2**	177,250	**71.1**	4,928	**2.0**	4,067	**1.6**	6,499	**2.6**	3,707	**1.5**
Total	681,759	152,874	**22.4**	476,461	**69.9**	13,309	**2.0**	11,444	**1.7**	17,569	**2.6**	10,102	**1.5**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004.

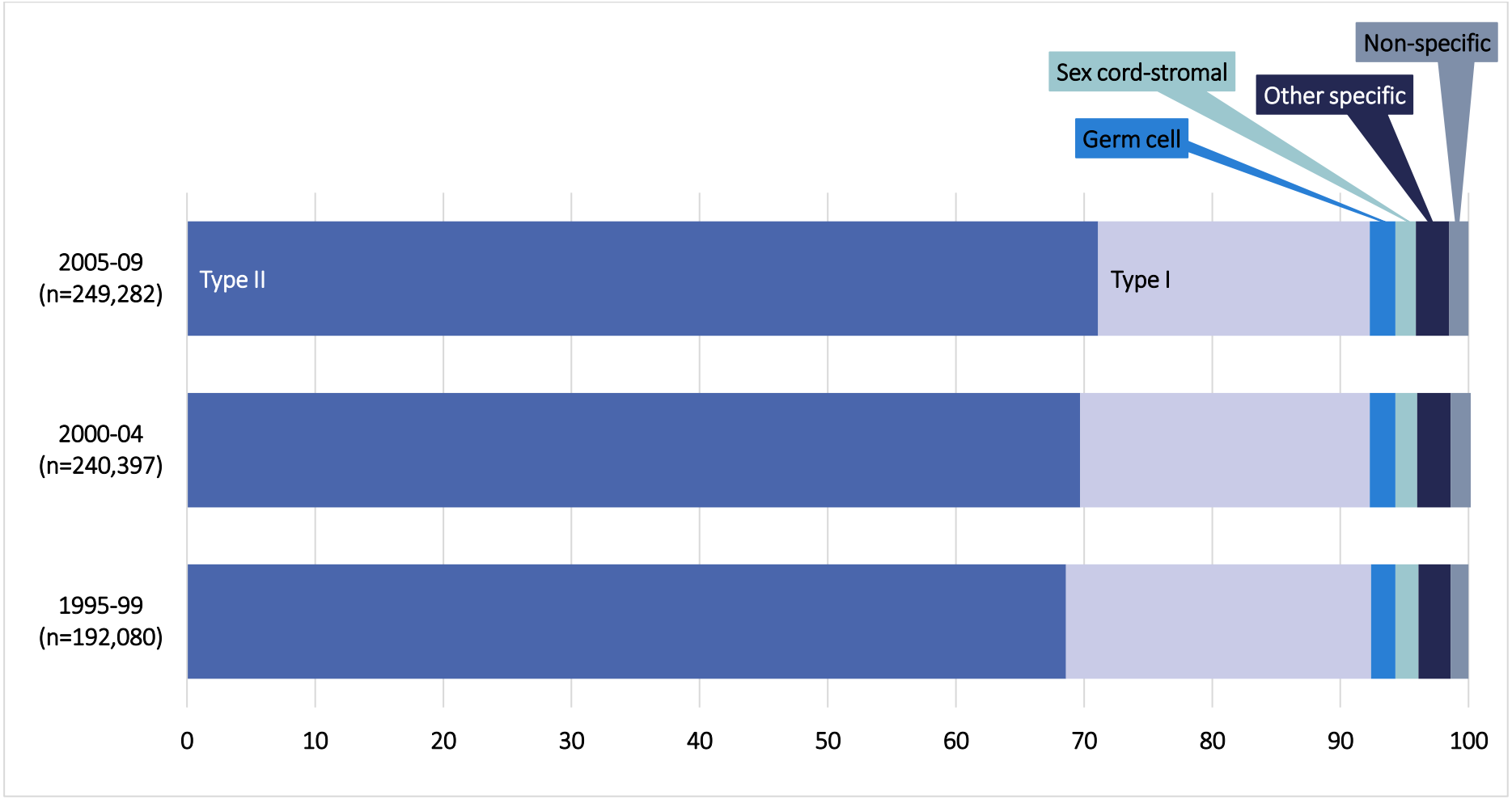


Figure 4.3 Worldwide distribution (%) of ovarian cancer histology: 51 countries, 1995-2009

During 2005-2009, type II ovarian cancer was the most common group in all continents, although the proportion was much higher in Oceania (73.1%), North America (73.0%) and Europe (72.6%) than in Central and South America (65.7%) and Asia (56.1%) [Figure 4.4, Table 4.5]. The range at the national level, however, was much wider. The highest proportion of type II tumours was in Latvia (78.9%), with the lowest proportion in Thailand (40.4%) [Table 4.6]. There was little between-country variation in the proportion of type II tumours in Central and South America, North America and Oceania [Figures 4.5-4.6]. However, the proportion varied widely between countries in Asia, where the proportion of type II tumours was lower than that of type I epithelial tumours in Hong Kong and Thailand [Figure 4.6]. There was also variation in the proportion of type II tumours in Europe [Figure 4.7], where type II tumours accounted for over 70% of tumours in 15 countries, 60% in 11 countries and only 50.2% in Russia [Table 4.6].

For type II epithelial tumours, the largest increase was seen in North America (from 69.1% in 1995-1999 to 73.0% in 2005-2009). Increases in the proportion of type II epithelial tumours were seen in most countries, though there were decreases in a few countries in Central and South America (Cuba and Ecuador), Asia (Japan) and Europe (Bulgaria, Croatia, Italy, Latvia, Lithuania and Russia). In a few countries, the proportion remained stable over time (Thailand, Austria, Iceland, Ireland, Poland and Slovenia) [Table 4.6].

Type I epithelial tumours were the second most common group for all continents during 2005-2009. The highest proportion was seen in Asia (32.5%), while North America showed the lowest proportion (19.4%) [Table 4.5]. The proportion was similar in all countries in Central and South America, North America and Oceania [Table 4.6]. In Europe, however, there was wider variation, the proportion ranging from 11.3% in Latvia to 28.7% in Finland [Table 4.6]. The variation was even wider for countries in Asia, with the lowest proportion in Israel (12.8%) and the highest in Hong Kong (51.7%) [Figure 4.6].

Continued on page 119

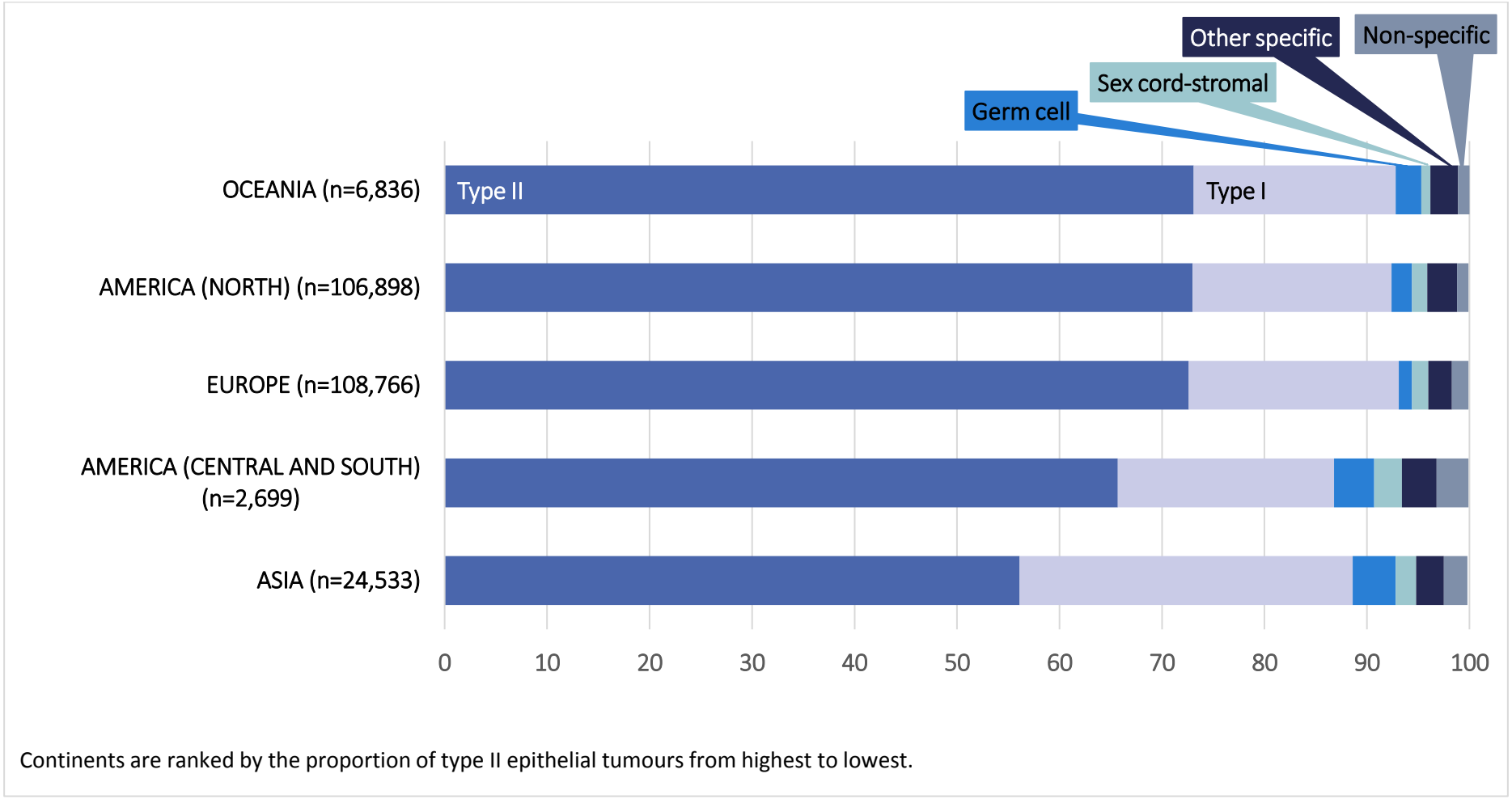


Figure 4.4 Distribution (%) of ovarian cancer histological groups by continent, 2005-2009

Table 4.5 Distribution (%) of histological groups by continent and calendar period of diagnosis, 1995-2009

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
AMERICA (CENTRAL AND SOUTH)													
1995-99	1,113	220	**19.8**	720	**64.7**	50	**4.5**	30	**2.7**	61	**5.5**	32	**2.9**
2000-04	3,278	587	**17.9**	2,209	**67.4**	124	**3.8**	90	**2.7**	131	**4.0**	137	**4.2**
2005-09	2,699	570	**21.1**	1,772	**65.7**	106	**3.9**	74	**2.7**	92	**3.4**	85	**3.1**
AMERICA (NORTH)													
1995-99	87,459	20,783	**23.8**	60,433	**69.1**	1,591	**1.8**	1,360	**1.6**	2,413	**2.8**	879	**1.0**
2000-04	101,774	22,007	**21.6**	72,480	**71.2**	1,907	**1.9**	1,454	**1.4**	2,734	**2.7**	1,192	**1.2**
2005-09	106,898	20,710	**19.4**	78,075	**73.0**	2,167	**2.0**	1,656	**1.5**	3,079	**2.9**	1,211	**1.1**
ASIA													
1995-99	12,920	4,324	**33.5**	6,775	**52.4**	770	**6.0**	268	**2.1**	361	**2.8**	422	**3.3**
2000-04	19,312	6,588	**34.1**	10,242	**53.0**	940	**4.9**	422	**2.2**	609	**3.2**	511	**2.6**
2005-09	24,533	7,979	**32.5**	13,775	**56.1**	1,042	**4.2**	497	**2.0**	667	**2.7**	573	**2.3**
EUROPE													
1995-99	84,056	18,887	**22.5**	59,229	**70.5**	1,149	**1.4**	1,633	**1.9**	1,897	**2.3**	1,261	**1.5**
2000-04	108,891	23,625	**21.7**	77,376	**71.1**	1,537	**1.4**	1,965	**1.8**	2,526	**2.3**	1,862	**1.7**
2005-09	108,766	22,313	**20.5**	78,957	**72.6**	1,453	**1.3**	1,784	**1.6**	2,491	**2.3**	1,768	**1.6**
OCEANIA													
1995-99	6,532	1,556	**23.8**	4,546	**69.6**	133	**2.0**	89	**1.4**	156	**2.4**	52	**0.8**
2000-04	7,142	1,466	**20.5**	5,201	**72.8**	180	**2.5**	66	**0.9**	182	**2.5**	47	**0.7**
2005-09	6,386	1,259	**19.7**	4,671	**73.1**	160	**2.5**	56	**0.9**	170	**2.7**	70	**1.1**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004.

Table 4.6 Distribution (%) of histological groups by country and calendar period of diagnosis, 1995-2009

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
AMERICA (CENTRAL AND SOUTH)													
Argentinian registries													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	182	39	**21.4**	117	**64.3**	6	**3.3**	5	**2.7**	5	**2.7**	10	**5.5**
2005-09	598	112	**18.7**	403	**67.4**	28	**4.7**	14	**2.3**	9	**1.5**	32	**5.4**
Brazilian registries													
1995-99	168	49	**29.2**	92	**54.8**	3	**1.8**	3	**1.8**	20	**11.9**	1	**0.6**
2000-04	434	96	**22.1**	281	**64.7**	15	**3.5**	6	**1.4**	27	**6.2**	9	**2.1**
2005-09	252	60	**23.8**	160	**63.5**	13	**5.2**	4	**1.6**	8	**3.2**	7	**2.8**
Colombia (Cali)													
1995-99	302	78	**25.8**	181	**59.9**	12	**4.0**	8	**2.6**	12	**4.0**	11	**3.6**
2000-04	337	86	**25.5**	204	**60.5**	19	**5.6**	7	**2.1**	10	**3.0**	11	**3.3**
2005-09	335	81	**24.2**	216	**64.5**	13	**3.9**	13	**3.9**	4	**1.2**	8	**2.4**
Cuba*													
1995-99	455	71	**15.6**	320	**70.3**	22	**4.8**	10	**2.2**	19	**4.2**	13	**2.9**
2000-04	1,464	187	**12.8**	1,060	**72.4**	42	**2.9**	50	**3.4**	55	**3.8**	70	**4.8**
2005-09	560	130	**23.2**	371	**66.3**	9	**1.6**	25	**4.5**	19	**3.4**	6	**1.1**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Ecuador (Quito)													
1995-99	188	22	**11.7**	127	**67.6**	13	**6.9**	9	**4.8**	10	**5.3**	7	**3.7**
2000-04	209	32	**15.3**	133	**63.6**	15	**7.2**	9	**4.3**	13	**6.2**	7	**3.3**
2005-09	270	43	**15.9**	173	**64.1**	21	**7.8**	7	**2.6**	16	**5.9**	10	**3.7**
Puerto Rico*													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	652	147	**22.5**	414	**63.5**	27	**4.1**	13	**2.0**	21	**3.2**	30	**4.6**
2005-09	684	144	**21.1**	449	**65.6**	22	**3.2**	11	**1.6**	36	**5.3**	22	**3.2**
AMERICA (NORTH)													
Canada*													
1995-99	10,366	2,828	**27.3**	6,859	**66.2**	226	**2.2**	128	**1.2**	251	**2.4**	74	**0.7**
2000-04	11,347	2,787	**24.6**	7,906	**69.7**	209	**1.8**	114	**1.0**	247	**2.2**	84	**0.7**
2005-09	12,196	2,676	**21.9**	8,762	**71.8**	258	**2.1**	133	**1.1**	276	**2.3**	91	**0.7**
US registries													
1995-99	77,093	17,955	**23.3**	53,574	**69.5**	1,365	**1.8**	1,232	**1.6**	2,162	**2.8**	805	**1.0**
2000-04	90,427	19,220	**21.3**	64,574	**71.4**	1,698	**1.9**	1,340	**1.5**	2,487	**2.8**	1,108	**1.2**
2005-09	94,702	18,034	**19.0**	69,313	**73.2**	1,909	**2.0**	1,523	**1.6**	2,803	**3.0**	1,120	**1.2**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
ASIA													
Chinese registries													
1995-99	131	31	**23.7**	76	**58.0**	4	**3.1**	2	**1.5**	2	**1.5**	16	**12.2**
2000-04	1,139	246	**21.6**	669	**58.7**	49	**4.3**	27	**2.4**	33	**2.9**	115	**10.1**
2005-09	3,150	687	**21.8**	2,031	**64.5**	116	**3.7**	64	**2.0**	93	**3.0**	159	**5.0**
Cyprus*													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	225	42	**18.7**	163	**72.4**	2	**0.9**	3	**1.3**	13	**5.8**	2	**0.9**
Hong Kong*													
1995-99	527	280	**53.1**	247	**46.9**	-	.	-	.	-	.	-	.
2000-04	1,012	522	**51.6**	490	**48.4**	-	.	-	.	-	.	-	.
2005-09	437	226	**51.7**	211	**48.3**	-	.	-	.	-	.	-	.
Indian registries													
1995-99	391	46	**11.8**	252	**64.5**	27	**6.9**	13	**3.3**	1	**0.3**	52	**13.3**
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	-	-	.	-	.	-	.	-	.	-	.	-	.
Indonesia (Jakarta)													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	182	73	**40.1**	86	**47.3**	14	**7.7**	7	**3.8**	1	**0.5**	1	**0.5**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Israel*													
1995-99	1,690	336	**19.9**	1,195	**70.7**	34	**2.0**	15	**0.9**	53	**3.1**	57	**3.4**
2000-04	1,921	309	**16.1**	1,407	**73.2**	57	**3.0**	9	**0.5**	78	**4.1**	61	**3.2**
2005-09	1,957	251	**12.8**	1,522	**77.8**	40	**2.0**	11	**0.6**	71	**3.6**	62	**3.2**
Japanese registries													
1995-99	1,790	537	**30.0**	958	**53.5**	58	**3.2**	16	**0.9**	72	**4.0**	149	**8.3**
2000-04	3,124	1,176	**37.6**	1,573	**50.4**	93	**3.0**	21	**0.7**	126	**4.0**	135	**4.3**
2005-09	3,647	1,508	**41.3**	1,732	**47.5**	129	**3.5**	26	**0.7**	119	**3.3**	133	**3.6**
Jordan*													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	305	61	**20.0**	196	**64.3**	22	**7.2**	11	**3.6**	8	**2.6**	7	**2.3**
2005-09	382	58	**15.2**	246	**64.4**	31	**8.1**	18	**4.7**	19	**5.0**	10	**2.6**
Korea*													
1995-99	4,526	1,648	**36.4**	2,274	**50.2**	356	**7.9**	123	**2.7**	29	**0.6**	96	**2.1**
2000-04	6,036	2,132	**35.3**	3,162	**52.4**	382	**6.3**	215	**3.6**	42	**0.7**	103	**1.7**
2005-09	7,859	2,512	**32.0**	4,550	**57.9**	392	**5.0**	207	**2.6**	64	**0.8**	134	**1.7**
Malaysia (Penang)													
1995-99	144	52	**36.1**	75	**52.1**	11	**7.6**	4	**2.8**	-	**.**	2	**1.4**
2000-04	220	93	**42.3**	104	**47.3**	11	**5.0**	8	**3.6**	2	**0.9**	2	**0.9**
2005-09	281	93	**33.1**	164	**58.4**	14	**5.0**	7	**2.5**	2	**0.7**	1	**0.4**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Saudi Arabia*													
1995-99	392	95	**24.2**	234	**59.7**	36	**9.2**	14	**3.6**	5	**1.3**	8	**2.0**
2000-04	552	118	**21.4**	335	**60.7**	54	**9.8**	19	**3.4**	19	**3.4**	7	**1.3**
2005-09	-	-	.	-	.	-	.	-	.	-	.	-	.
Taiwan*													
1995-99	2,768	1,098	**39.7**	1,177	**42.5**	215	**7.8**	65	**2.3**	183	**6.6**	30	**1.1**
2000-04	3,998	1,568	**39.2**	1,783	**44.6**	226	**5.7**	93	**2.3**	277	**6.9**	51	**1.3**
2005-09	5,165	2,112	**40.9**	2,400	**46.5**	248	**4.8**	126	**2.4**	252	**4.9**	27	**0.5**
Thai registries													
1995-99	171	76	**44.4**	70	**40.9**	16	**9.4**	6	**3.5**	2	**1.2**	1	**0.6**
2000-04	478	218	**45.6**	200	**41.8**	30	**6.3**	9	**1.9**	10	**2.1**	11	**2.3**
2005-09	549	252	**45.9**	222	**40.4**	30	**5.5**	23	**4.2**	10	**1.8**	12	**2.2**
Turkey (Izmir)													
1995-99	390	125	**32.1**	217	**55.6**	13	**3.3**	10	**2.6**	14	**3.6**	11	**2.8**
2000-04	527	145	**27.5**	323	**61.3**	16	**3.0**	10	**1.9**	14	**2.7**	19	**3.6**
2005-09	699	165	**23.6**	448	**64.1**	26	**3.7**	5	**0.7**	23	**3.3**	32	**4.6**
EUROPE													
Austria*													
1995-99	4,331	674	**15.6**	3,287	**75.9**	95	**2.2**	63	**1.5**	83	**1.9**	129	**3.0**
2000-04	4,180	603	**14.4**	3,168	**75.8**	45	**1.1**	67	**1.6**	86	**2.1**	211	**5.0**
2005-09	3,653	552	**15.1**	2,744	**75.1**	47	**1.3**	64	**1.8**	93	**2.5**	153	**4.2**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Belgium*													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	948	228	**24.1**	653	**68.9**	16	**1.7**	14	**1.5**	25	**2.6**	12	**1.3**
2005-09	4,720	980	**20.8**	3,444	**73.0**	60	**1.3**	39	**0.8**	153	**3.2**	44	**0.9**
Bulgaria*													
1995-99	2,792	448	**16.0**	2,045	**73.2**	34	**1.2**	155	**5.6**	73	**2.6**	37	**1.3**
2000-04	3,368	691	**20.5**	2,323	**69.0**	45	**1.3**	142	**4.2**	104	**3.1**	63	**1.9**
2005-09	3,933	785	**20.0**	2,750	**69.9**	44	**1.1**	166	**4.2**	133	**3.4**	55	**1.4**
Croatia*													
1995-99	771	138	**17.9**	597	**77.4**	12	**1.6**	5	**0.6**	12	**1.6**	7	**0.9**
2000-04	1,998	428	**21.4**	1,491	**74.6**	20	**1.0**	31	**1.6**	20	**1.0**	8	**0.4**
2005-09	1,930	428	**22.2**	1,422	**73.7**	29	**1.5**	28	**1.5**	12	**0.6**	11	**0.6**
Czech Republic*													
1995-99	5,223	1,339	**25.6**	3,330	**63.8**	76	**1.5**	209	**4.0**	131	**2.5**	138	**2.6**
2000-04	5,502	1,366	**24.8**	3,565	**64.8**	81	**1.5**	172	**3.1**	160	**2.9**	158	**2.9**
2005-09	5,220	1,090	**20.9**	3,632	**69.6**	55	**1.1**	140	**2.7**	143	**2.7**	160	**3.1**
Denmark*													
1995-99	3,068	796	**25.9**	2,080	**67.8**	44	**1.4**	47	**1.5**	78	**2.5**	23	**0.7**
2000-04	2,991	750	**25.1**	2,050	**68.5**	54	**1.8**	41	**1.4**	58	**1.9**	38	**1.3**
2005-09	2,997	633	**21.1**	2,161	**72.1**	27	**0.9**	8	**0.3**	74	**2.5**	94	**3.1**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Estonia*													
1995-99	792	133	**16.8**	511	**64.5**	5	**0.6**	47	**5.9**	16	**2.0**	80	**10.1**
2000-04	710	116	**16.3**	495	**69.7**	10	**1.4**	19	**2.7**	18	**2.5**	52	**7.3**
2005-09	613	95	**15.5**	432	**70.5**	10	**1.6**	21	**3.4**	23	**3.8**	32	**5.2**
Finland*													
1995-99	2,325	901	**38.8**	1,266	**54.5**	21	**0.9**	26	**1.1**	28	**1.2**	83	**3.6**
2000-04	2,512	895	**35.6**	1,431	**57.0**	41	**1.6**	21	**0.8**	20	**0.8**	104	**4.1**
2005-09	2,485	712	**28.7**	1,561	**62.8**	30	**1.2**	11	**0.4**	53	**2.1**	118	**4.7**
French registries													
1995-99	2,495	580	**23.2**	1,724	**69.1**	51	**2.0**	28	**1.1**	87	**3.5**	25	**1.0**
2000-04	2,870	621	**21.6**	2,035	**70.9**	56	**2.0**	27	**0.9**	98	**3.4**	33	**1.1**
2005-09	242	62	**25.6**	163	**67.4**	7	**2.9**	-	.	9	**3.7**	1	**0.4**
German registries													
1995-99	5,295	912	**17.2**	4,003	**75.6**	50	**0.9**	118	**2.2**	110	**2.1**	102	**1.9**
2000-04	9,047	1,574	**17.4**	6,921	**76.5**	95	**1.1**	160	**1.8**	172	**1.9**	125	**1.4**
2005-09	10,566	1,809	**17.1**	8,223	**77.8**	110	**1.0**	114	**1.1**	207	**2.0**	103	**1.0**
Iceland*													
1995-99	113	21	**18.6**	86	**76.1**	3	**2.7**	2	**1.8**	1	**0.9**	-	.
2000-04	127	24	**18.9**	94	**74.0**	2	**1.6**	1	**0.8**	6	**4.7**	-	.
2005-09	118	20	**16.9**	90	**76.3**	1	**0.8**	-	.	7	**5.9**	-	.

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Ireland*													
1995-99	1,332	323	**24.2**	948	**71.2**	21	**1.6**	10	**0.8**	15	**1.1**	15	**1.1**
2000-04	1,477	375	**25.4**	1,043	**70.6**	19	**1.3**	9	**0.6**	15	**1.0**	16	**1.1**
2005-09	1,607	382	**23.8**	1,146	**71.3**	23	**1.4**	20	**1.2**	24	**1.5**	12	**0.7**
Italian registries													
1995-99	6,772	1,384	**20.4**	4,711	**69.6**	85	**1.3**	83	**1.2**	298	**4.4**	211	**3.1**
2000-04	8,394	1,724	**20.5**	5,811	**69.2**	89	**1.1**	78	**0.9**	383	**4.6**	309	**3.7**
2005-09	5,087	1,104	**21.7**	3,448	**67.8**	60	**1.2**	47	**0.9**	234	**4.6**	194	**3.8**
Latvia*													
1995-99	1,219	71	**5.8**	1,064	**87.3**	23	**1.9**	33	**2.7**	28	**2.3**	-	.
2000-04	1,205	104	**8.6**	1,013	**84.1**	13	**1.1**	46	**3.8**	20	**1.7**	9	**0.7**
2005-09	1,233	139	**11.3**	973	**78.9**	9	**0.7**	75	**6.1**	27	**2.2**	10	**0.8**
Lithuania*													
1995-99	1,630	116	**7.1**	1,367	**83.9**	21	**1.3**	58	**3.6**	31	**1.9**	37	**2.3**
2000-04	1,781	203	**11.4**	1,428	**80.2**	17	**1.0**	44	**2.5**	63	**3.5**	26	**1.5**
2005-09	1,780	295	**16.6**	1,346	**75.6**	23	**1.3**	47	**2.6**	53	**3.0**	16	**0.9**
Malta*													
1995-99	149	50	**33.6**	85	**57.0**	5	**3.4**	3	**2.0**	5	**3.4**	1	**0.7**
2000-04	197	60	**30.5**	113	**57.4**	4	**2.0**	3	**1.5**	3	**1.5**	14	**7.1**
2005-09	191	47	**24.6**	120	**62.8**	4	**2.1**	1	**0.5**	7	**3.7**	12	**6.3**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Netherlands*													
1995-99	6,624	1,714	**25.9**	4,484	**67.7**	88	**1.3**	173	**2.6**	157	**2.4**	8	**0.1**
2000-04	6,289	1,508	**24.0**	4,385	**69.7**	109	**1.7**	101	**1.6**	177	**2.8**	9	**0.1**
2005-09	6,403	1,437	**22.4**	4,631	**72.3**	95	**1.5**	82	**1.3**	150	**2.3**	8	**0.1**
Norway*													
1995-99	2,358	534	**22.6**	1,639	**69.5**	37	**1.6**	61	**2.6**	69	**2.9**	18	**0.8**
2000-04	2,506	534	**21.3**	1,783	**71.1**	52	**2.1**	26	**1.0**	82	**3.3**	29	**1.2**
2005-09	2,416	385	**15.9**	1,848	**76.5**	44	**1.8**	29	**1.2**	73	**3.0**	37	**1.5**
Poland*													
1995-99	3,158	683	**21.6**	2,177	**68.9**	64	**2.0**	136	**4.3**	34	**1.1**	64	**2.0**
2000-04	13,114	3,017	**23.0**	8,945	**68.2**	237	**1.8**	474	**3.6**	188	**1.4**	253	**1.9**
2005-09	14,837	3,455	**23.3**	10,206	**68.8**	251	**1.7**	463	**3.1**	191	**1.3**	271	**1.8**
Portugal*													
1995-99	574	120	**20.9**	392	**68.3**	23	**4.0**	11	**1.9**	28	**4.9**	-	.
2000-04	2,153	454	**21.1**	1,497	**69.5**	46	**2.1**	32	**1.5**	99	**4.6**	25	**1.2**
2005-09	1,978	419	**21.2**	1,388	**70.2**	33	**1.7**	21	**1.1**	97	**4.9**	20	**1.0**
Romania (Cluj)													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	196	47	**24.0**	129	**65.8**	2	**1.0**	4	**2.0**	6	**3.1**	8	**4.1**

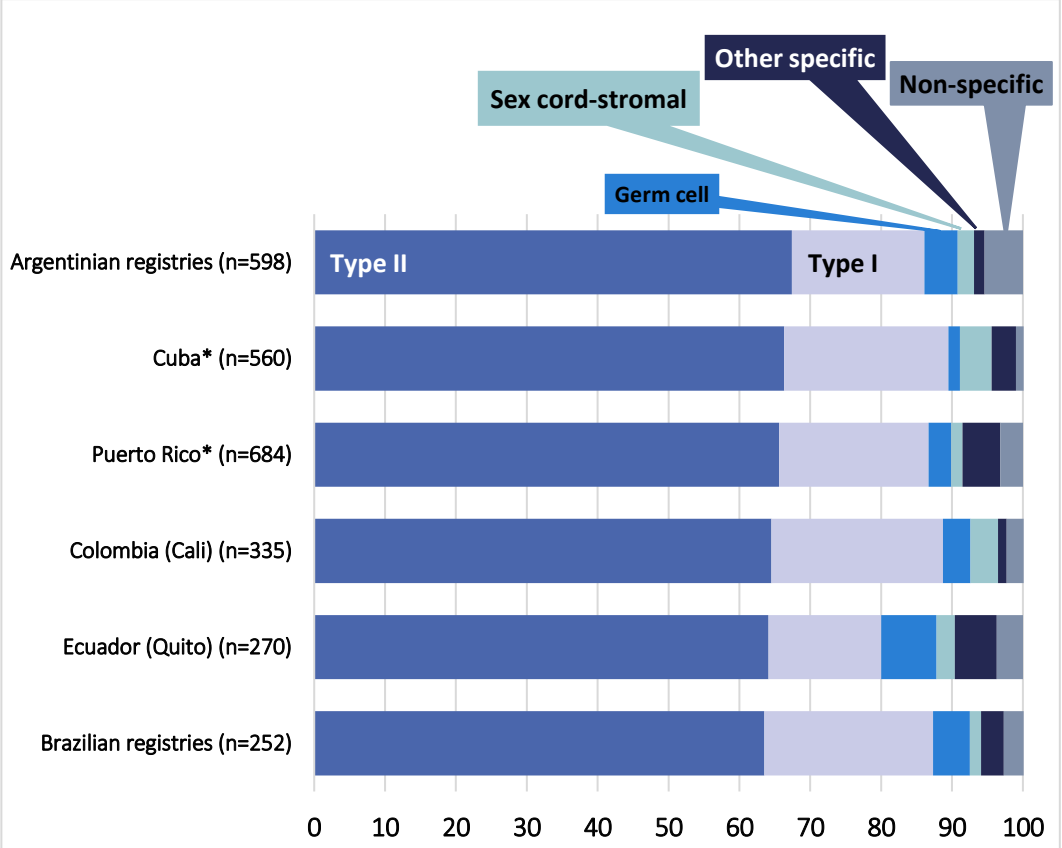
[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Russia (Arkhangelsk)													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	440	76	**17.3**	255	**58.0**	9	**2.0**	61	**13.9**	3	**0.7**	36	**8.2**
2005-09	402	76	**18.9**	202	**50.2**	7	**1.7**	46	**11.4**	-	.	71	**17.7**
Slovakia*													
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	1,983	555	**28.0**	1,243	**62.7**	41	**2.1**	63	**3.2**	56	**2.8**	25	**1.3**
2005-09	1,339	351	**26.2**	868	**64.8**	29	**2.2**	37	**2.8**	44	**3.3**	10	**0.7**
Slovenia*													
1995-99	824	194	**23.5**	567	**68.8**	15	**1.8**	11	**1.3**	33	**4.0**	4	**0.5**
2000-04	911	236	**25.9**	604	**66.3**	18	**2.0**	8	**0.9**	39	**4.3**	6	**0.7**
2005-09	986	256	**26.0**	677	**68.7**	8	**0.8**	7	**0.7**	37	**3.8**	1	**0.1**
Spanish registries													
1995-99	2,728	890	**32.6**	1,591	**58.3**	51	**1.9**	25	**0.9**	138	**5.1**	33	**1.2**
2000-04	2,862	827	**28.9**	1,784	**62.3**	64	**2.2**	21	**0.7**	136	**4.8**	30	**1.0**
2005-09	2,553	674	**26.4**	1,675	**65.6**	49	**1.9**	19	**0.7**	114	**4.5**	22	**0.9**
Swiss registries													
1995-99	1,413	325	**23.0**	1,002	**70.9**	19	**1.3**	18	**1.3**	45	**3.2**	4	**0.3**
2000-04	1,376	285	**20.7**	1,013	**73.6**	24	**1.7**	14	**1.0**	35	**2.5**	5	**0.4**
2005-09	1,581	297	**18.8**	1,172	**74.1**	19	**1.2**	7	**0.4**	82	**5.2**	4	**0.3**

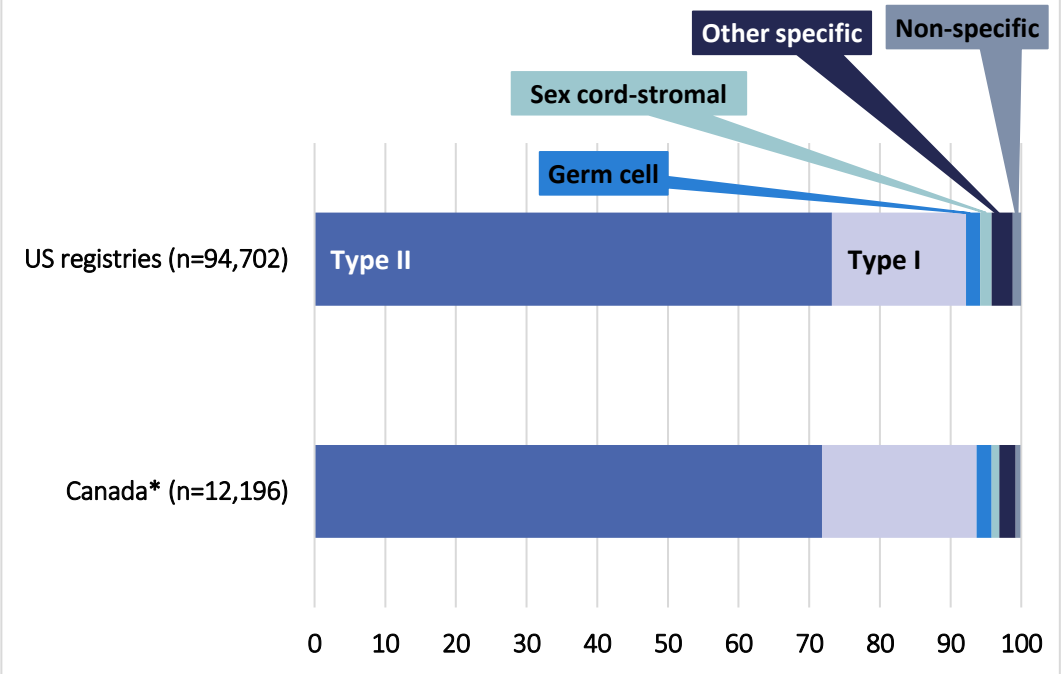
[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

	Total[a]	Type I epithelial[b]		Type II epithelial[c]		Germ cell		Sex cord-stromal		Other specific[d]		Non-specific[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%
United Kingdom*													
1995-99	28,070	6,541	**23.3**	20,273	**72.2**	306	**1.1**	311	**1.1**	397	**1.4**	242	**0.9**
2000-04	29,950	6,371	**21.3**	22,233	**74.2**	330	**1.1**	290	**1.0**	460	**1.5**	266	**0.9**
2005-09	29,700	5,783	**19.5**	22,506	**75.8**	377	**1.3**	288	**1.0**	445	**1.5**	301	**1.0**
OCEANIA													
Australian registries													
1995-99	5,281	1,203	**22.8**	3,757	**71.1**	102	**1.9**	71	**1.3**	130	**2.5**	18	**0.3**
2000-04	5,895	1,161	**19.7**	4,363	**74.0**	145	**2.5**	47	**0.8**	144	**2.4**	35	**0.6**
New Zealand*													
1995-99	1,251	353	**28.2**	789	**63.1**	31	**2.5**	18	**1.4**	26	**2.1**	34	**2.7**
2000-04	1,247	305	**24.5**	838	**67.2**	35	**2.8**	19	**1.5**	38	**3.0**	12	**1.0**
2005-09	1,432	288	**20.1**	1,027	**71.7**	40	**2.8**	11	**0.8**	38	**2.7**	28	**2.0**

[a] Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological groups (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Morphologically verified tumours with ICD-O-3 morphology codes 8000-8004. *100% coverage of the national population.

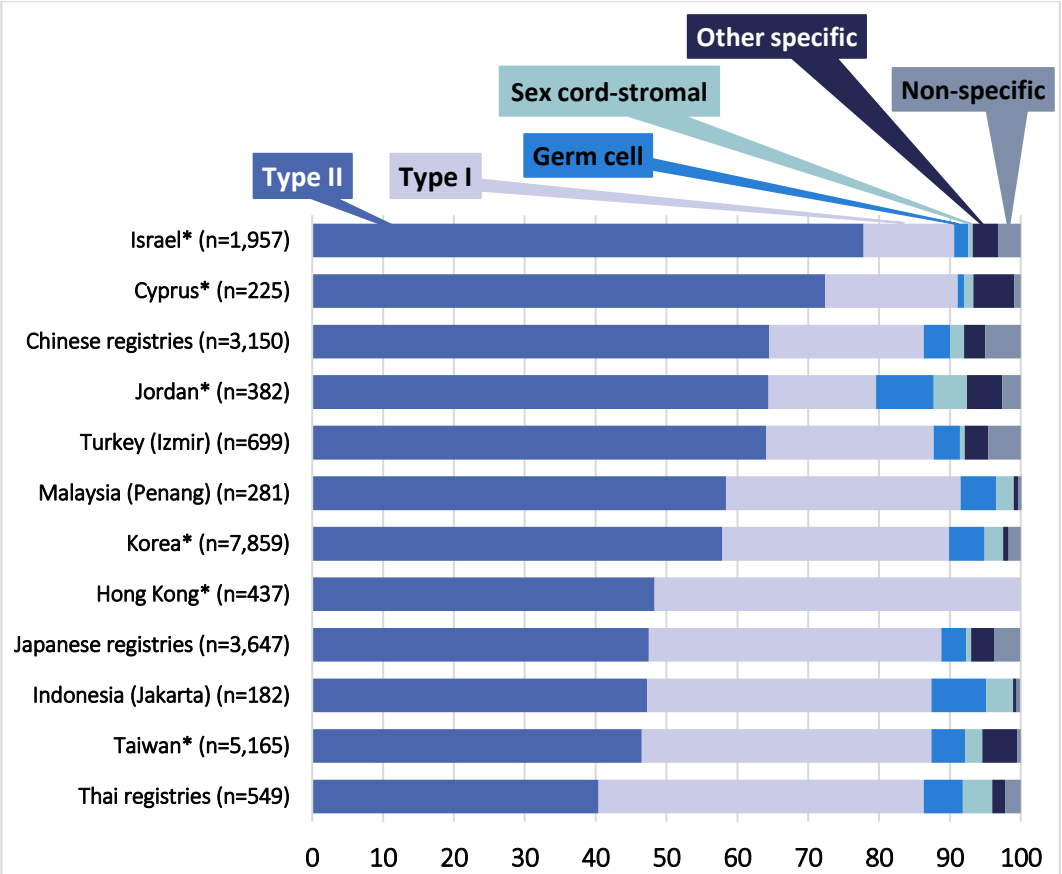


*100% coverage of the national population. N = number of women. Continents are ranked by the proportion of type II epithelial tumours from highest to lowest.

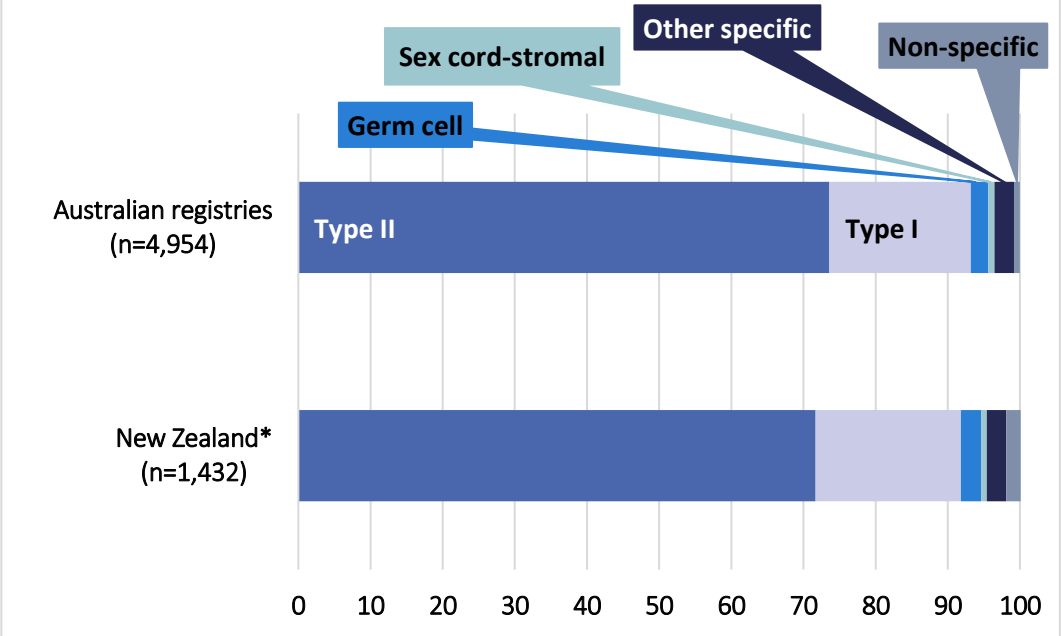


*100% coverage of the national population. N = number of women. Continents are ranked by the proportion of type II epithelial tumours from highest to lowest.

Figure 4.5 Distribution (%) of ovarian cancer histological groups by country (Central and South America and North America), 2005-2009

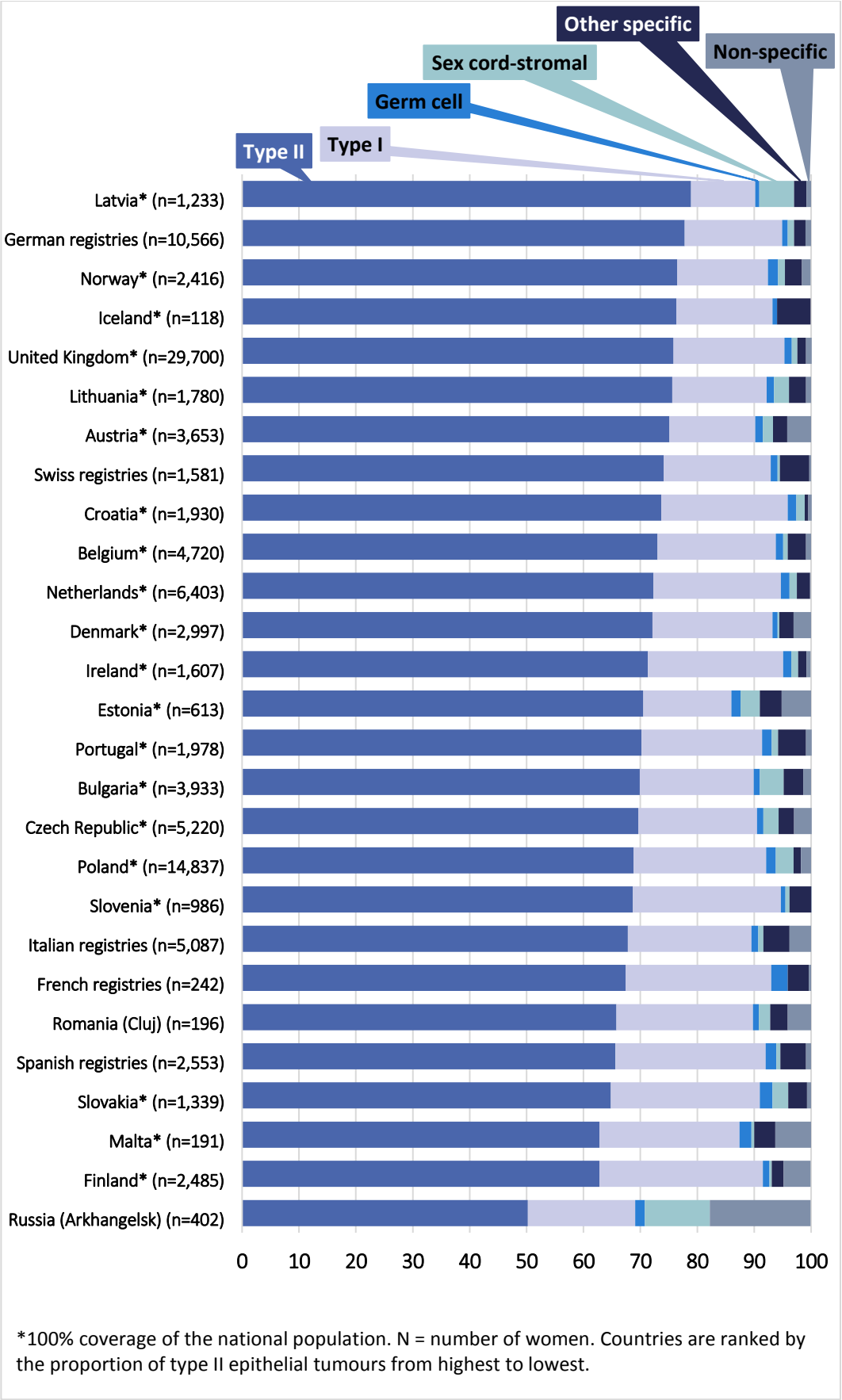


*100% coverage of the national population. N = number of women. Countries are ranked by the proportion of type II epithelial tumours from highest to lowest.



*100% coverage of the national population. N = number of women. Countries are ranked by the proportion of type II epithelial tumours from highest to lowest.

Figure 4.6 Distribution (%) of ovarian cancer histological groups by country (Asia and Oceania), 2005-2009



*100% coverage of the national population. N = number of women. Countries are ranked by the proportion of type II epithelial tumours from highest to lowest.

Figure 4.7 Distribution (%) of ovarian cancer histological groups by country (Europe), 2005-2009

The proportion of type I epithelial tumours decreased slightly over time in all continents except Central and South America [Table 4.5]. The largest decrease was seen in North America from 23.8% in 1995-99 to 19.4% in 2005-2009. Most countries saw decreases in the proportion of type I epithelial tumours, but the proportion increased in a few countries in Central and South America (Cuba and Ecuador), Asia (Japan, Taiwan and Thailand) and Europe (Bulgaria, Croatia, France, Italy, Latvia, Lithuania, Russia and Slovenia). The countries in which the proportion of type I increased often saw corresponding decreases in type II epithelial tumours over time as well, because the proportions of other histological groups remained stable.

Germ cell tumours were uncommon everywhere; during 2005-2009 the proportion in Asia (4.2%) was the highest in any continent, over three times the proportion seen in Europe (1.3%) [Table 4.5]. The proportion of germ cell tumours was similar for all countries during the same period in Europe (1.3%), North America (2.0%) and Oceania (2.5%). However, there was wide variation between countries in Central and South America and Asia. In Central and South America, the lowest proportion (1.6%) was seen in Cuba and the highest (7.8%) in Ecuador [Table 4.6]. Among Asian countries, the variation was wider, with the lowest proportion in Cyprus (0.9%), and the highest in Jordan (8.1%). The proportion of germ cell tumours increased between 1995-1999 and 2005-2009 in Oceania, decreased in Central and South America and Asia and remained constant in North America and Europe [Table 4.5].

Sex cord-stromal tumours were even more uncommon than germ cell tumours. The proportion also varied widely between countries in Asia, Central and South America and Europe. During 2005-2009, the proportion was similar for both countries in North America (1.5%) and in Oceania (0.9%) [Table 4.6]. The widest between-country variation was seen in Europe, with only 0.3% of tumours diagnosed as sex cord-stromal in Denmark, but

11.4% in Russia. In Central and South America, the proportion ranged from 1.6% in Brazil and Puerto Rico to 4.5% in Cuba. The lowest proportion in Asia was in Israel (0.6%), while the highest proportion was in Jordan (4.7%). The proportion of sex cord-stromal tumours remained constant over time in all continents except Oceania, where it decreased slightly from 1.4% in 1995-1999 to 0.9% in 2005-2009.

The highest proportion of tumours coded to other specific non-epithelial histology was in Central and South America during 2005-2009 (3.4%). The proportion was generally less than 5% in all countries, and between-country variation within each continent was small. The widest variation in the proportions was seen in Asia (0.5% in Indonesia and 5.8% in Cyprus) and Europe (0.6% in Croatia and 5.9% in Iceland) [Table 4.6]. In all continents except Central and South America, the proportion of other specific non-epithelial tumours did not change over time. In Central and South America, however, the proportion decreased from 5.5% to 3.4%.

Non-specific tumours generally accounted for 3% or less of ovarian tumours in all countries. During 2005-2009, the highest proportion of these tumours was seen Central and South America (3.1%) [Table 4.5]. At the national level, the variation was much wider. The highest proportion was recorded in Russia (17.7%), much higher than the next highest proportion (Malta, 6.3%). The lowest proportions of non-specific tumours were seen in the Netherlands and Slovenia (0.1%) [Table 4.6]. Tumours of non-specific morphology remained rare and the proportion did not change much over time in all continents, though there was a small decrease from 3.3% to 2.3% in Asia [Table 4.5].

Within the type I epithelial group, the distribution of histological subtypes varied by country, continent and calendar period. Histological subtypes grouped as type II epithelial also varied by country, continent and calendar period. Serous carcinoma was the most common type of epithelial tumour worldwide and in all three calendar periods [Table 4.7].

Table 4.7 Epithelial ovarian cancer subtypes: worldwide distribution (%) by calendar period, 1995-2009, 51 countries

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional cell		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1995-99	192,080	7,063	**3.7**	19,238	**10.0**	17,684	**9.2**	1,022	**0.5**	763	**0.4**	68,980	**35.9**	4,600	**2.4**	58,123	**30.3**
2000-04	240,397	9,705	**4.0**	23,512	**9.8**	18,797	**7.8**	1,227	**0.5**	1,032	**0.4**	94,318	**39.2**	7,170	**3.0**	66,020	**27.5**
2005-09	249,282	11,057	**4.4**	22,151	**8.9**	17,029	**6.8**	1,297	**0.5**	1,297	**0.5**	107,836	**43.3**	10,342	**4.1**	59,072	**23.7**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

The proportion of serous tumours increased over the 15-year period from 35.9% to 43.3%. "Undifferentiated and other epithelial carcinoma" was the second most common subtype, but the proportion decreased over time from 30.3% to 23.7%. Endometrioid tumours were the most common subtype of type I epithelial tumours, and the proportion of these tumours decreased slightly from 10.0% to 8.9% over time. Mucinous tumours comprised 9.2% of the total distribution during 1995-1999, but only 6.8% from 2005 to 2009. The proportion of clear cell tumours, however, increased very slightly over time from 3.7% to 4.4%. There was also an increase in the proportion of mixed epithelial-stromal tumours (2.4% to 4.1%), while the proportions of squamous cell and transitional cell tumours were around 0.5% each and remained stable over time.

Serous carcinoma was the most common epithelial subtype in all continents except Central and South America for all years and Europe during 1995-99 [Table 4.8]. The proportion of serous tumours increased over time, including in Central and South America.

Undifferentiated carcinoma and other epithelial carcinomas decreased over time in all continents: this was the second most common subtype everywhere except in Central and South America, and in Europe from 1995-1999 where it was the most common subtype instead of serous.

In North America, Europe and Oceania the distribution of the epithelial subtypes was similar. After serous and undifferentiated carcinoma, endometrioid and mucinous carcinomas were the next most common subtypes, followed by clear cell, mixed epithelial-stromal, squamous and transitional cell.

The distribution in Asia was slightly different from those in other continents. Mucinous tumours were generally more common in Asia than in other countries and were more common than endometrioid tumours. Over time, the proportions of endometrioid and

Table 4.8 Epithelial ovarian cancer subtypes: distribution (%) by continent and calendar period, 1995-2009

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AMERICA (CENTRAL AND SOUTH)																	
1995-99	1,113	15	**1.3**	106	**9.5**	91	**8.2**	6	**0.5**	2	**0.2**	275	**24.7**	10	**0.9**	435	**39.1**
2000-04	3,278	55	**1.7**	185	**5.6**	292	**8.9**	38	**1.2**	17	**0.5**	849	**25.9**	23	**0.7**	1,337	**40.8**
2005-09	2,699	73	**2.7**	222	**8.2**	236	**8.7**	28	**1.0**	11	**0.4**	815	**30.2**	45	**1.7**	912	**33.8**
AMERICA (NORTH)																	
1995-99	87,459	3,416	**3.9**	9,673	**11.1**	6,931	**7.9**	356	**0.4**	407	**0.5**	35,210	**40.3**	2,669	**3.1**	22,554	**25.8**
2000-04	101,774	4,279	**4.2**	10,588	**10.4**	6,204	**6.1**	452	**0.4**	484	**0.5**	44,428	**43.7**	4,295	**4.2**	23,757	**23.3**
2005-09	106,898	4,632	**4.3**	9,590	**9.0**	5,473	**5.1**	495	**0.5**	520	**0.5**	49,290	**46.1**	7,003	**6.6**	21,782	**20.4**
ASIA																	
1995-99	12,920	729	**5.6**	1,333	**10.3**	1,998	**15.5**	185	**1.4**	79	**0.6**	4,054	**31.4**	157	**1.2**	2,564	**19.8**
2000-04	19,312	1,548	**8.0**	2,007	**10.4**	2,654	**13.7**	224	**1.2**	155	**0.8**	6,567	**34.0**	305	**1.6**	3,370	**17.5**
2005-09	24,533	2,366	**9.6**	2,405	**9.8**	2,666	**10.9**	259	**1.1**	283	**1.2**	9,080	**37.0**	543	**2.2**	4,152	**16.9**
EUROPE																	
1995-99	84,056	2,588	**3.1**	7,579	**9.0**	8,024	**9.5**	440	**0.5**	256	**0.3**	26,657	**31.7**	1,528	**1.8**	31,044	**36.9**
2000-04	108,891	3,468	**3.2**	10,141	**9.3**	9,176	**8.4**	487	**0.4**	353	**0.3**	39,142	**35.9**	2,208	**2.0**	36,026	**33.1**
2005-09	108,766	3,650	**3.4**	9,469	**8.7**	8,256	**7.6**	491	**0.5**	447	**0.4**	45,470	**41.8**	2,465	**2.3**	31,022	**28.5**
OCEANIA																	
1995-99	6,532	315	**4.8**	547	**8.4**	640	**9.8**	35	**0.5**	19	**0.3**	2,784	**42.6**	236	**3.6**	1,526	**23.4**
2000-04	7,142	355	**5.0**	591	**8.3**	471	**6.6**	26	**0.4**	23	**0.3**	3,332	**46.7**	339	**4.7**	1,530	**21.4**
2005-09	6,386	336	**5.3**	465	**7.3**	398	**6.2**	24	**0.4**	36	**0.6**	3,181	**49.8**	286	**4.5**	1,204	**18.9**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

mucinous tumours generally decreased, while the proportion of clear cell and mixed epithelial-stromal tumours increased.

The proportion of squamous and transitional cell tumours were relatively constant over time in all continents [Table 4.8].

The distribution of epithelial subtypes varied between countries within continents [Table 4.9]. The proportion of serous carcinoma was highest in Iceland (60.2%) and lowest in Indonesia (15.9%) during 2005-2009. In Cuba, undifferentiated and other epithelial carcinoma was the most common subtype, where the proportion was the highest worldwide (48.4%). The lowest proportion of undifferentiated and other epithelial carcinoma was seen in Turkey (Izmir) (11.4%) during the same period. The highest proportion of endometrioid tumours was seen in Indonesia (Jakarta) (18.1%), and was nearly eight times as high as the proportion in Latvia (2.4%). Mucinous tumours were more common in East Asian countries, and the highest proportion of these tumours was seen in Thailand (18.0%), while only 3.2% of tumours were of this subtype in Israel. Over 20% of tumours were classified as clear cell carcinoma in Hong Kong, while only 0.2% were this subtype in Jordan. Mixed epithelial tumours were highest in the US (6.6%) and lowest in Latvia (0.1%). The proportions of squamous and transitional tumours were below 2% in all countries.

Continued on page 136

Table 4.9 Epithelial ovarian cancer subtypes: distribution (%) by country and calendar period, 1995-2009

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AMERICA (CENTRAL AND SOUTH)																	
Argentinian registries																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	182	2	**1.1**	11	**6.0**	24	**13.2**	-	.	2	**1.1**	48	**26.4**	1	**0.5**	68	**37.4**
2005-09	598	7	**1.2**	37	**6.2**	62	**10.4**	5	0.8	1	**0.2**	159	**26.6**	7	**1.2**	237	**39.6**
Brazilian registries																	
1995-99	168	4	**2.4**	19	**11.3**	24	**14.3**	2	1.2	-	.	41	**24.4**	1	**0.6**	50	**29.8**
2000-04	434	5	**1.2**	40	**9.2**	46	**10.6**	4	0.9	1	**0.2**	126	**29.0**	1	**0.2**	154	**35.5**
2005-09	252	10	**4.0**	16	**6.3**	33	**13.1**	-	.	1	**0.4**	92	**36.5**	1	**0.4**	67	**26.6**
Colombia (Cali)																	
1995-99	302	5	**1.7**	33	**10.9**	39	**12.9**	1	0.3	-	.	102	**33.8**	3	**1.0**	76	**25.2**
2000-04	337	11	**3.3**	34	**10.1**	37	**11.0**	2	0.6	2	**0.6**	122	**36.2**	2	**0.6**	80	**23.7**
2005-09	335	14	**4.2**	29	**8.7**	36	**10.7**	2	0.6	-	.	120	**35.8**	5	**1.5**	91	**27.2**
Cuba*																	
1995-99	455	4	**0.9**	47	**10.3**	15	**3.3**	3	0.7	2	**0.4**	65	**14.3**	4	**0.9**	251	**55.2**
2000-04	1,464	10	**0.7**	35	**2.4**	109	**7.4**	27	1.8	6	**0.4**	235	**16.1**	7	**0.5**	818	**55.9**
2005-09	560	6	**1.1**	82	**14.6**	28	**5.0**	12	2.1	2	**0.4**	99	**17.7**	1	**0.2**	271	**48.4**
Ecuador (Quito)																	
1995-99	188	2	**1.1**	7	**3.7**	13	**6.9**	-	.	-	.	67	**35.6**	2	**1.1**	58	**30.9**
2000-04	209	4	**1.9**	9	**4.3**	18	**8.6**	-	.	1	**0.5**	64	**30.6**	1	**0.5**	68	**32.5**
2005-09	270	6	**2.2**	13	**4.8**	24	**8.9**	-	.	-	.	89	**33.0**	4	**1.5**	80	**29.6**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Puerto Rico*																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	652	23	**3.5**	56	**8.6**	58	**8.9**	5	0.8	5	**0.8**	254	**39.0**	11	**1.7**	149	**22.9**
2005-09	684	30	**4.4**	45	**6.6**	53	**7.7**	9	1.3	7	**1.0**	256	**37.4**	27	**3.9**	166	**24.3**
AMERICA (NORTH)																	
Canada*																	
1995-99	10,366	492	**4.7**	1,319	**12.7**	910	**8.8**	63	0.6	44	**0.4**	4,519	**43.6**	305	**2.9**	2,035	**19.6**
2000-04	11,347	643	**5.7**	1,275	**11.2**	730	**6.4**	90	0.8	49	**0.4**	5,117	**45.1**	335	**3.0**	2,454	**21.6**
2005-09	12,196	657	**5.4**	1,182	**9.7**	705	**5.8**	77	0.6	55	**0.5**	5,641	**46.3**	768	**6.3**	2,353	**19.3**
US registries																	
1995-99	77,093	2,924	**3.8**	8,354	**10.8**	6,021	**7.8**	293	0.4	363	**0.5**	30,691	**39.8**	2,364	**3.1**	20,519	**26.6**
2000-04	90,427	3,636	**4.0**	9,313	**10.3**	5,474	**6.1**	362	0.4	435	**0.5**	39,311	**43.5**	3,960	**4.4**	21,303	**23.6**
2005-09	94,702	3,975	**4.2**	8,408	**8.9**	4,768	**5.0**	418	0.4	465	**0.5**	43,649	**46.1**	6,235	**6.6**	19,429	**20.5**
ASIA																	
Chinese registries																	
1995-99	131	1	**0.8**	1	**0.8**	28	**21.4**	1	0.8	-	.	27	**20.6**	-	.	49	**37.4**
2000-04	1,139	47	**4.1**	62	**5.4**	105	**9.2**	13	1.1	19	**1.7**	324	**28.4**	18	**1.6**	327	**28.7**
2005-09	3,150	235	**7.5**	189	**6.0**	182	**5.8**	23	0.7	58	**1.8**	1,084	**34.4**	41	**1.3**	906	**28.8**
Cyprus*																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	225	14	**6.2**	13	**5.8**	13	**5.8**	1	0.4	1	**0.4**	103	**45.8**	3	**1.3**	57	**25.3**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hong Kong*																	
1995-99	527	87	**16.5**	90	**17.1**	96	**18.2**	3	0.6	4	**0.8**	146	**27.7**	1	**0.2**	100	**19.0**
2000-04	1,012	193	**19.1**	155	**15.3**	159	**15.7**	3	0.3	12	**1.2**	301	**29.7**	4	**0.4**	185	**18.3**
2005-09	437	89	**20.4**	71	**16.2**	61	**14.0**	1	0.2	4	**0.9**	133	**30.4**	9	**2.1**	69	**15.8**
Indian registries																	
1995-99	391	6	**1.5**	10	**2.6**	28	**7.2**	2	0.5	-	.	79	**20.2**	-	.	173	**44.2**
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
Indonesia (Jakarta)																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	182	14	**7.7**	33	**18.1**	23	**12.6**	3	1.6	-	.	29	**15.9**	1	**0.5**	56	**30.8**
Israel*																	
1995-99	1,690	24	**1.4**	208	**12.3**	89	**5.3**	10	0.6	5	**0.3**	704	**41.7**	30	**1.8**	461	**27.3**
2000-04	1,921	29	**1.5**	191	**9.9**	77	**4.0**	4	0.2	8	**0.4**	959	**49.9**	30	**1.6**	418	**21.8**
2005-09	1,957	27	**1.4**	144	**7.4**	63	**3.2**	6	0.3	11	**0.6**	1,078	**55.1**	15	**0.8**	429	**21.9**
Japanese registries																	
1995-99	1,790	171	**9.6**	140	**7.8**	209	**11.7**	11	0.6	6	**0.3**	550	**30.7**	28	**1.6**	380	**21.2**
2000-04	3,124	434	**13.9**	331	**10.6**	377	**12.1**	21	0.7	13	**0.4**	907	**29.0**	52	**1.7**	614	**19.7**
2005-09	3,647	593	**16.3**	412	**11.3**	440	**12.1**	42	1.2	21	**0.6**	1,033	**28.3**	69	**1.9**	630	**17.3**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Jordan*																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	305	1	**0.3**	18	**5.9**	40	**13.1**	2	0.7	-	.	92	**30.2**	12	**3.9**	92	**30.2**
2005-09	382	2	**0.5**	21	**5.5**	29	**7.6**	5	1.3	1	**0.3**	154	**40.3**	9	**2.4**	83	**21.7**
Korea*																	
1995-99	4,526	164	**3.6**	419	**9.3**	904	**20.0**	116	2.6	45	**1.0**	1,510	**33.4**	70	**1.5**	694	**15.3**
2000-04	6,036	341	**5.6**	549	**9.1**	1,055	**17.5**	118	2.0	69	**1.1**	2,273	**37.7**	101	**1.7**	788	**13.1**
2005-09	7,859	574	**7.3**	691	**8.8**	997	**12.7**	121	1.5	129	**1.6**	3,476	**44.2**	151	**1.9**	923	**11.7**
Malaysia (Penang)																	
1995-99	144	18	**12.5**	16	**11.1**	17	**11.8**	1	0.7	-	.	37	**25.7**	-	.	38	**26.4**
2000-04	220	27	**12.3**	21	**9.5**	44	**20.0**	1	0.5	-	.	40	**18.2**	1	**0.5**	63	**28.6**
2005-09	281	34	**12.1**	32	**11.4**	22	**7.8**	5	1.8	-	.	50	**17.8**	3	**1.1**	111	**39.5**
Saudi Arabia*																	
1995-99	392	1	**0.3**	30	**7.7**	60	**15.3**	3	0.8	1	**0.3**	138	**35.2**	2	**0.5**	94	**24.0**
2000-04	552	10	**1.8**	35	**6.3**	64	**11.6**	5	0.9	4	**0.7**	208	**37.7**	5	**0.9**	122	**22.1**
2005-09	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
Taiwan*																	
1995-99	2,768	222	**8.0**	359	**13.0**	471	**17.0**	28	1.0	18	**0.7**	668	**24.1**	19	**0.7**	490	**17.7**
2000-04	3,998	386	**9.7**	537	**13.4**	579	**14.5**	41	1.0	25	**0.6**	1,108	**27.7**	51	**1.3**	624	**15.6**
2005-09	5,165	690	**13.4**	652	**12.6**	676	**13.1**	43	0.8	51	**1.0**	1,495	**28.9**	187	**3.6**	718	**13.9**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Thai registries																	
1995-99	171	6	**3.5**	6	**3.5**	57	**33.3**	7	4.1	-	.	28	**16.4**	1	**0.6**	41	**24.0**
2000-04	478	50	**10.5**	48	**10.0**	106	**22.2**	12	2.5	2	**0.4**	120	**25.1**	8	**1.7**	72	**15.1**
2005-09	549	63	**11.5**	79	**14.4**	99	**18.0**	6	1.1	5	**0.9**	117	**21.3**	15	**2.7**	90	**16.4**
Turkey (Izmir)																	
1995-99	390	29	**7.4**	54	**13.8**	39	**10.0**	3	0.8	-	.	167	**42.8**	6	**1.5**	44	**11.3**
2000-04	527	30	**5.7**	60	**11.4**	48	**9.1**	4	0.8	3	**0.6**	235	**44.6**	23	**4.4**	65	**12.3**
2005-09	699	31	**4.4**	68	**9.7**	61	**8.7**	3	0.4	2	**0.3**	328	**46.9**	40	**5.7**	80	**11.4**
EUROPE																	
Austria*																	
1995-99	4,331	50	**1.2**	290	**6.7**	295	**6.8**	17	0.4	22	**0.5**	1,161	**26.8**	77	**1.8**	2,049	**47.3**
2000-04	4,180	47	**1.1**	293	**7.0**	236	**5.6**	19	0.5	8	**0.2**	1,255	**30.0**	69	**1.7**	1,844	**44.1**
2005-09	3,653	57	**1.6**	290	**7.9**	176	**4.8**	18	0.5	11	**0.3**	1,254	**34.3**	68	**1.9**	1,422	**38.9**
Belgium*																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	948	37	**3.9**	91	**9.6**	94	**9.9**	3	0.3	3	**0.3**	444	**46.8**	25	**2.6**	184	**19.4**
2005-09	4,720	155	**3.3**	350	**7.4**	430	**9.1**	20	0.4	25	**0.5**	2,539	**53.8**	123	**2.6**	782	**16.6**
Bulgaria*																	
1995-99	2,792	78	**2.8**	101	**3.6**	243	**8.7**	18	0.6	8	**0.3**	832	**29.8**	19	**0.7**	1,194	**42.8**
2000-04	3,368	93	**2.8**	149	**4.4**	421	**12.5**	20	0.6	8	**0.2**	1,174	**34.9**	23	**0.7**	1,126	**33.4**
2005-09	3,933	64	**1.6**	211	**5.4**	486	**12.4**	9	0.2	15	**0.4**	1,571	**39.9**	25	**0.6**	1,154	**29.3**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Croatia*																	
1995-99	771	2	**0.3**	58	**7.5**	71	**9.2**	5	0.6	2	**0.3**	134	**17.4**	1	**0.1**	462	**59.9**
2000-04	1,998	16	**0.8**	227	**11.4**	173	**8.7**	10	0.5	2	**0.1**	558	**27.9**	19	**1.0**	914	**45.7**
2005-09	1,930	51	**2.6**	204	**10.6**	162	**8.4**	6	0.3	5	**0.3**	752	**39.0**	24	**1.2**	646	**33.5**
Czech Republic*																	
1995-99	5,223	91	**1.7**	560	**10.7**	639	**12.2**	30	0.6	19	**0.4**	2,011	**38.5**	46	**0.9**	1,273	**24.4**
2000-04	5,502	97	**1.8**	661	**12.0**	557	**10.1**	35	0.6	16	**0.3**	2,084	**37.9**	70	**1.3**	1,411	**25.6**
2005-09	5,220	112	**2.1**	490	**9.4**	414	**7.9**	43	0.8	31	**0.6**	2,275	**43.6**	107	**2.0**	1,250	**23.9**
Denmark*																	
1995-99	3,068	123	**4.0**	345	**11.2**	300	**9.8**	18	0.6	10	**0.3**	1,238	**40.4**	89	**2.9**	753	**24.5**
2000-04	2,991	137	**4.6**	308	**10.3**	279	**9.3**	16	0.5	10	**0.3**	1,310	**43.8**	75	**2.5**	665	**22.2**
2005-09	2,997	107	**3.6**	260	**8.7**	235	**7.8**	12	0.4	19	**0.6**	1,577	**52.6**	101	**3.4**	483	**16.1**
Estonia*																	
1995-99	792	19	**2.4**	25	**3.2**	83	**10.5**	5	0.6	1	**0.1**	317	**40.0**	5	**0.6**	189	**23.9**
2000-04	710	15	**2.1**	17	**2.4**	82	**11.5**	1	0.1	1	**0.1**	368	**51.8**	9	**1.3**	118	**16.6**
2005-09	613	20	**3.3**	25	**4.1**	42	**6.9**	4	0.7	4	**0.7**	316	**51.5**	4	**0.7**	112	**18.3**
Finland*																	
1995-99	2,325	91	**3.9**	503	**21.6**	295	**12.7**	11	0.5	1	**0.0**	992	**42.7**	46	**2.0**	228	**9.8**
2000-04	2,512	116	**4.6**	480	**19.1**	282	**11.2**	8	0.3	9	**0.4**	1,142	**45.5**	44	**1.8**	245	**9.8**
2005-09	2,485	130	**5.2**	315	**12.7**	249	**10.0**	5	0.2	13	**0.5**	1,283	**51.6**	45	**1.8**	233	**9.4**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
French registries																	
1995-99	2,495	80	**3.2**	225	**9.0**	264	**10.6**	6	0.2	5	**0.2**	1,112	**44.6**	40	**1.6**	572	**22.9**
2000-04	2,870	80	**2.8**	258	**9.0**	253	**8.8**	13	0.5	17	**0.6**	1,351	**47.1**	70	**2.4**	614	**21.4**
2005-09	242	10	**4.1**	35	**14.5**	14	**5.8**	1	0.4	2	**0.8**	109	**45.0**	4	**1.7**	50	**20.7**
German registries																	
1995-99	5,295	82	**1.5**	335	**6.3**	454	**8.6**	24	0.5	17	**0.3**	1,593	**30.1**	89	**1.7**	2,321	**43.8**
2000-04	9,047	163	**1.8**	662	**7.3**	672	**7.4**	34	0.4	43	**0.5**	3,646	**40.3**	183	**2.0**	3,092	**34.2**
2005-09	10,566	199	**1.9**	774	**7.3**	724	**6.9**	62	0.6	50	**0.5**	4,971	**47.0**	204	**1.9**	3,048	**28.8**
Iceland*																	
1995-99	113	3	**2.7**	7	**6.2**	9	**8.0**	1	0.9	1	**0.9**	58	**51.3**	1	**0.9**	27	**23.9**
2000-04	127	9	**7.1**	9	**7.1**	6	**4.7**	-	.	-	.	72	**56.7**	2	**1.6**	20	**15.7**
2005-09	118	1	**0.8**	10	**8.5**	9	**7.6**	-	.	-	.	71	**60.2**	3	**2.5**	16	**13.6**
Ireland*																	
1995-99	1,332	42	**3.2**	104	**7.8**	169	**12.7**	5	0.4	3	**0.2**	485	**36.4**	27	**2.0**	436	**32.7**
2000-04	1,477	78	**5.3**	130	**8.8**	161	**10.9**	4	0.3	2	**0.1**	525	**35.5**	34	**2.3**	484	**32.8**
2005-09	1,607	83	**5.2**	153	**9.5**	134	**8.3**	8	0.5	4	**0.2**	649	**40.4**	59	**3.7**	438	**27.3**
Italian registries																	
1995-99	6,772	153	**2.3**	568	**8.4**	596	**8.8**	44	0.6	23	**0.3**	2,215	**32.7**	109	**1.6**	2,387	**35.2**
2000-04	8,394	229	**2.7**	763	**9.1**	661	**7.9**	45	0.5	26	**0.3**	3,112	**37.1**	215	**2.6**	2,484	**29.6**
2005-09	5,087	152	**3.0**	529	**10.4**	364	**7.2**	37	0.7	22	**0.4**	1,942	**38.2**	122	**2.4**	1,384	**27.2**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Latvia*																	
1995-99	1,219	13	**1.1**	13	**1.1**	35	**2.9**	8	0.7	2	**0.2**	361	**29.6**	1	**0.1**	702	**57.6**
2000-04	1,205	13	**1.1**	25	**2.1**	60	**5.0**	4	0.3	2	**0.2**	363	**30.1**	5	**0.4**	645	**53.5**
2005-09	1,233	23	**1.9**	30	**2.4**	69	**5.6**	10	0.8	7	**0.6**	448	**36.3**	1	**0.1**	524	**42.5**
Lithuania*																	
1995-99	1,630	14	**0.9**	15	**0.9**	38	**2.3**	47	2.9	2	**0.1**	232	**14.2**	12	**0.7**	1,123	**68.9**
2000-04	1,781	29	**1.6**	70	**3.9**	87	**4.9**	15	0.8	2	**0.1**	409	**23.0**	3	**0.2**	1,016	**57.0**
2005-09	1,780	45	**2.5**	121	**6.8**	114	**6.4**	6	0.3	9	**0.5**	812	**45.6**	9	**0.5**	525	**29.5**
Malta*																	
1995-99	149	7	**4.7**	10	**6.7**	33	**22.1**	-	.	-	.	40	**26.8**	4	**2.7**	41	**27.5**
2000-04	197	12	**6.1**	22	**11.2**	26	**13.2**	-	.	-	.	59	**29.9**	-	.	54	**27.4**
2005-09	191	7	**3.7**	22	**11.5**	18	**9.4**	-	.	-	.	51	**26.7**	5	**2.6**	64	**33.5**
Netherlands*																	
1995-99	6,624	266	**4.0**	609	**9.2**	793	**12.0**	18	0.3	28	**0.4**	2,235	**33.7**	153	**2.3**	2,096	**31.6**
2000-04	6,289	285	**4.5**	590	**9.4**	593	**9.4**	15	0.2	25	**0.4**	2,497	**39.7**	168	**2.7**	1,720	**27.3**
2005-09	6,403	311	**4.9**	613	**9.6**	469	**7.3**	15	0.2	29	**0.5**	2,964	**46.3**	150	**2.3**	1,517	**23.7**
Norway*																	
1995-99	2,358	118	**5.0**	247	**10.5**	159	**6.7**	6	0.3	4	**0.2**	1,067	**45.3**	44	**1.9**	528	**22.4**
2000-04	2,506	102	**4.1**	238	**9.5**	186	**7.4**	2	0.1	6	**0.2**	1,163	**46.4**	68	**2.7**	552	**22.0**
2005-09	2,416	85	**3.5**	171	**7.1**	119	**4.9**	8	0.3	2	**0.1**	1,257	**52.0**	44	**1.8**	547	**22.6**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Poland																	
1995-99	3,158	64	**2.0**	281	**8.9**	304	**9.6**	20	0.6	14	**0.4**	949	**30.1**	63	**2.0**	1,165	**36.9**
2000-04	13,114	219	**1.7**	1,561	**11.9**	1,118	**8.5**	48	0.4	71	**0.5**	4,668	**35.6**	136	**1.0**	4,141	**31.6**
2005-09	14,837	263	**1.8**	1,859	**12.5**	1,213	**8.2**	42	0.3	78	**0.5**	5,956	**40.1**	215	**1.4**	4,035	**27.2**
Portugal*																	
1995-99	574	18	**3.1**	39	**6.8**	56	**9.8**	3	0.5	4	**0.7**	174	**30.3**	8	**1.4**	210	**36.6**
2000-04	2,153	63	**2.9**	142	**6.6**	217	**10.1**	29	1.3	3	**0.1**	680	**31.6**	40	**1.9**	777	**36.1**
2005-09	1,978	53	**2.7**	168	**8.5**	166	**8.4**	21	1.1	11	**0.6**	614	**31.0**	54	**2.7**	720	**36.4**
Romania (Cluj)																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2005-09	196	4	**2.0**	21	**10.7**	14	**7.1**	4	2.0	4	**2.0**	102	**52.0**	1	**0.5**	26	**13.3**
Russia (Arkhangelsk)																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	440	12	**2.7**	11	**2.5**	41	**9.3**	4	0.9	8	**1.8**	125	**28.4**	1	**0.2**	129	**29.3**
2005-09	402	7	**1.7**	25	**6.2**	33	**8.2**	3	0.7	8	**2.0**	90	**22.4**	3	**0.7**	109	**27.1**
Slovakia*																	
1995-99	-	-	.	-	.	-	.	-	.	-	.	-	.	-	.	-	.
2000-04	1,983	69	**3.5**	214	**10.8**	261	**13.2**	4	0.2	7	**0.4**	834	**42.1**	18	**0.9**	391	**19.7**
2005-09	1,339	45	**3.4**	156	**11.7**	142	**10.6**	4	0.3	4	**0.3**	606	**45.3**	21	**1.6**	241	**18.0**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Slovenia*																	
1995-99	824	20	**2.4**	119	**14.4**	52	**6.3**	2	0.2	1	**0.1**	344	**41.7**	6	**0.7**	217	**26.3**
2000-04	911	39	**4.3**	134	**14.7**	58	**6.4**	3	0.3	2	**0.2**	429	**47.1**	29	**3.2**	146	**16.0**
2005-09	986	38	**3.9**	151	**15.3**	61	**6.2**	1	0.1	5	**0.5**	526	**53.3**	23	**2.3**	128	**13.0**
Spanish registries																	
1995-99	2,728	140	**5.1**	378	**13.9**	336	**12.3**	26	1.0	10	**0.4**	884	**32.4**	25	**0.9**	682	**25.0**
2000-04	2,862	133	**4.6**	370	**12.9**	297	**10.4**	15	0.5	12	**0.4**	1,044	**36.5**	47	**1.6**	693	**24.2**
2005-09	2,553	143	**5.6**	274	**10.7**	231	**9.0**	5	0.2	21	**0.8**	1,030	**40.3**	59	**2.3**	586	**23.0**
Swiss registries																	
1995-99	1,413	49	**3.5**	115	**8.1**	147	**10.4**	9	0.6	5	**0.4**	644	**45.6**	44	**3.1**	314	**22.2**
2000-04	1,376	45	**3.3**	138	**10.0**	96	**7.0**	3	0.2	3	**0.2**	651	**47.3**	51	**3.7**	311	**22.6**
2005-09	1,581	45	**2.8**	141	**8.9**	88	**5.6**	7	0.4	16	**1.0**	782	**49.5**	48	**3.0**	342	**21.6**
United Kingdom*																	
1995-99	28,070	1,065	**3.8**	2,632	**9.4**	2,653	**9.5**	117	0.4	74	**0.3**	7,579	**27.0**	619	**2.2**	12,075	**43.0**
2000-04	29,950	1,330	**4.4**	2,578	**8.6**	2,259	**7.5**	137	0.5	67	**0.2**	9,179	**30.6**	804	**2.7**	12,250	**40.9**
2005-09	29,700	1,440	**4.8**	2,071	**7.0**	2,080	**7.0**	140	0.5	52	**0.2**	10,923	**36.8**	943	**3.2**	10,640	**35.8**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

		Type I epithelial										Type II epithelial					
	Total[a]	Clear cell		Endometrioid[b]		Mucinous		Squamous		Transitional		Serous[c]		Mixed[d]		Undifferentiated[e]	
	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
OCEANIA																	
Australian registries																	
1995-99	5,281	265	**5.0**	422	**8.0**	482	**9.1**	21	0.4	13	**0.2**	2,347	**44.4**	191	**3.6**	1,219	**23.1**
2000-04	5,895	295	**5.0**	458	**7.8**	380	**6.4**	12	0.2	16	**0.3**	2,788	**47.3**	282	**4.8**	1,293	**21.9**
2005-09	4,954	259	**5.2**	372	**7.5**	309	**6.2**	12	0.2	19	**0.4**	2,482	**50.1**	217	**4.4**	945	**19.1**
New Zealand*																	
1995-99	1,251	50	**4.0**	125	**10.0**	158	**12.6**	14	1.1	6	**0.5**	437	**34.9**	45	**3.6**	307	**24.5**
2000-04	1,247	60	**4.8**	133	**10.7**	91	**7.3**	14	1.1	7	**0.6**	544	**43.6**	57	**4.6**	237	**19.0**
2005-09	1,432	77	**5.4**	93	**6.5**	89	**6.2**	12	0.8	17	**1.2**	699	**48.8**	69	**4.8**	259	**18.1**

[a] Total including non-epithelial tumours. Borderline tumours (ICD-O-3 morphology codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) and those with missing morphology were excluded from the analysis of the distribution of histological subtypes (see text). Only microscopically verified tumours or those with a clinical diagnosis but specific morphology code were included. African countries were not included because fewer than 100 women were available for each calendar period. [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial. [d] Mixed epithelial-stromal tumours. [e] Undifferentiated and other specific epithelial carcinomas.

4.4 Discussion

This is the largest study of the distribution of ovarian cancer histology. It is based on individual patient records from 218 population-based cancer registries in 51 countries. Data were available for 681,759 women, including 249,282 diagnosed between 2005 and 2009. Type II epithelial tumours were the most common histological group in each continent, but the distribution of histological groups varied greatly worldwide, and, to a lesser extent, by time. The distribution was similar in Europe, North America and Oceania, while a much higher proportion of type I epithelial tumours was in Asia.

Tumours of the anatomic ovary were the most common in all continents, but the proportion decreased over time except in Central and South America. The distribution of topographical sub-sites for tumours diagnosed between 2005 and 2009 was largely similar for most continents. The proportion of tumours of the ovary was lower in North America and Oceania (85-86%) than in Asia, Central and South America and Europe (90-93%). The decrease in the proportion of ovarian tumours over time is most likely due to the increasing adoption of guidelines for diagnosing primary peritoneal tumours, which were established in 1993[20,211].

Additionally, there has been improvement in the understanding of the extra-ovarian nature of the development of "ovarian" tumours, including the proposal that serous tubal intraepithelial carcinoma may be a precursor lesion both for high-grade serous ovarian carcinoma and for high-grade serous peritoneal carcinoma[6,12,31-33,212]. Therefore, pathological the examination of the fallopian tubes of high-risk women during prophylactic bilateral salpingo-oophorectomies could explain the increase in the proportion in which the topography was coded to fallopian tube, because serous tubal intraepithelial carcinoma will be diagnosed as a fallopian tube cancer before it has spread to and involved the ovaries, which may require a diagnosis of ovarian cancer based on restrictive guidelines[10,12]. The decrease in the proportion of tumours diagnosed as ovarian

and the corresponding increase in the proportions coded to the peritoneum and fallopian tube may represent an improvement in the accuracy of diagnosing pelvic tumours.

Previous studies of the histological subtypes of ovarian cancer have focused on epithelial tumours, and they have generally been limited to a small number of countries. One meta-analysis included data for 98,099 women from 41 studies published between 1992 and 2012, only 12 of which used data from population-based registries[213]. The results were similar to those found in this study, with type II epithelial tumours more common than type I epithelial tumours.

Some of the variations in the distribution of ovarian cancer histology may be explained by ethnicity. A higher proportion of type II epithelial tumours diagnosed between 2005 and 2009 was reported in Israel (77.8%) than in most other countries. This may be attributable to the fact that a high percentage of the population in Israel is of Jewish ancestry, in whom BRCA1 and BRCA2 gene mutations are more common than in other populations. Serous tumours, which are classified as type II epithelial, are the most common histological subtype among women with BRCA1 and BRCA2 mutations[214]. The proportion of serous carcinoma in Israel was the second highest proportion worldwide.

The proportions of type I and type II epithelial tumours were markedly different between the US and Japan. In Japan, 41.3% of tumours were type I epithelial and 47.5% were type II epithelial, compared to 19.0% and 73.2% in the US. The lower proportion of serous tumours in Japan and other East Asian countries is due in part to the higher proportion of mucinous, clear cell and endometrioid tumours. These differences are most probably due to the higher incidence of endometriosis, a potential pre-cursor of clear cell and endometrioid tumours[215], in East Asian women[216].

The proportion of mucinous tumours varied, ranging from over 10% in most Asian countries to 5-6% in most North American, European and Oceanian countries. The higher

proportion in Japan is not clearly explained. Many tumours classified as mucinous may in fact be metastatic to the ovary from the gastrointestinal tract, including the stomach, which has a high incidence in Asia[23,217]. The reduction in the worldwide proportion of mucinous ovarian cancer from 9.2% in 1995-1999 to 6.8% in 2005-2009 may be partially attributable to more accurate immunohistochemical and imaging assessment, which allows for the exclusion of primary mucinous tumours from a different primary site, particularly those of the gastrointestinal tract. It can otherwise be difficult to differentiate a true primary mucinous ovarian cancer from mucinous tumours that are metastatic to the ovary[218].

Germ cell tumours of the ovary should be considered separately in survival analysis, because they typically have higher survival than epithelial ovarian cancers. The proportion of germ cell tumours was less than 3% in most countries, but in some Asian and Central and South American countries, the proportions were much higher (5-8%). These differences are important, because the incidence of germ cell tumours is highest among young women and survival is usually very high, even when the tumour is diagnosed at an advanced stage, if optimal treatment is achievable[219]. The higher proportion of germ cell tumours in Asia and Central and South America may therefore be due to the younger age profile of populations in these regions.

The proportion of sex cord-stromal tumours was less than 2% in most countries, but much higher in some European countries. These differences are also important in the comparison of survival from all ovarian cancers combined, because survival is much higher for sex cord-stromal tumours than for epithelial ovarian cancers[220]. While sex cord-stromal tumours can occur at any age, incidence is highest among middle-aged women; thus, the higher proportion in some European countries may be due to the age structure of the population.

Variation in the distribution of histological groups of ovarian cancer may impact international comparisons of survival from all ovarian cancers combined if survival in countries with more favourable histological distributions, where more tumours are classified as type I epithelial, germ cell or sex cord-stromal, is compared with survival in countries with higher proportions of type II epithelial tumours. In the main CONCORD-2 analysis[188], age-standardised 5-year survival from all ovarian tumours combined was higher in some East Asian countries than in Europe, North America and Oceania. In Hong Kong, 5-year survival was 52.9% for women diagnosed from 2005 to 2009, much higher than the highest level of survival in Europe (Finland: 44.9%), North America (US: 40.9%) and Oceania (Australia: 37.5%)[188]. The proportion of type I epithelial tumours in Hong Kong (51.7%) was the highest among the 51 countries, and Hong Kong was one of only two countries where type I epithelial tumours were more common than type II epithelial tumours. Thus, the higher survival for all ovarian cancers combined in Hong Kong may be partially explained by the more favourable distribution of histology. A favourable distribution was also seen in Ecuador, with one of the highest proportions of germ cell tumours (7.8%), and age-standardised 5-year survival was 47.0% for all tumours combined[188]. Survival for each histological groups is examined in the next chapter.

For many areas of the world, data from population-based cancer registries are still insufficient to allow meaningful comparisons of ovarian cancer histology. Lack of accurate cancer registration in many areas, and the high proportion of non-specific morphology in many countries, still limits worldwide comparison of survival by histology.

During 2005-2009, the highest proportion of tumours of non-specific morphology was seen in Russia (17.7%), which may explain the low proportion of type II epithelial tumours in the country, because many non-specific tumours will be diagnosed at an advanced stage. In order to classify a tumour as a specific histological subtype, such as serous or

endometrioid, a tissue biopsy or surgical resection is required; thus, histology may not be correctly classified into a specific subtype if the disease is diagnosed at an advanced stage, because surgery may not be performed. In Central and South America, the largest registry (Puerto Rico) provided data only for 684 women, of which 24.3% were recorded as having been diagnosed with undifferentiated or other epithelial carcinoma.

Variation between pathologists in the description of and classification of ovarian tumours into specific histological subtypes may affect the distribution of subtypes within a country, and thus, comparisons of the distributions of subtypes between countries. Various studies conducted from 1984 to 1994 of the reproducibility of the World Health Organization's 1973 histological classification of ovarian tumours[221] showed only moderate levels of reproducibility (kappa statistics of 0.46 to 0.55)[211]. Lower levels of agreement between pathologists about the correct subtype were seen for high-grade carcinomas (serous versus endometrioid), undifferentiated subtypes and mixed subtypes. The WHO classification for ovarian tumours was updated in 1999[222], 2003[19] and 2014[2]. Because tumours diagnosed from 1995 to 2009 were included in the analysis, pathologists could have used either the 1973, 1999 or 2003 criteria to assign a histological subtype to a tumour included in the study. The definitions of the various histological subtypes do not change drastically over time from 1973 to 2003, so the edition used by the pathologist is not necessarily relevant. However, the definitions of the subtypes are general and the 2003 criteria did not include changes or criteria that could improve reproducibility; thus, observer variation remains an issue[211].

Studies of immunohistochemical biomarkers and molecular genetic features for certain histological subtypes may allow for more reproducible diagnoses. TP53 mutations are found in 80% of women diagnosed with high-grade serous carcinoma, while KRAS, BRAF and ERBB2 mutations are more common in women with low-grade serous carcinoma.

Mutations of CTNNB1, PTEN, PIK3CA are common in endometrioid tumours and KRAS mutations can be found in 50% of mucinous tumours. For clear cell carcinoma, mutations or ARID1A and PIK3CA are common[2,10-12]. With this knowledge and the updated WHO classification of 2014, reproducibility of the histological typing of ovarian cancers should improve.

The accuracy of histology data is also reliant upon data transmission to the cancer registries and recording of morphology codes, so the distribution of subtypes may be affected by registry procedures and the classifications in use. For example, in Sweden, only 324 of 12,969 (2.5%) women with ovarian cancer were reported as being diagnosed with a specific morphology, compared with 6,311 of 7,322 women (86.2%) in Finland. Previous reports on ovarian cancer in Sweden showed over 98% specific morphology codes[120]. Therefore, the higher proportion of non-specific morphology in the data submitted by Sweden to the CONCORD-2 study was due to a choice in data submission by the Swedish cancer registry, and thus not an accurate representation of the distribution of histological groups within the country. Additionally, the distribution for Hong Kong included only epithelial tumours, because other ovarian cancer subtypes were not submitted by the registry. While Sweden was excluded from these analyses as a result, Hong Kong was included because comparison of the most common groups, type I and type II epithelial, was still achievable.

In order to classify serous tumours appropriately into histological groups, knowledge of the tumour grade is important. However, data on tumour grade are not routinely collected by cancer registries. For ovarian cancer, most serous carcinomas are high-grade, and will have been correctly classified in our analysis as type II epithelial, but a small proportion are low-grade, and should have been classified as type I epithelial[10-12,14,35,223]. Because the proportion of low-grade serous tumours is small[2], the effect of any

misclassification on the distribution of histology is expected to be minimal. The distinction between high-grade and low-grade serous carcinoma is important, because these subtypes have distinct developmental pathways and are thought to be different diseases[10,12]. Low-grade serous carcinoma is more common in younger women, and is thought to arise from borderline serous tumours. In contrast, high-grade serous carcinoma is more common in older women and is thought to arise from tubal disease[10,12,30]. Similarly, endometrioid tumours are classified as either low- or high-grade, and classification into type I or type II epithelial has previously depended on tumour grade[12]. Most endometrioid ovarian tumours will be low-grade[2], and some pathologists have argued that high-grade endometrioid tumours may not exist[12,14]. Distinguishing between high-grade endometrioid and high-grade serous tumours is difficult, and when distinction between endometrioid and serous tumours is unclear, most high-grade tumours may be classified as high-grade serous, because this subtype is more common than high-grade endometrioid[12,14]. Following an update in 2016 of the original definitions of type I and type II epithelial tumours, all endometrioid tumours should now be categorised as type I, regardless of tumour grade[10]. Future analyses of ovarian cancer survival should, if possible, incorporate a distinction between high- and low-grade serous carcinoma, to reflect the current understanding of ovarian cancer pathogenesis and behaviour, and to classify serous carcinomas appropriately into type I and type II epithelial tumours.

Tumours for which the morphology was coded as simply carcinoma, not otherwise specified (NOS) (ICD-O-3 morphology code 8010), large cell carcinoma, NOS (8012) or adenocarcinoma, NOS (8140) were all categorised as “undifferentiated and other epithelial” tumours, and grouped with type II epithelial tumours. There may be some misclassification of these tumours, because these morphology codes are not specific codes, so classification into type I or type II is difficult. However, carcinoma (NOS), large

cell carcinoma (NOS) and adenocarcinoma (NOS) are treated clinically as if they were high-grade serous carcinomas, which are classified as type II. These three tumour types comprise 20.9% of all tumours included in the analysis.

Only morphologically verified tumours, or those with specific morphologies that implied morphological verification, were included in the analysis. This restriction may affect the distribution of histological subtypes, because the histology of advanced-stage tumours that are not fully investigated may be coded as non-specific or missing. If more advanced-stage tumours are not morphologically verified and therefore excluded from analysis, the distribution of histological groups may appear more favourable than it actually is.

This worldwide study of ovarian cancer histology has identified striking variations in histological distribution, using individual data on 681,759 women from 218 population-based cancer registries in 51 countries. The two main histological groups of ovarian cancer have different prognosis, primarily due to differences in the distribution of stage, sensitivity to chemotherapy and response to surgical resection. International comparisons of ovarian cancer survival should therefore include consideration of histology, to help identify the extent to which the distribution of histological groups contributes to international differences in ovarian cancer survival, which is typically reported for all histological subtypes combined. Registration of both the morphology and the grade of ovarian cancers is important to help categorise these tumours more accurately into histological groups, especially type I and type II epithelial.

Increased support for the development of high-quality population-based cancer registries in low-income countries will improve international comparisons of ovarian cancer survival. To understand further the impact on survival for all ovarian cancers combined, international differences in ovarian cancer survival by histological group are examined in Chapter 5.

Chapter 5: Ovarian cancer survival by histological group

5.1 Introduction

The CONCORD-2 study showed wide variation in 5-year net survival for ovarian cancer among 779,302 women diagnosed during 1995-2009 in 61 countries[188]. While age-standardised survival from ovarian cancer was generally around 30-40% in most countries, there was a wide range from the lowest to the highest survival worldwide. Most international comparisons of ovarian cancer survival include all histological subtypes combined[3,122,188]. The different histological subtypes have unique molecular pathways and treatment, and survival also differs widely, especially for type I and type II epithelial tumours[11-13,15]. This chapter examines patterns of survival for each histological group, in order to gain a better understanding of international differences in ovarian cancer survival.

Type I epithelial tumours include low-grade serous, endometrioid, clear cell, mucinous, squamous and transitional cell (Brenner) carcinomas, while type II epithelial tumours include high-grade serous, undifferentiated and mixed epithelial stromal carcinomas. Type II epithelial tumours account for approximately 70% of all malignant ovarian tumours, while only 22% of ovarian tumours are type I epithelial. Type I epithelial tumours often present at an early stage and have better prognosis than type II epithelial tumours, which typically present at an advanced stage[12]. Germ cell and sex cord-stromal tumours are rarer subtypes of ovarian cancer, but they generally have much better prognosis than type II epithelial tumours.

5.2 Material and methods

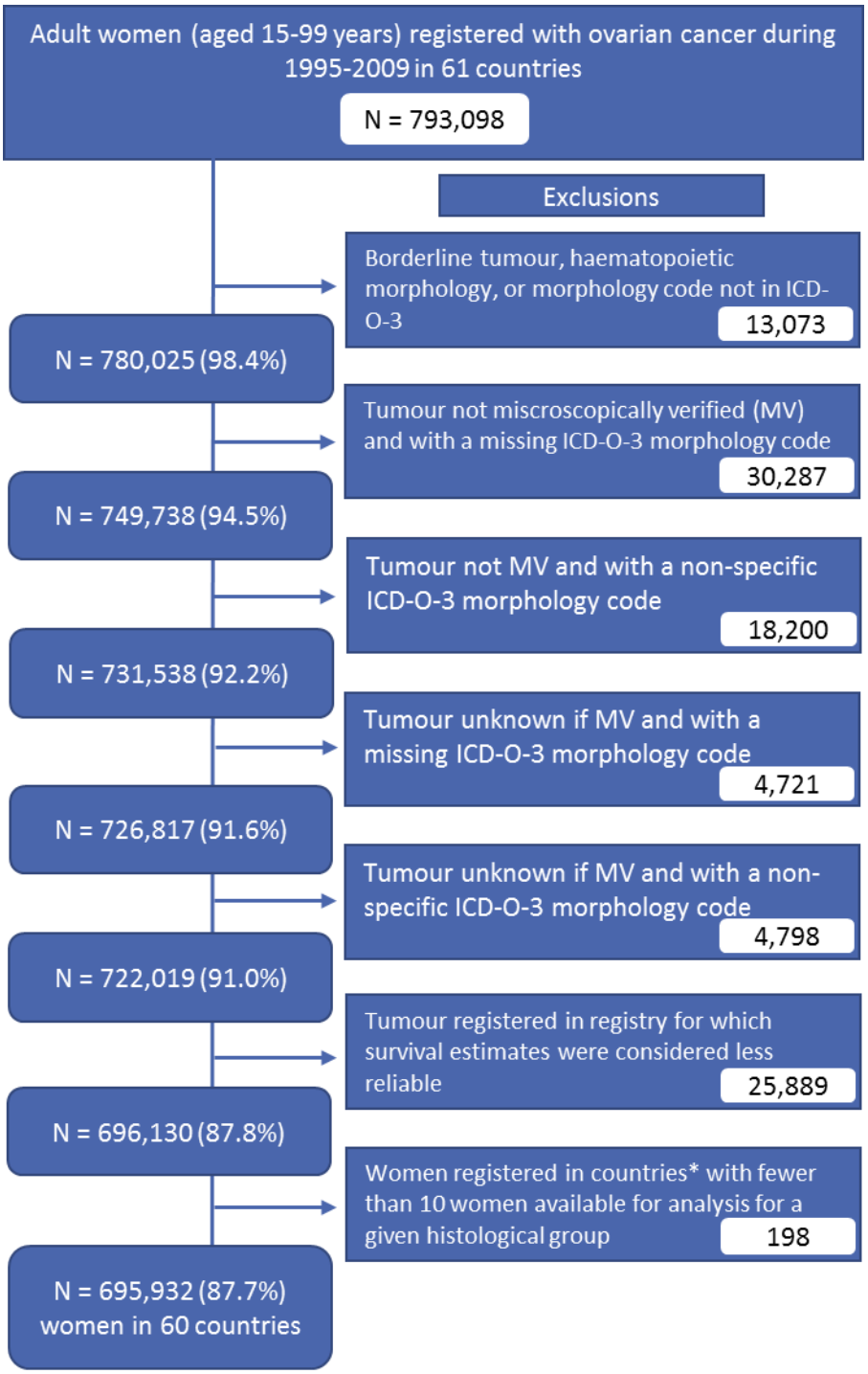
The CONCORD-2 study was based on data for over 25.7 million patients diagnosed with one of 10 common cancers, contributed by 279 population-based cancer registries in 67

countries. The data included 779,302 women diagnosed with ovarian cancer in 61 countries during the 15-year period of 1995 to 2009. The protocol, ethical approvals, quality control procedures and analytic methods for CONCORD-2 have been described elsewhere[188] and in Chapter 3[a].

Data for 793,098 women (aged 15-99 years) diagnosed from 1995 to 2009 with a cancer of the ovary, fallopian tube, uterine ligaments and adnexa, other specified and unspecified female genital organs, peritoneum and retroperitoneum were available for analysis [Figure 5.1]. This number is slightly larger than the number of women included in the analysis for the main CONCORD-2 article, because of a data submission error that was corrected after the analysis for the main article had been completed. Data submitted by Ontario for women diagnosed from 1995 to 2007 did not initially include tumours of the ovary, but included only tumours of the fallopian tube and peritoneum. The registry resubmitted data including all sub-sites for the entire 15-year period, resulting in an increase of 13,796 women.

Recent evidence suggests that high-grade serous carcinoma, the most common type of ovarian cancer, originates in the fallopian tube. Therefore, cancers of the fallopian tube and other specified and unspecified female genital organs were included in a broader definition of ovarian cancer[12]. Similarly, primary peritoneal and retroperitoneal carcinomas are managed in the same way as advanced-stage epithelial ovarian cancer, and they are also included[12]. The term “ovarian” in this chapter refers to tumours at all these sub-sites, unless the context makes clear that it refers to tumours of the anatomic ovary.

[a] The material in Chapters 4-7 is based on examination of the distribution of and survival from ovarian cancer histology, stage at diagnosis and race/ethnicity. A few paragraphs of material and methods are repeated in each of these chapters for ease of reference and to ensure consistency of the descriptions. A detailed definition and description of the data and methods can be found in Chapter 3.



*In Gibraltar, fewer than 10 women were available for each of the histological groups. Gibraltar was thus excluded, so data from n=60 countries were included in the analysis.

Figure 5.1 Data exclusion flow chart for net survival analysis by ovarian cancer histological group, 1995-2009

Follow-up until 31 December 2009 for each woman's vital status was available. Women diagnosed with ovarian cancer as a second or higher-order primary tumour are included in the analysis, in addition to those for whom ovarian cancer was their first cancer. Women whose cancer registration was from a death certificate or autopsy only were excluded, because their true survival time was unknown.

In ICD-O-2, ovarian cystadenomas were coded as invasive, i.e. with a behaviour code of 3. The behaviour code changed, however, from invasive to benign (0) or of borderline malignancy (1) in ICD-O-3, which was introduced in 2000. Due to this change in classification, some women diagnosed with borderline tumours were included in the data submissions. Ovarian cancer registrations were checked to select ICD-O-3 morphologies that are no longer considered to be invasive malignancies, and these tumours were excluded from analysis, even if diagnosed prior to 2000, because their inclusion would inflate survival estimates. Cancer registrations with a haematological morphology (lymphoma or leukaemia) arising in the ovary, fallopian tube, uterine ligaments or adnexa, peritoneum or retroperitoneum were also excluded from the analysis.

Six "histological groups" were defined based on ICD-O-3 codes, the literature[210] and clinical advice: type I epithelial, type II epithelial, germ cell, sex cord-stromal, other specific non-epithelial, and non-specific morphology [Table 5.1]. "Histological subtypes" grouped as type I epithelial included clear cell, endometrioid, mucinous, squamous and transitional cell (Brenner) carcinomas. Serous, mixed epithelial-stromal and "undifferentiated or other classified epithelial carcinomas" were grouped as type II epithelial. Tumours with a non-specific morphology code (8000-8004), or with a code of 9999 (specific to the CONCORD-2 protocol indicating that the morphology code was missing), were analysed separately. Throughout this chapter, "histological group" refers to the broader categories of tumours, each comprising one or more of the "histological

Table 5.1 Ovarian cancer histological groups and subtypes

Histological group[a]	Histological subtype	ICD-O-3 morphology code
Type I epithelial	Clear cell carcinoma	8005, 8310, 8443, 9110
	Endometrioid carcinoma[b]	8380, 8382-8383, 8560, 8570
	Mucinous carcinoma	8470-8471, 8480-8482, 8490
	Squamous carcinoma	8051-8084
	Transitional cell or Brenner carcinoma	8120-8131, 9000
Type II epithelial	Serous carcinoma[c]	8050, 8441, 8450, 8460-8461
	Mixed epithelial-stromal carcinoma	8313, 8323, 8381, 8930-8991, 9010-9030
	Undifferentiated or other epithelial	8010-8015, 8020-8046, 8090-8110, 8140-8231, 8246-8300, 8311-8312, 8314-8322, 8324-8325, 8336-8337, 8341-8375, 8384-8440, 8452-8454, 8500-8551, 8561-8562, 8571-8589
Germ cell	Germ cell	8240-8245, 8330-8335, 8340, 9060-9105, 9380-9523
Sex cord-stromal	Sex cord-stromal	8590-8671, 8810
Other specific non-epithelial	Other specific non-epithelial	8680-8806, 8811-8921, 9040-9055, 9120-9373, 9530-9589
Non-specific	Non-specific	8000-8004

Table presented here for ease of reference (originally presented in Chapter 4, page 81).
[a] Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) were excluded from the analysis of survival by histological group. Tumours with missing morphology codes were analysed separately (see text). [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial.

subtypes". All microscopically verified tumours were included in the analysis. Tumours that were not reported as microscopically verified but for which a specific ICD-O-3 morphology code was available (any valid ICD-O-3 morphology code except 8000-8004) were also included.

Survival from ovarian cancer was estimated by histological group for each country. Only countries with at least 10 women available for any given histological group for all years combined were included in the analysis for that histological group. Registries for which net survival estimates were considered as less reliable in the main CONCORD-2 analysis[188] were also excluded. Data from countries that were included in the analysis of specific histological groups were included in the analysis for non-specific morphology, provided that there were at least 10 women with non-specific tumours available for all years combined. Only four countries were included in the analysis for tumours with a missing morphology code, because most microscopically verified tumours had a known morphology code. If fewer than 50 women were available for survival analysis by histological group in a given calendar period, the data for two or more calendar periods were merged. Overall, 695,932 women (87.7% of the 793,098 eligible) from 60 countries were included in the analysis [Figure 5.1].

Net survival is defined as the probability of survival for cancer patients up to a given point in time after diagnosis (for example, 5 years) if death from cancer were to be the only cause of death. Net survival controls for the background mortality of competing causes of death in a population. Life tables of all-cause mortality rates by single year of age (0-99 years), region, sex, calendar year and, where possible, race were used to control for variations in background mortality. The Pohar Perme estimator of net survival[224], which allows for the fact that competing risks of death increase with age, was used to estimate

net survival. The Pohar Perme estimator was implemented using *stns*[208] in Stata version 14[207]. Standard errors were calculated using the Greenwood method[209].

Net survival is reported for each country and histological group with 95% confidence intervals (CI). Survival by histological group was estimated for three calendar periods of diagnosis: 1995-1999, 2000-2004 and 2005-2009. The cohort approach was used for 1995-1999 and 2000-2004 because five or more years of follow-up were available for all women, while a period approach was used for 2005-2009[a].

Survival for specific histological subtypes was estimated for the three calendar periods for the United States and the United Kingdom separately. The larger number of women included in the data submissions from the US and the UK allowed for more detailed analysis of the specific type I epithelial and type II epithelial subtypes. Registrations from the United States and the United Kingdom comprised over 50% of the data (37.7% from the US and 12.6% from the UK) for all years combined.

Survival for each histological group by topographical sub-site was estimated for each calendar period of diagnosis for the US and the UK separately. Tumours grouped as "fallopian tube" (ICD-O-3 codes C57.0-C57.4, C57.7-C57.9) include those coded to the uterine ligaments and adnexa and other specified and unspecified female genital organs, as well as fallopian tube neoplasms. Tumours grouped as "peritoneal" (ICD-O-3 codes C48.0-C48.2) include tumours of the peritoneum and retroperitoneum. Tumours grouped as "ovarian" include only tumours coded as ovarian (ICD-O-3 code C56.9). This analysis was conducted to determine whether survival varies by sub-site within histological groups.

[a] See Chapter 3 for a more detailed explanation of these methods.

Survival estimates for all ages combined were age-standardised, where possible, with the International Cancer Standard Survival (ICSS) weights for a cancer for which incidence increases with age[206]. Age at diagnosis was categorised into five age groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. If an age-specific estimate could not be produced, or fewer than 10 women were available for analysis in an age group, data for adjacent age groups were pooled and the re-estimated survival was used for both of the original age groups. If two or more age-specific estimates could not be produced, or fewer than 10 women were available for analysis in two or more age groups, then only the unstandardised estimate is reported.

5.3 Results

5.3.1 Histological group by country and calendar period

Data for a total of 695,932 women in 60 countries were available for analysis [Figure 5.1], including 98.3% with a specific morphology, 1.6% with non-specific morphology and 0.1% with missing morphology [Table 5.2]. Most women (488,634, 70.2%) were diagnosed with type II epithelial tumours. The mean age at diagnosis varied between histological groups, ranging from 36 years for germ cell tumours to 66 years for tumours of non-specific morphology.

Type I epithelial

Net survival for women diagnosed with type I epithelial tumours five years after diagnosis was fairly high, generally 40-60% [Figures 5.2 -5.4]. During 2005 to 2009, age-standardised 5-year survival for type I epithelial tumours varied widely, with the highest survival in Hong Kong (82.9%, 95% CI: 72.4-93.4%) and the lowest in Argentina (30.8%, 16.3-45.2%) [Table 5.3].

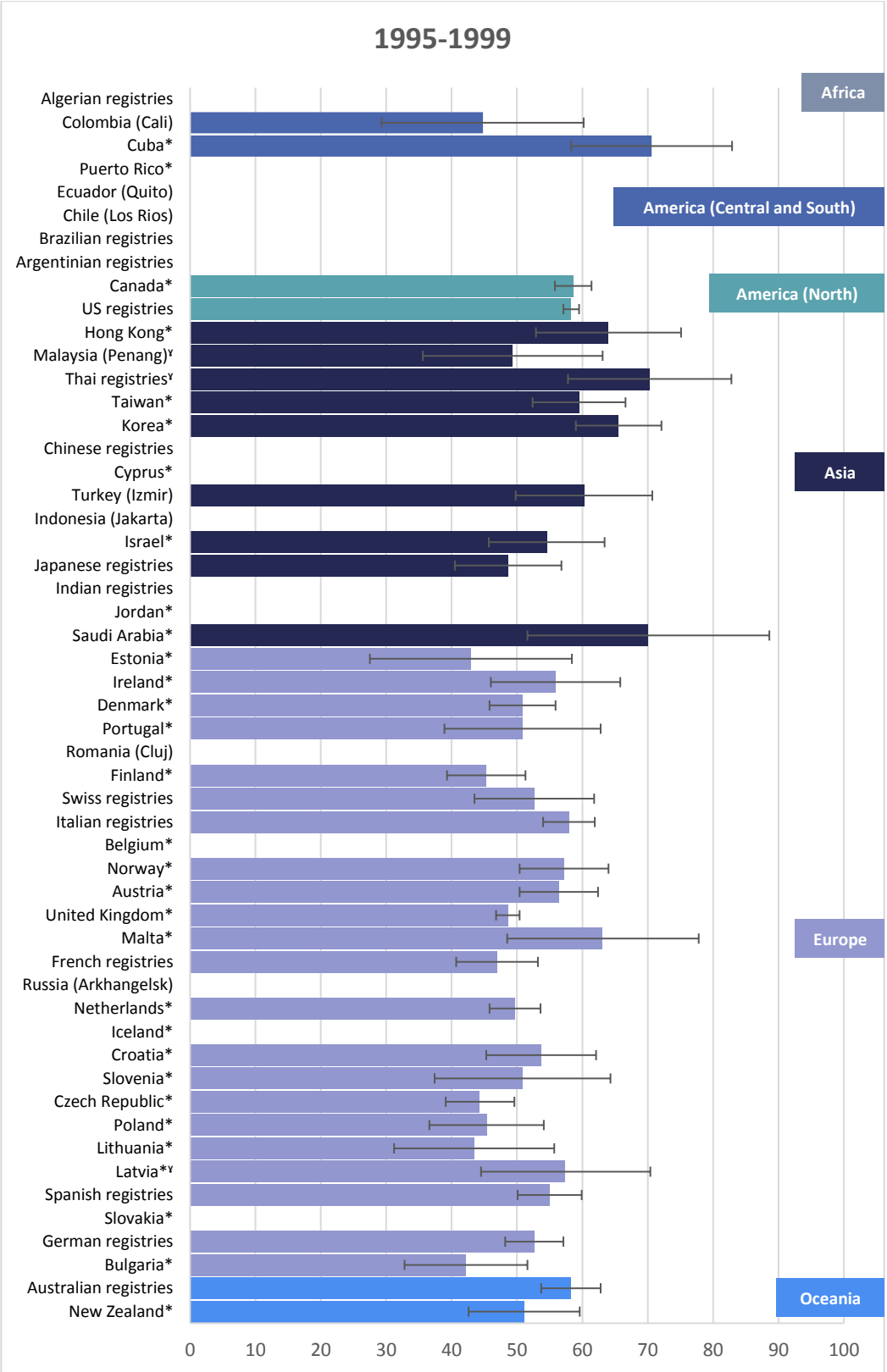
Age-standardised survival from type I epithelial tumours also varied within each continent and over time. The between-country variation in survival was widest in Central and South

Continued on page 163

Table 5.2 Worldwide distribution (%) of ovarian cancer histology and mean age at diagnosis, 1995-2009, 60 countries

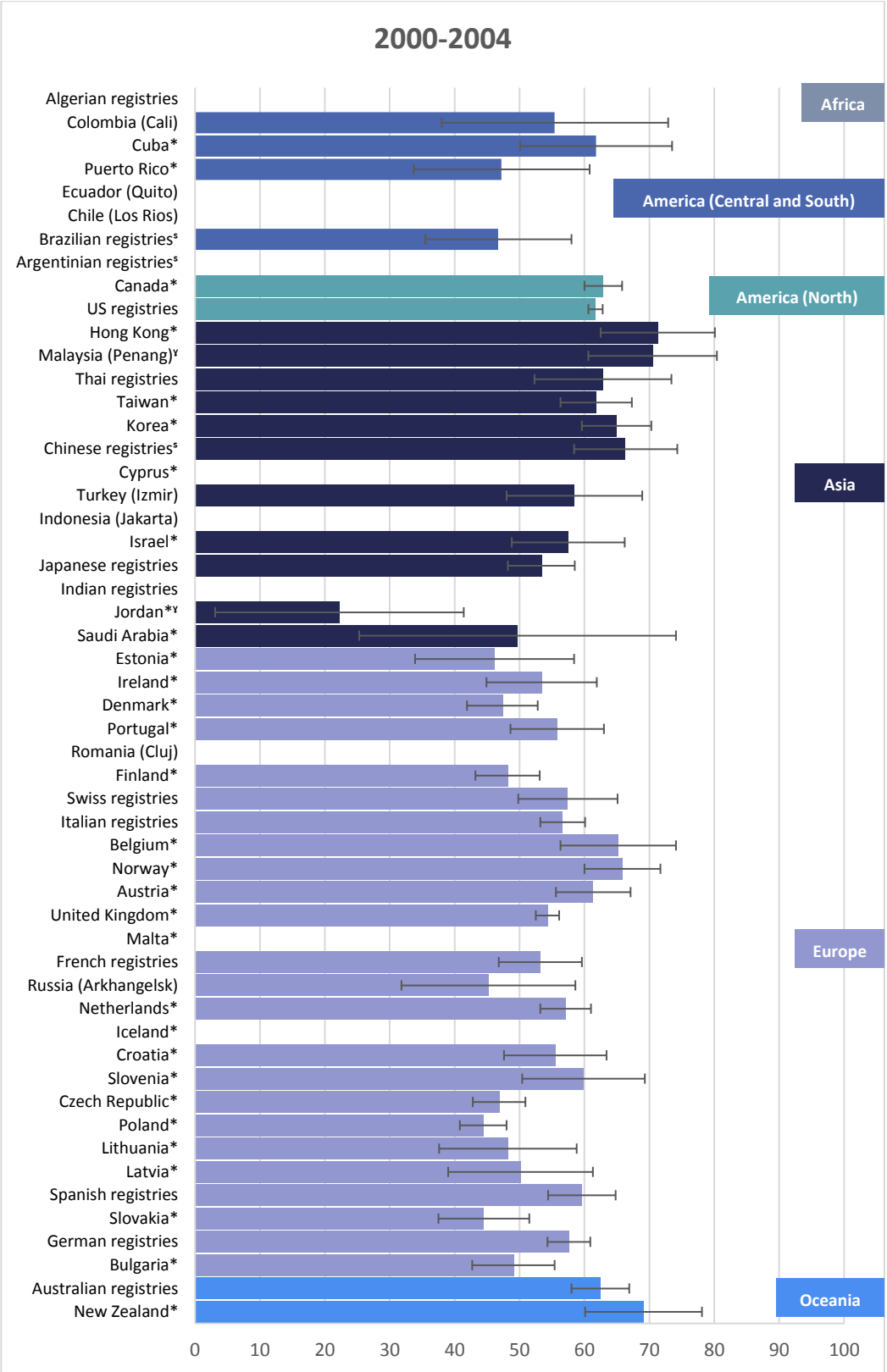
Histological group	No.	%	Mean age (SD)[a] (years)
Type I epithelial[b]	152,970	22.0	58 (14)
Type II epithelial[c]	488,634	70.2	64 (14)
Germ cell	13,306	1.9	36 (18)
Sex cord-stromal	11,430	1.6	54 (16)
Other specific non-epithelial	17,619	2.5	61 (15)
Non-specific tumours	11,282	1.6	66 (17)
Missing morphology	691	0.1	64 (16)
Total	695,932	100.0	62 (15)

[a] Standard deviation. [b] No information on grade was available, therefore all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available, therefore all serous tumours were classified as type II epithelial.



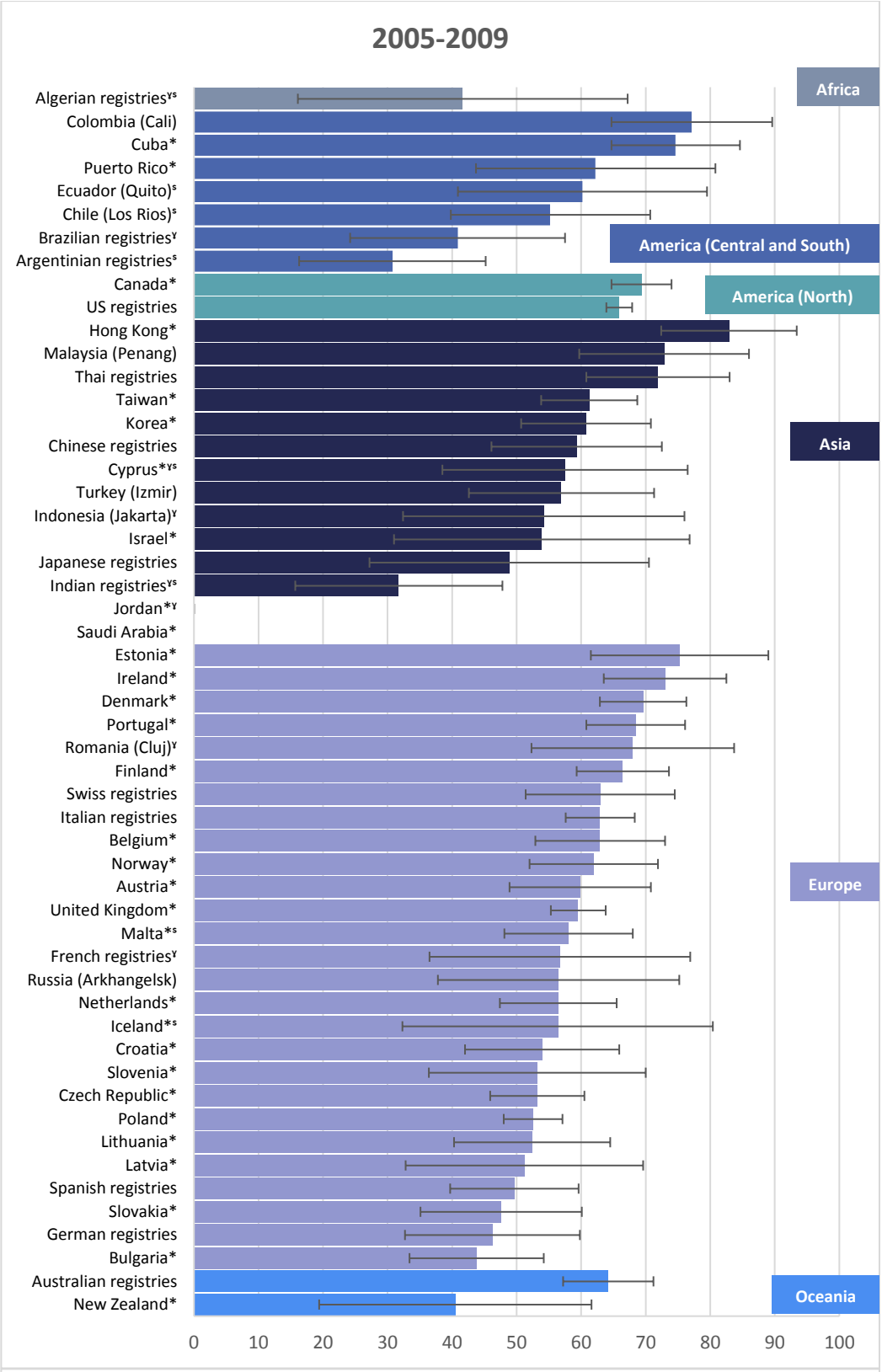
*Data with 100% coverage of the national population. ɣ Estimate not age-standardised. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for women diagnosed in the calendar period of 2005-2009.

Figure 5.2 Five-year age-standardised net survival (%) for type I epithelial tumours, 1995-1999



*Data with 100% coverage of the national population. ¥ Estimate not age-standardised. $ Data for two or more calendar periods of diagnosis have been merged. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for women diagnosed in the calendar period of 2005-2009.

Figure 5.3 Five-year age-standardised net survival (%) for type I epithelial tumours, 2000-2004



*Data with 100% coverage of the national population. [y] Estimate not age-standardised. [s] Data for two or more calendar periods of diagnosis have been merged. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for women diagnosed in the calendar period of 2005-2009.

Figure 5.4 Five-year age-standardised net survival (%) for type I epithelial tumours, 2005-2009

Table 5.3 Five-year age-standardised net survival (NS, %) (95% CI) by histological group (epithelial tumours), country and calendar period, 1995-2009, 60 countries

		Type I epithelial[c]				Type II epithelial[d]			
	No. of registries	No. of patients[e]	NS (%)	95% CI		No. of patients[e]	NS (%)	95% CI	
AFRICA									
Algerian registries									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	2	26	***41.6***	*16.1*	*67.2*	86	***37.1***	*24.6*	*49.5*
Libya (Benghazi)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		44	***5.6***	0.0	13.5
Mauritius*									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		25	***73.9***	52.9	94.8
South Africa (Eastern Cape)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		20	***100.0***	86.1	100.0
Tunisia (Central)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		21	***47.3***	25.0	69.6
AMERICA (CENTRAL AND SOUTH)									
Argentinian registries									
1995-1999	-	-	.	.		-	.	.	
2000-2004	3	-	.	.		117	**19.6**	11.4	27.8
2005-2009	3	151	**30.8**	16.3	45.2	403	**30.5**	21.9	39.2
Brazilian registries									
1995-1999	3	-	.	.		92	**29.1**	15.7	42.5
2000-2004	4	145	**46.7**	35.5	58.0	281	**38.3**	29.6	47.0
2005-2009	4	60	***40.9***	*24.2*	*57.5*	160	**29.2**	17.7	40.7
Chile (Los Rios)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	56	**55.2**	39.8	70.7	75	**18.1**	6.3	29.9

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]					Type II epithelial[d]				
	No. of registries	No. of patients[e]	NS (%)	95% CI			No. of patients[e]	NS (%)	95% CI		
Colombia (Cali)											
1995-1999	1	78	**44.8**	29.3	-	60.2	181	**29.1**	18.2	-	40.0
2000-2004	1	86	**55.4**	38.0	-	72.9	204	**27.1**	21.8	-	32.5
2005-2009	1	81	**77.1**	64.7	-	89.6	216	**32.0**	20.5	-	43.4
Cuba*											
1995-1999	1	71	***70.6***	*58.3*	-	*82.9*	320	**53.4**	45.1	-	61.7
2000-2004	1	187	**61.8**	50.1	-	73.5	1,060	**44.7**	39.9	-	49.5
2005-2009	1	130	**74.6**	64.7	-	84.6	371	**39.2**	29.3	-	49.1
Ecuador (Quito)											
1995-1999	1	-	.		.		127	**35.3**	21.0	-	49.6
2000-2004	1	-	.		.		133	**35.1**	21.6	-	48.7
2005-2009	1	97	**60.2**	40.9	-	79.5	173	**55.0**	44.6	-	65.5
Puerto Rico*											
1995-1999	-	-	.		.		-	.		.	
2000-2004	1	147	**47.2**	33.7	-	60.8	414	**29.5**	23.3	-	35.7
2005-2009	1	144	**62.2**	43.7	-	80.8	449	**36.2**	26.9	-	45.5
AMERICA (NORTH)											
Canada*											
1995-1999	13	2,828	**58.6**	55.8	-	61.4	6,859	**28.0**	26.6	-	29.3
2000-2004	13	2,787	**62.9**	60.0	-	65.8	7,906	**29.8**	28.5	-	31.1
2005-2009	13	2,676	**69.4**	64.7	-	74.0	8,762	**33.7**	30.9	-	36.6
US registries											
1995-1999	34	17,955	**58.3**	57.1	-	59.5	53,574	**33.4**	32.9	-	33.9
2000-2004	38	19,220	**61.7**	60.6	-	62.8	64,574	**34.4**	33.9	-	34.8
2005-2009	38	18,034	**65.9**	63.9	-	67.9	69,313	**36.1**	34.5	-	37.6
ASIA											
Chinese registries											
1995-1999	3	-	.		.		76	**40.5**	27.8	-	53.2
2000-2004	18	277	**66.3**	58.4	-	74.3	669	**41.9**	34.1	-	49.6
2005-2009	19	687	**59.3**	46.1	-	72.5	2,031	**45.0**	38.4	-	51.6
Cyprus*											
1995-1999	-	-	.		.		-	.		.	
2000-2004	-	-	.		.		-	.		.	
2005-2009	1	45	***57.5***	*38.5*	-	*76.5*	195	**42.0**	26.9	-	57.2

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]				Type II epithelial[d]			
	No. of registries	No. of patients[e]	NS (%)	95% CI		No. of patients[e]	NS (%)	95% CI	
Hong Kong*									
1995-1999	1	280	**64.0**	52.9	75.1	247	**26.0**	16.8	35.3
2000-2004	1	522	**71.3**	62.5	80.1	490	**33.0**	26.9	39.0
2005-2009	1	226	**82.9**	72.4	93.4	211	**61.5**	54.8	68.2
Indian registries									
1995-1999	2	-	.	.		252	**22.4**	13.0	31.9
2000-2004	-	-	.	.		-	.	.	
2005-2009	2	57	***31.7***	*15.7*	*47.8*	54	***21.6***	*7.4*	*35.8*
Indonesia (Jakarta)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	73	***54.2***	*32.4*	*76.0*	86	.	.	
Israel*									
1995-1999	1	336	**54.6**	45.7	63.4	1,195	**35.6**	31.4	39.8
2000-2004	1	309	**57.5**	48.8	66.2	1,407	**36.1**	32.0	40.1
2005-2009	1	251	**53.9**	31.0	76.8	1,522	**28.4**	11.3	45.4
Japanese registries									
1995-1999	2	537	**48.7**	40.5	56.8	958	**26.2**	21.1	31.2
2000-2004	6	1,176	**53.4**	48.2	58.5	1,573	**30.5**	26.9	34.1
2005-2009	8	1,508	**48.9**	27.2	70.5	1,732	**37.0**	32.0	41.9
Jordan*									
1995-1999	-	-	.	.		-	.	.	
2000-2004	1	61	***22.2***	*3.1*	*41.4*	196	**18.3**	6.4	30.3
2005-2009	1	58	***0.0***	*0.0*	*0.0*	246	***0.0***	*0.0*	*0.0*
Korea*									
1995-1999	1	1,648	**65.5**	59.0	72.1	2,274	**37.9**	33.3	42.4
2000-2004	1	2,132	**64.9**	59.6	70.3	3,162	**37.7**	33.5	42.0
2005-2009	1	2,512	**60.8**	50.7	70.8	4,550	**39.5**	33.8	45.1
Malaysia (Penang)									
1995-1999	1	52	***49.3***	*35.6*	*63.1*	75	**52.4**	38.0	66.7
2000-2004	1	93	***70.5***	*60.6*	*80.4*	104	**27.5**	14.3	40.7
2005-2009	1	93	**72.9**	59.7	86.0	164	**47.3**	31.6	63.1
Mongolia*									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		52	***68.3***	*51.2*	*85.3*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]				Type II epithelial[d]			
	No. of registries	No. of patients[e]	NS (%)	95% CI		No. of patients[e]	NS (%)	95% CI	
Qatar*									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	-	.	.		22	***31.9***	*6.7* -	*57.1*
Saudi Arabia*									
1995-1999	1	95	**70.1**	51.6 -	88.6	234	**42.9**	23.2 -	62.5
2000-2004	1	118	**49.7**	25.3 -	74.1	336	**31.9**	16.9 -	46.9
2005-2009	-	-	.	.		-	.	.	
Taiwan*									
1995-1999	1	1,098	**59.5**	52.4 -	66.6	1,177	**35.0**	29.2 -	40.7
2000-2004	1	1,568	**61.8**	56.3 -	67.3	1,783	**35.8**	31.3 -	40.3
2005-2009	1	2,112	**61.3**	53.8 -	68.7	2,400	***35.3***	*12.3* -	*58.3*
Thai registries									
1995-1999	1	76	***70.3***	*57.8* -	*82.8*	70	***45.1***	*31.3* -	*59.0*
2000-2004	3	218	**62.9**	52.3 -	73.4	200	**32.1**	18.0 -	46.1
2005-2009	3	252	**71.9**	60.8 -	83.0	222	**44.4**	35.2 -	53.6
Turkey (Izmir)									
1995-1999	1	125	**60.3**	49.8 -	70.7	217	**40.5**	31.8 -	49.2
2000-2004	1	145	**58.4**	48.0 -	68.9	323	**39.3**	27.8 -	50.8
2005-2009	1	165	**56.9**	42.6 -	71.3	448	**31.2**	11.2 -	51.3
EUROPE									
Austria*									
1995-1999	2	674	**56.4**	50.4 -	62.4	3,287	**39.6**	37.1 -	42.0
2000-2004	2	603	**61.3**	55.6 -	67.1	3,168	**36.7**	34.5 -	39.0
2005-2009	2	552	**59.9**	48.9 -	70.8	2,744	**40.0**	36.0 -	44.1
Belgium*									
1995-1999	-	-	.	.		-	.	.	
2000-2004	1	228	**65.2**	56.3 -	74.1	653	**35.8**	31.1 -	40.6
2005-2009	1	980	**62.9**	52.9 -	73.0	3,444	**35.4**	31.3 -	39.4
Bulgaria*									
1995-1999	1	448	**42.2**	32.8 -	51.6	2,045	**30.2**	25.6 -	34.9
2000-2004	1	691	**49.1**	42.7 -	55.4	2,323	**33.9**	30.2 -	37.7
2005-2009	1	785	**43.8**	33.4 -	54.2	2,750	**32.6**	23.8 -	41.3
Croatia*									
1995-1999	1	138	**53.7**	45.3 -	62.1	597	**35.7**	28.9 -	42.5
2000-2004	1	428	**55.5**	47.6 -	63.4	1,491	**33.4**	29.3 -	37.5
2005-2009	1	428	**54.0**	42.0 -	65.9	1,422	**28.1**	20.2 -	35.9

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]				Type II epithelial[d]			
	No. of registries	No. of patients[e]	NS (%)	95% CI		No. of patients[e]	NS (%)	95% CI	
Czech Republic*									
1995-1999	1	1,339	**44.3**	39.1	49.6	3,330	**30.8**	28.0	33.5
2000-2004	1	1,366	**46.9**	42.8	50.9	3,565	**32.9**	30.4	35.5
2005-2009	1	1,090	**53.2**	45.9	60.5	3,632	**40.4**	36.7	44.1
Denmark*									
1995-1999	1	796	**50.8**	45.8	55.9	2,080	**23.9**	21.3	26.5
2000-2004	1	750	**47.4**	41.9	52.8	2,050	**28.4**	25.6	31.3
2005-2009	1	633	**69.6**	62.9	76.3	2,161	**30.1**	23.2	37.0
Estonia*									
1995-1999	1	133	**43.0**	27.5	58.4	511	**26.0**	18.6	33.4
2000-2004	1	116	**46.2**	33.9	58.4	495	**32.9**	26.2	39.5
2005-2009	1	95	**75.3**	61.5	89.0	432	**31.2**	22.5	39.8
Finland*									
1995-1999	1	901	**45.3**	39.3	51.3	1,266	**38.7**	34.9	42.5
2000-2004	1	895	**48.2**	43.2	53.1	1,431	**40.1**	36.2	44.0
2005-2009	1	712	**66.4**	59.3	73.6	1,561	**46.3**	40.9	51.7
French registries									
1995-1999	10	580	**47.0**	40.7	53.2	1,724	**28.9**	25.7	32.1
2000-2004	10	621	**53.2**	46.8	59.6	2,035	**35.8**	33.2	38.4
2005-2009	10	62	***56.7***	*36.5*	*76.9*	163	**24.8**	9.0	40.7
German registries									
1995-1999	4	912	**52.7**	48.2	57.1	4,003	**34.0**	31.9	36.0
2000-2004	8	1,574	**57.6**	54.3	60.9	6,921	**36.6**	35.1	38.1
2005-2009	8	1,809	**46.3**	32.7	59.8	8,223	**35.4**	32.3	38.5
Iceland*									
1995-1999	1	-	.		.	86	**21.1**	9.8	32.4
2000-2004	1	-	.		.	94	**30.6**	15.5	45.7
2005-2009	1	65	**56.4**	32.3	80.4	90	***41.5***	*26.9*	*56.1*
Ireland*									
1995-1999	1	323	**55.9**	46.0	65.8	948	**21.9**	17.9	25.9
2000-2004	1	375	**53.4**	44.9	61.9	1,043	**24.7**	20.8	28.6
2005-2009	1	382	**73.0**	63.5	82.5	1,146	**25.7**	13.0	38.3
Italian registries									
1995-1999	25	1,384	**58.0**	54.0	61.9	4,711	**33.2**	31.3	35.1
2000-2004	30	1,724	**56.6**	53.2	60.1	5,811	**36.1**	34.3	37.9
2005-2009	30	1,104	**62.9**	57.6	68.3	3,448	**38.4**	32.5	44.2

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]				Type II epithelial[d]			
	No. of registries	No. of patients[e]	NS (%)	95% CI		No. of patients[e]	NS (%)	95% CI	
Latvia*									
1995-1999	1	71	***57.4***	*44.5*	*70.4*	1,064	**34.8**	28.9	40.7
2000-2004	1	104	**50.2**	39.0	61.3	1,013	**37.5**	32.4	42.5
2005-2009	1	139	**51.2**	32.8	69.6	973	**34.8**	26.6	43.0
Lithuania*									
1995-1999	1	116	**43.5**	31.2	55.7	1,367	**31.7**	27.6	35.8
2000-2004	1	203	**48.2**	37.6	58.8	1,428	**29.2**	25.5	33.0
2005-2009	1	295	**52.4**	40.3	64.5	1,346	**25.3**	14.5	36.1
Malta*									
1995-1999	1	50	**63.1**	48.5	77.8	85	***26.0***	*16.4*	*35.6*
2000-2004	1	-	.	.		113	**32.2**	22.4	42.0
2005-2009	1	107	**58.0**	48.1	68.0	120	***29.7***	*18.7*	*40.7*
Netherlands*									
1995-1999	1	1,714	**49.7**	45.8	53.6	4,484	**27.7**	25.8	29.5
2000-2004	1	1,508	**57.1**	53.2	61.0	4,385	**29.1**	27.4	30.9
2005-2009	1	1,437	**56.4**	47.4	65.5	4,631	**28.1**	19.0	37.1
Norway*									
1995-1999	1	534	**57.2**	50.4	64.0	1,639	**29.2**	26.2	32.3
2000-2004	1	534	**65.8**	60.0	71.7	1,783	**33.8**	30.9	36.7
2005-2009	1	385	**61.9**	52.0	71.9	1,848	**34.2**	28.4	40.0
Poland*									
1995-1999	4	683	**45.4**	36.6	54.1	2,177	**30.9**	27.1	34.7
2000-2004	5	3,017	**44.4**	40.8	48.0	8,945	**31.3**	29.4	33.1
2005-2009	5	3,455	**52.5**	48.0	57.1	10,206	**31.3**	28.1	34.5
Portugal*									
1995-1999	1	120	**50.8**	38.9	62.8	392	**30.0**	23.7	36.4
2000-2004	4	454	**55.8**	48.6	63.0	1,497	**35.5**	31.9	39.1
2005-2009	4	419	**68.4**	60.8	76.1	1,388	**36.3**	29.0	43.6
Romania (Cluj)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.	
2005-2009	1	47	***68.0***	*52.3*	*83.7*	129	**49.7**	33.8	65.7
Russia (Arkhangelsk)									
1995-1999	-	-	.	.		-	.	.	
2000-2004	1	76	**45.2**	31.8	58.6	255	**23.7**	12.4	34.9
2005-2009	1	76	**56.5**	37.8	75.2	202	**32.3**	17.0	47.7

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Type I epithelial[c]			Type II epithelial[d]		
	No. of registries	No. of patients[e]	NS (%)	95% CI	No. of patients[e]	NS (%)	95% CI
Slovakia*							
1995-1999	-	-	.	.	-	.	.
2000-2004	1	555	**44.5**	37.5 - 51.5	1,243	**30.8**	26.6 - 35.1
2005-2009	1	351	**47.6**	35.1 - 60.1	868	**29.5**	23.8 - 35.1
Slovenia*							
1995-1999	1	194	**50.9**	37.4 - 64.3	567	**27.8**	22.6 - 33.0
2000-2004	1	236	**59.8**	50.4 - 69.3	604	**30.4**	25.0 - 35.9
2005-2009	1	256	**53.2**	36.4 - 70.0	677	**30.3**	21.8 - 38.8
Spanish registries							
1995-1999	10	890	**55.0**	50.1 - 59.9	1,591	**28.5**	25.1 - 31.9
2000-2004	10	827	**59.6**	54.4 - 64.8	1,784	**31.9**	28.8 - 35.1
2005-2009	10	674	**49.7**	39.7 - 59.6	1,675	**35.7**	31.2 - 40.3
Sweden*							
1995-1999	1	-	.	.	4,062	**40.3**	38.3 - 42.3
2000-2004	1	-	.	.	3,950	**41.1**	39.0 - 43.2
2005-2009	1	-	.	.	3,729	**35.0**	26.7 - 43.3
Swiss registries							
1995-1999	7	325	**52.7**	43.5 - 61.8	1,002	**28.9**	24.7 - 33.0
2000-2004	7	285	**57.4**	49.8 - 65.1	1,013	**31.7**	28.0 - 35.4
2005-2009	8	297	**63.0**	51.4 - 74.5	1,172	**38.0**	32.3 - 43.7
United Kingdom*							
1995-1999	12	6,541	**48.6**	46.8 - 50.4	20,273	**21.6**	20.8 - 22.3
2000-2004	12	6,371	**54.3**	52.5 - 56.1	22,233	**22.7**	22.0 - 23.4
2005-2009	12	5,783	**59.5**	55.3 - 63.8	22,506	**25.0**	23.6 - 26.5
OCEANIA							
Australian registries							
1995-1999	6	1,203	**58.3**	53.7 - 62.8	3,757	**29.3**	27.3 - 31.2
2000-2004	6	1,161	**62.5**	58.0 - 66.9	4,363	**30.2**	28.4 - 32.0
2005-2009	6	971	**64.2**	57.2 - 71.2	3,644	**31.2**	25.5 - 36.8
New Zealand*							
1995-1999	1	353	**51.1**	42.6 - 59.6	789	**23.8**	19.8 - 27.8
2000-2004	1	305	**69.1**	60.1 - 78.1	838	**23.9**	20.3 - 27.6
2005-2009	1	288	**40.5**	19.4 - 61.6	1,027	**23.4**	14.3 - 32.6

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Endometrioid tumours are defined as type I epithelial. [d] Serous tumours are defined as type II epithelial. [e] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

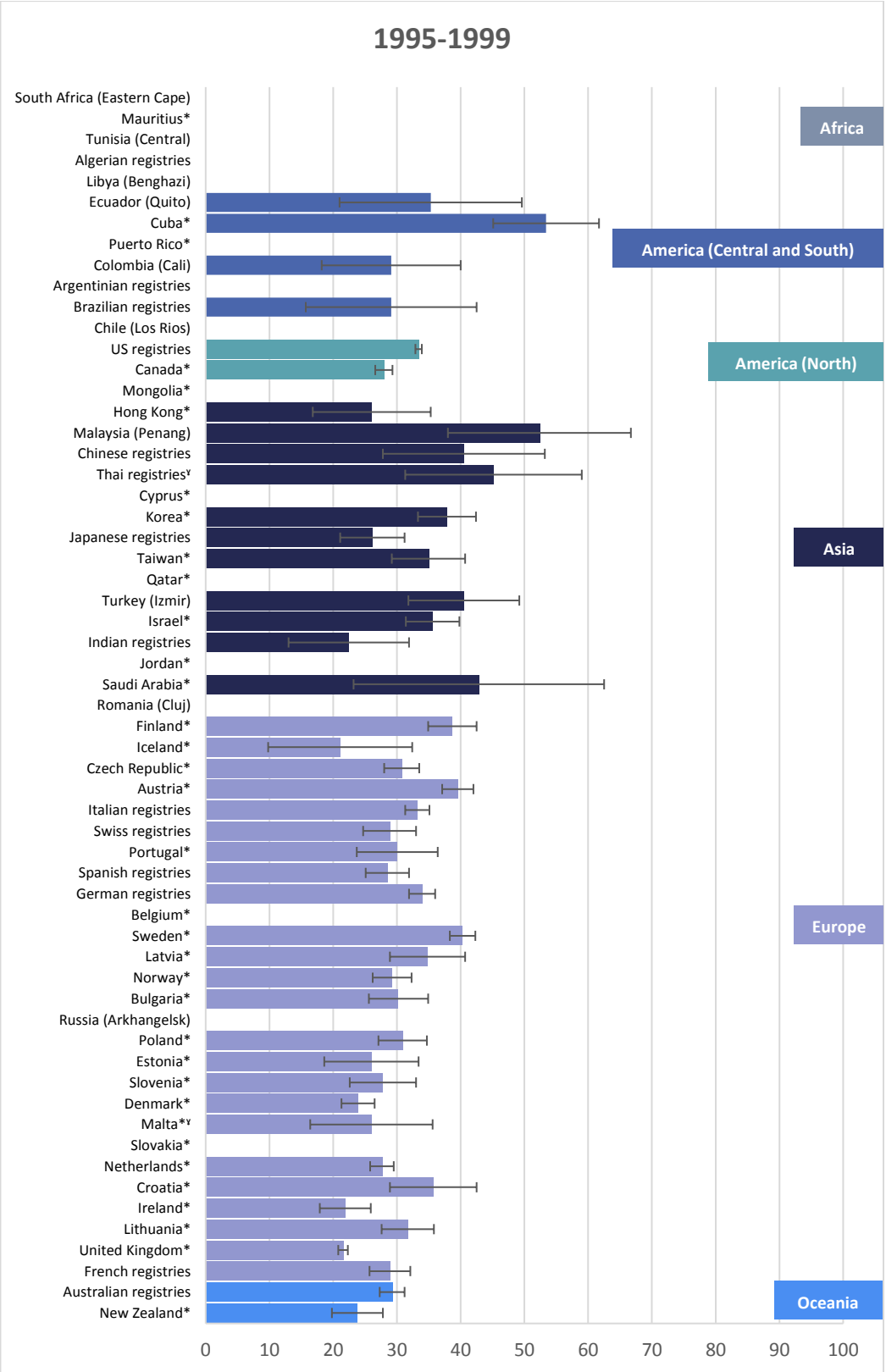
America (from 30.8% (16.3-45.2%) in Argentina to 77.1% (64.7-89.6%) in Colombia) for women diagnosed during 2005-2009. In Central and South America and North America age-standardised net survival from type I tumours increased over time in all countries for which data were available. In Asia, Europe, and Oceania, most countries saw an improvement in survival from type I tumours, but survival actually fell over time for some countries in these regions (from 66.3% to 59.3% in China, 52.7% to 46.3% in Germany and 51.1% to 40.5% in New Zealand) [Table 5.3].

Type II epithelial

Survival from type II epithelial tumours five years after diagnosis was lower than that of type I epithelial tumours, around only 20-40% [Figures 5.5 – 5.7]. For women diagnosed between 2005 and 2009, the highest age-standardised survival was seen in Hong Kong (61.5%, 54.8-68.2%), compared with only 18.1% (6.3-29.9%) for women in Chile (Los Rios) [Table 5.3].

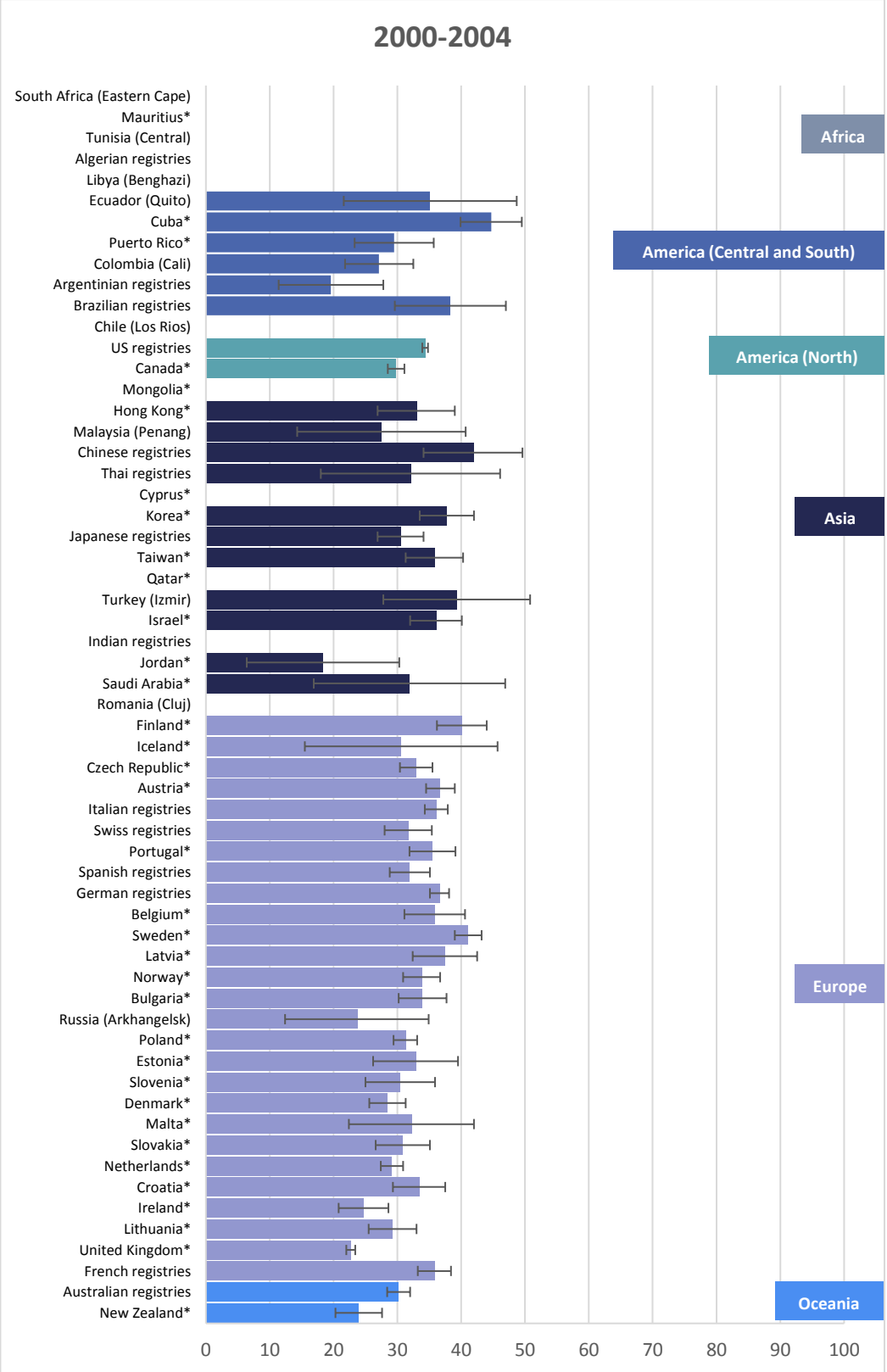
Age-standardised survival from type II epithelial tumours increased over time for most countries worldwide, though there were decreases in some countries. In Cuba, for example, survival was 53.4% (45.1-61.7%) for women diagnosed during 1995-1999, but only 39.2% (29.3-49.1%) during 2005-2009. Between-country variation was widest in Central and South America, where age-standardised 5-year survival was only 18.1% (6.3-29.9%) in Chile (Los Rios), but 55.0% (44.6-65.5%) in Ecuador (Quito). Type II epithelial was the only histological group for which survival estimates could be produced for all five African countries, but none of these estimates were age standardised. The number of women available in each of the African countries was small, and thus the confidence intervals for the survival estimates were wide.

Continued on page 167



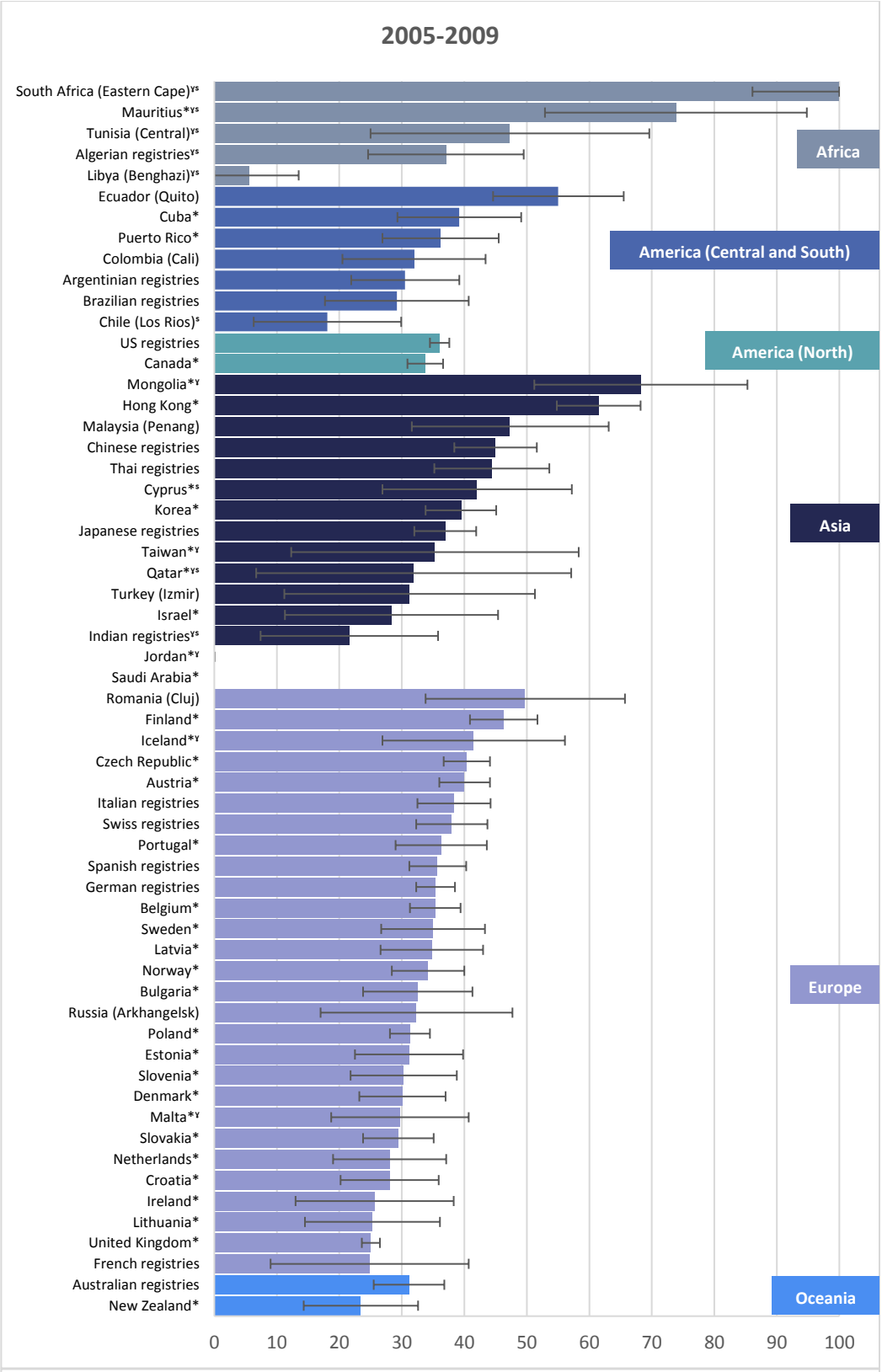
*Data with 100% coverage of the national population. ¥ Estimate not age-standardised. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for men diagnosed in the calendar period of 2005-2009.

Figure 5.5 Five-year age-standardised net survival (%) for type II epithelial tumours, 1995-1999



*Data with 100% coverage of the national population. ¥ Estimate not age-standardised. $ Data for two or more calendar periods of diagnosis have been merged. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for women diagnosed in the calendar period of 2005-2009.

Figure 5.6 Five-year age-standardised net survival (%) from type II epithelial tumours, 2000-2004



*Data with 100% coverage of the national population. ʸ Estimate not age-standardised. ˢ Data for two or more calendar periods of diagnosis have been merged. 95% CI represented by error bars. Ranked from highest to lowest net survival by continent for women diagnosed in the calendar period of 2005-2009.

Figure 5.7 Five-year age-standardised net survival (%) from type II epithelial tumours, 2005-2009

Germ cell

Survival from germ cell tumours could only be presented for all women diagnosed between 1995 and 2009 combined instead of for each calendar period separately, because these tumours are so uncommon. As a result, more than half the survival estimates for germ cell tumours were not age standardised (27 of 46 countries). This is because younger women have the highest incidence of germ cell tumours and this histological group is extremely rare in older women[36,39]. Therefore, only for a few countries were enough women available in each age group to allow for age standardisation. Considering the age-standardised estimates for all 15 years combined, the highest was seen in Australia (76.0%, 57.6-94.5%, n=367 women) and the lowest in China (41.5%, 23.6-59.4%, n=169 women) [Table 5.4].

Sex cord-stromal

Sex cord-stromal tumours are also rare, and survival could only be estimated in each calendar period separately in 11 of 46 countries for all three calendar periods [Table 5.4]. During 2005-2009, age-standardised net survival was over 90% at 5 years after diagnosis in Korea (100.0%, 96.0-100.0%, n=207 women) and Portugal (94.1%, 83.3-100.0%, n=64 women). However, survival varied widely between countries, and the lowest survival during the same period was almost half that seen in Korea (Japan, 58.9%, 34.2-83.7%, n=63 women). Of the 11 countries for which survival could be estimated for each calendar period separately, survival from sex cord-stromal tumours remained stable or increased over time in all countries except the Netherlands, where survival decreased from 83.6% (72.8-94.4%) in 1995-1999 to 70.9% (55.7-86.2%) in 2005-2009.

Other specific non-epithelial

Survival from other specific non-epithelial tumours was generally around 30-60%, slightly higher than that of type II epithelial tumours. The variation in age-standardised survival was wide, ranging from only 0.3% (0.0-0.8%) in Bulgaria (n=133) to 60.0% (48.4-71.5%) in

Continued on page 183

Table 5.4 Five-year age-standardised net survival (NS, %) (95% CI) by histological group (non-epithelial tumours), country and calendar period, 1995-2009, 60 countries

		Germ cell			Sex cord-stromal			Other specific		
Period of diagnosis	No. of registries	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
AFRICA										
Algerian registries										
1995-1999	-	-	.	.	-	.	.	-	.	.
2000-2004	-	-	.	.	-	.	.	-	.	.
2005-2009	2	-	.	.	10	***60.0***	*28.0* - *92.0*	-	.	.
Libya (Benghazi)										
1995-1999	-	-	.	.	-	.	.	-	.	.
2000-2004	-	-	.	.	-	.	.	-	.	.
2005-2009	1	-	.	.	-	.	.	-	.	.
Mauritius*										
1995-1999	-	-	.	.	-	.	.	-	.	.
2000-2004	-	-	.	.	-	.	.	-	.	.
2005-2009	1	-	.	.	-	.	.	-	.	.
South Africa (Eastern Cape)										
1995-1999	-	-	.	.	-	.	.	-	.	.
2000-2004	-	-	.	.	-	.	.	-	.	.
2005-2009	1	-	.	.	-	.	.	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Tunisia (Central)													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	
AMERICA (CENTRAL AND SOUTH)													
Argentinian registries													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	3	-	.	.		-	.	.		-	.	.	
2005-2009	3	34	***80.9***	*61.3*	*100.0*	19	***74.4***	*50.1*	*98.8*	14	***55.5***	*27.7*	*83.3*
Brazilian registries													
1995-1999	3	-	.	.		-	.	.		-	.	.	
2000-2004	4	-	.	.		-	.	.		-	.	.	
2005-2009	4	31	***67.9***	*49.5*	*86.3*	13	***61.0***	*31.3*	*90.7*	55	**36.1**	18.5	53.7
Chile (Los Rios)													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Colombia (Cali)													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	44	***76.5***	*57.7* -	*95.2*	28	***54.1***	*31.8* -	*76.3*	26	***74.0***	*51.6* -	*96.4*
Cuba*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	73	***70.9***	*60.2* -	*81.5*	85	***76.6***	*66.3* -	*86.9*	93	**60.0**	48.4 -	71.5
Ecuador (Quito)													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	49	***82.9***	*71.6* -	*94.1*	25	***58.3***	*37.8* -	*78.8*	39	***36.3***	*16.7* -	*55.8*
Puerto Rico*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	49	***87.5***	*77.2* -	*97.8*	24	***81.3***	*62.3* -	*100.0*	57	**32.0**	17.5 -	46.4

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

		Germ cell				Sex cord-stromal				Other specific			
Period of diagnosis	No. of registries	No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
AMERICA (NORTH)													
Canada*													
1995-1999	13	-	.	.		128	**87.4**	76.0	98.8	251	**39.4**	29.3	49.4
2000-2004	13	-	.	.		114	**89.9**	76.6	100.0	247	**41.9**	33.9	49.9
2005-2009	13	693	**70.8**	57.2	84.5	133	**87.1**	73.0	100.0	276	**45.4**	35.5	55.3
US registries													
1995-1999	34	-	.	.		1,232	**79.9**	75.0	84.9	2,162	**40.3**	37.6	43.0
2000-2004	38	-	.	.		1,340	**84.0**	79.3	88.7	2,487	**42.1**	39.5	44.8
2005-2009	38	4,972	**70.6**	66.1	75.0	1,523	**84.9**	77.7	92.0	2,803	**46.3**	41.8	50.8
ASIA													
Chinese registries													
1995-1999	3	-	.	.		-	.	.		-	.	.	
2000-2004	18	-	.	.		-	.	.		-	.	.	
2005-2009	19	169	**41.5**	23.6	59.4	93	**83.4**	71.7	95.0	128	**26.1**	14.7	37.5
Cyprus*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		14	***79.0***	*53.8*	*100.0*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Hong Kong*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	
Indian registries													
1995-1999	2	-	.	.		13	***90.8***	*65.4*	- *100.0*	-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	2	34	***83.4***	*68.8*	- *98.1*	-	.	.		-	.	.	
Indonesia (Jakarta)													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	14	***68.1***	*23.7*	- *100.0*	-	.	.		-	.	.	
Israel*													
1995-1999	1	-	.	.		-	.	.		53	***42.2***	*28.1*	- *56.4*
2000-2004	1	-	.	.		-	.	.		78	**55.6**	41.8	- 69.4
2005-2009	1	131	***92.9***	*88.0*	- *97.9*	35	***78.6***	*60.3*	- *97.0*	71	**38.5**	17.9	- 59.1

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell: No. of patients[c]	Germ cell: NS (%)	Germ cell: 95% CI		Sex cord-stromal: No. of patients[c]	Sex cord-stromal: NS (%)	Sex cord-stromal: 95% CI		Other specific: No. of patients[c]	Other specific: NS (%)	Other specific: 95% CI	
Japanese registries													
1995-1999	2	-	.	.		-	.	.		72	**26.1**	11.8	40.3
2000-2004	6	-	.	.		-	.	.		126	**28.8**	20.2	37.3
2005-2009	8	280	**50.6**	33.9	67.3	63	**58.9**	34.2	83.7	119	**40.4**	28.9	51.8
Jordan*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	53	.	.		29	***0.0***	*0.0*	*0.0*	27	.	.	
Korea*													
1995-1999	1	-	.	.		123	**74.3**	61.1	87.5	-	.	.	
2000-2004	1	-	.	.		215	**88.9**	81.4	96.5	71	***51.0***	*39.0*	*63.0*
2005-2009	1	1,130	***72.4***	58.3	86.5	207	**100.0**	96.0	100.0	64	***73.0***	*60.2*	*85.8*
Malaysia (Penang)													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	36	***80.4***	*66.8*	*94.0*	19	***62.0***	*36.7*	*87.4*	-	.	.	

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell: No. of patients[c]	Germ cell: NS (%)	Germ cell: 95% CI		Sex cord-stromal: No. of patients[c]	Sex cord-stromal: NS (%)	Sex cord-stromal: 95% CI		Other specific: No. of patients[c]	Other specific: NS (%)	Other specific: 95% CI	
Mongolia*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	
Qatar*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	
Saudi Arabia*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	90	**100.0**	100.0	- 100.0	33	***69.3***	*43.4*	- *95.3*	24	***37.0***	*10.8*	- *63.3*
2005-2009	-	-	.	.		-	.	.		-	.	.	
Taiwan*													
1995-1999	1	-	.	.		65	***82.3***	*72.1*	- *92.5*	183	**41.7**	32.3	- 51.0
2000-2004	1	-	.	.		93	***88.8***	*81.0*	- *96.7*	277	**39.4**	28.5	- 50.3
2005-2009	1	689	**57.4**	46.0	- 68.7	126	**85.0**	68.0	- 100.0	252	**43.5**	35.3	- 51.7

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell: No. of patients[c]	Germ cell: NS (%)	Germ cell: 95% CI		Sex cord-stromal: No. of patients[c]	Sex cord-stromal: NS (%)	Sex cord-stromal: 95% CI		Other specific: No. of patients[c]	Other specific: NS (%)	Other specific: 95% CI	
Thai registries													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	3	-	.	.		-	.	.		-	.	.	
2005-2009	3	76	***88.0***	*79.7*	*96.3*	38	***79.3***	*59.7*	*99.0*	22	***21.1***	*2.2*	*39.9*
Turkey (Izmir)													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	55	***80.8***	*68.3*	*93.3*	25	***71.9***	*51.6*	*92.2*	51	***25.1***	*4.3*	*45.9*
EUROPE													
Austria*													
1995-1999	2	-	.	.		63	**78.2**	66.6	89.8	83	**35.1**	22.2	48.0
2000-2004	2	-	.	.		67	**65.8**	49.8	81.8	86	**35.9**	22.7	49.1
2005-2009	2	187	**69.7**	51.4	88.0	64	**86.7**	75.0	98.5	93	**43.9**	28.3	59.5
Belgium*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	76	***90.4***	*82.0*	*98.7*	53	**82.4**	67.8	96.9	178	**42.1**	26.9	57.4

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Bulgaria*													
1995-1999	1	-	.	.		155	**63.8**	54.5	73.1	73	**32.9**	19.9	45.8
2000-2004	1	-	.	.		142	**80.2**	70.5	89.9	104	**30.5**	18.7	42.3
2005-2009	1	123	**42.5**	25.5	59.4	166	**64.4**	48.0	80.9	133	**0.3**	0.0	0.8
Croatia*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	61	***78.4***	*67.1*	*89.6*	64	***76.4***	*62.9*	*90.0*	44	***32.4***	*17.1*	*47.8*
Czech Republic*													
1995-1999	1	-	.	.		209	**67.6**	55.1	80.0	131	**33.2**	16.8	49.6
2000-2004	1	-	.	.		172	**67.5**	52.6	82.5	160	**31.8**	21.9	41.7
2005-2009	1	212	**46.9**	29.3	64.4	140	**81.6**	68.3	95.0	143	**43.2**	24.8	61.6
Denmark*													
1995-1999	1	-	.	.		-	.	.		78	**35.2**	22.7	47.7
2000-2004	1	-	.	.		-	.	.		58	**32.5**	24.0	41.0
2005-2009	1	125	**47.2**	33.5	61.0	96	**73.3**	55.5	91.1	74	***47.9***	*34.0*	*61.8*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Estonia*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	25	***67.7***	*48.5*	*86.9*	87	***71.0***	*59.5*	*82.5*	57	***39.2***	*24.0*	*54.4*
Finland*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	92	***75.1***	*64.9*	*85.3*	58	**60.8**	43.8	77.8	101	**33.7**	18.2	49.2
French registries													
1995-1999	10	-	.	.		-	.	.		87	**43.3**	28.9	57.6
2000-2004	10	-	.	.		55	***98.9***	*92.6*	*100.0*	-	.	.	
2005-2009	10	114	***78.1***	*70.1*	*86.1*	-	.	.		107	**44.6**	35.3	53.9
German registries													
1995-1999	4	-	.	.		118	**74.2**	61.0	87.5	110	**38.5**	27.8	49.3
2000-2004	8	-	.	.		160	**74.6**	63.7	85.4	172	**39.8**	30.6	49.0
2005-2009	8	255	**43.6**	23.8	63.4	114	**77.4**	67.5	87.2	207	**30.8**	10.9	50.7

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Iceland*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		14	***40.9***	*15.2* -	*66.7*
Ireland*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	63	***77.0***	*66.4* -	*87.7*	39	***71.6***	*52.5* -	*90.6*	54	***29.4***	*14.8* -	*44.0*
Italian registries													
1995-1999	25	-	.	.		83	**65.7**	46.1 -	85.4	298	**34.8**	27.4 -	42.2
2000-2004	30	-	.	.		-	.	.		383	**39.0**	32.9 -	45.1
2005-2009	30	234	**62.3**	46.0 -	78.5	125	**66.4**	54.8 -	78.0	234	**37.1**	26.3 -	47.9
Latvia*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		79	***65.1***	*53.3* -	*76.9*	-	.	.	
2005-2009	1	45	***47.7***	*32.0* -	*63.4*	75	**65.2**	51.3 -	79.1	75	**36.4**	22.9 -	49.8

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Lithuania*													
1995-1999	1	-	.	.		58	**79.4**	65.4	93.3	-	.	.	
2000-2004	1	-	.	.		-	.	.		94	**27.9**	15.3	40.6
2005-2009	1	61	***76.1***	*64.5*	*87.6*	91	**87.5**	79.0	95.9	53	***30.5***	*12.0*	*48.9*
Malta*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	13	***100.0***	*100.0*	*100.0*	-	.	.		15	***35.4***	*8.5*	*62.4*
Netherlands*													
1995-1999	1	-	.	.		173	**83.6**	72.8	94.4	157	**35.7**	26.9	44.5
2000-2004	1	-	.	.		101	**81.5**	68.2	94.9	177	**37.0**	28.0	46.1
2005-2009	1	292	**66.2**	54.8	77.6	82	**70.9**	55.7	86.2	150	**54.0**	43.0	64.9
Norway*													
1995-1999	1	-	.	.		61	***94.4***	*85.9*	*100.0*	69	**33.4**	20.0	46.8
2000-2004	1	-	.	.		-	.	.		82	**30.7**	19.7	41.7
2005-2009	1	133	**65.9**	47.0	84.7	55	***92.9***	*85.5*	*100.0*	73	**31.5**	7.2	55.8

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Poland*													
1995-1999	4	-	.	.		136	**73.3**	63.4	83.1	-	.	.	
2000-2004	5	-	.	.		474	**80.3**	69.6	91.0	222	**32.3**	27.8	36.8
2005-2009	5	552	**47.2**	32.8	61.7	463	**89.1**	75.0	100.0	191	***27.6***	*8.1*	*47.2*
Portugal*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	4	-	.	.		-	.	.		127	**32.4**	22.8	42.0
2005-2009	4	102	***85.2***	*77.4*	*92.9*	64	**94.1**	83.3	100.0	97	**52.9**	39.3	66.5
Romania (Cluj)													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	-	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		-	.	.	
Russia (Arkhangelsk)													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	16	***75.4***	*53.8*	*97.0*	107	**82.4**	68.1	96.7	-	.	.	

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell				Sex cord-stromal				Other specific			
		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	
Slovakia*													
1995-1999	-	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	70	***81.3***	*70.5* -	*92.0*	100	**71.0**	54.4 -	87.5	100	**35.5**	23.0 -	48.1
Slovenia*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	41	***81.4***	*68.5* -	*94.3*	26	***98.0***	*84.3* -	*100.0*	109	**38.8**	26.0 -	51.5
Spanish registries													
1995-1999	10	-	.	.		-	.	.		138	**26.5**	17.0 -	36.0
2000-2004	10	-	.	.		-	.	.		136	**33.3**	8.8 -	57.9
2005-2009	10	164	**64.5**	45.5 -	83.4	65	**75.5**	59.4 -	91.6	114	**36.9**	27.6 -	46.2
Sweden*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	-	.	.		-	.	.		64	***14.6***	*4.9* -	*24.3*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Period of diagnosis	No. of registries	Germ cell: No. of patients[c]	Germ cell: NS (%)	Germ cell: 95% CI		Sex cord-stromal: No. of patients[c]	Sex cord-stromal: NS (%)	Sex cord-stromal: 95% CI		Other specific: No. of patients[c]	Other specific: NS (%)	Other specific: 95% CI	
Swiss registries													
1995-1999	7	-	.	.		-	.	.		-	.	.	
2000-2004	7	-	.	.		-	.	.		80	**42.9**	29.8	56.0
2005-2009	8	62	***88.9***	*76.0*	*100.0*	39	***77.5***	*60.1*	*94.9*	82	***55.5***	*40.6*	*70.4*
United Kingdom*													
1995-1999	12	-	.	.		311	**76.2**	67.8	84.6	397	**30.2**	23.6	36.7
2000-2004	12	-	.	.		290	**80.0**	72.0	88.0	460	**29.0**	23.3	34.7
2005-2009	12	1,013	**57.1**	48.0	66.1	288	**76.8**	59.5	94.2	445	**35.4**	26.6	44.3
OCEANIA													
Australian registries													
1995-1999	6	-	.	.		71	**74.9**	58.9	90.9	130	**40.1**	28.3	52.0
2000-2004	6	-	.	.		-	.	.		144	**43.3**	31.0	55.7
2005-2009	6	367	**76.0**	57.6	94.5	92	**69.6**	56.7	82.6	132	**32.4**	13.9	51.0
New Zealand*													
1995-1999	1	-	.	.		-	.	.		-	.	.	
2000-2004	1	-	.	.		-	.	.		-	.	.	
2005-2009	1	106	***92.4***	*86.3*	*98.6*	48	***76.8***	*62.3*	*91.3*	102	**40.1**	24.4	55.9

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with data for fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Table 5.5 due to merging of calendar periods.

Cuba (n=93). For only 16 of 45 countries could survival be estimated for all three calendar periods. Age-standardised net survival increased or remained stable in most countries, but decreases in survival were seen in Australia, Bulgaria, Germany, and Norway. The most striking decrease was seen in Bulgaria, where survival fell from 32.9% (19.9-45.8%) in 1995-1999 to only 0.3% (0.0-0.8%) in 2005-2009.

Non-specific morphology

Age-standardised net survival for tumours of non-specific morphology (ICD-O-3 codes 8000-8004) was generally lower than that for all specific morphologies combined, with a few notable exceptions [Table 5.5]. During 2005-2009 in Turkey, survival from tumours with non-specific morphology was 42.8% (27.4-58.3%) while survival from tumours with a specific morphology was only 36.8% (20.3-53.3%). Survival from tumours of non-specific morphology was 57.4% (52.8-62.0%; n=62) while survival from tumours with a specific morphology was 35.0% (26.7-43.3%) in Sweden. Only for 12 of the 45 countries could survival be estimated for all three calendar periods. Over time, age-standardised survival for tumours of non-specific morphology decreased over time in most countries, with the largest decrease seen in Korea (from 44.3%, 29.5-59.0% in 1995-1999 to 25.0% (21.5-28.5%) in 2005-2009). The largest increase in survival was seen in Austria (from 31.6% (21.0-42.1%) in 1995-1999 to 45.5% (37.5-53.6%) in 2005-2009).

Tumours with missing morphology

Tumours that were coded as microscopically verified but with missing ICD-O-3 morphology (coded for CONCORD-2 as 9999) were included in the data submissions from Ireland (n=4), Italy (n=12), Latvia (n=271), Lithuania (n=298), Mongolia (n=98) and Russia (n=12) [Table 5.5]. Survival was estimated for all these countries except for Ireland, because fewer than 10 women were available for analysis. The was a wide range in age-standardised survival during 2005-2009, from only 17.9% (4.5-31.4%) in Latvia to 48.2% (30.0-66.3%) in Mongolia. In Latvia, the only country for which age-standardised survival

Continued on page 199

Table 5.5 Five-year age-standardised net survival (NS, %) (95% CI) by country and calendar period for all tumours, tumours of specific morphology, tumours of non-specific morphology and tumours with missing morphology, 1995-2009, 60 countries

		All tumours				Specific morphology					Non-specific morphology					Missing morphology				
	No. of registries	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI		
AFRICA																				
Algerian registries																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	2	**30.8**	17.9	-	43.8	122	**30.8**	17.9	-	43.8	-	.	.			-	.	.		
Libya (Benghazi)																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***5.6***	*0.0*	-	*13.5*	44	***5.6***	*0.0*	-	*13.5*	-	.	.			-	.	.		
Mauritius*																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***73.5***	*57.7*	-	*89.3*	25	***73.9***	*52.9*	-	*94.8*	19	***74.4***	*51.9*	-	*96.9*	-	.	.		
South Africa (Eastern Cape)																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***100.0***	*86.1*	-	*100.0*	20	***100.0***	*86.1*	-	*100.0*	-	.	.			-	.	.		

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours				Specific morphology					Non-specific morphology					Missing morphology				
	No. of registries	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI		
Tunisia (Central)																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***47.3***	*25.0*	-	*69.6*	21	***47.3***	*25.0*	-	*69.6*	-	.	.			-	.	.		
AMERICA (CENTRAL AND SOUTH)																				
Argentinian registries																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	3	**26.7**	15.5	-	37.9	172	**28.4**	16.6	-	40.1	-	.	.			-	.	.		
2005-2009	3	**30.9**	23.3	-	38.5	566	**31.4**	23.7	-	39.2	42	***27.8***	*12.4*	-	*43.2*	-	.	.		
Brazilian registries																				
1995-1999	3	**34.6**	24.4	-	44.8	167	**34.7**	24.5	-	45.0	-	.	.			-	.	.		
2000-2004	4	**41.0**	34.1	-	47.8	425	**40.5**	33.5	-	47.4	-	.	.			-	.	.		
2005-2009	4	**31.7**	20.5	-	42.9	245	**31.3**	20.2	-	42.4	17	***76.4***	*53.1*	-	*99.7*	-	.	.		
Chile (Los Rios)																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	1	**33.1**	21.2	-	45.1	57	**38.9**	25.7	-	52.0	-	.	.			-	.	.		
2005-2009	1	***41.4***	*24.9*	-	*57.8*	74	**37.3**	20.9	-	53.7	-	.	.			-	.	.		

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI
Colombia (Cali)															
1995-1999	1	**32.4**	22.9	41.9	291	**31.9**	22.3	41.5	-	.	.		-	.	.
2000-2004	1	**34.0**	17.5	50.5	326	**33.9**	17.4	50.3	-	.	.		-	.	.
2005-2009	1	**42.3**	31.7	53.0	327	**43.0**	32.2	53.8	30	***40.0***	*20.7*	*59.2*	-	.	.
Cuba*															
1995-1999	1	**58.1**	50.7	65.6	442	**58.8**	51.2	66.4	-	.	.		-	.	.
2000-2004	1	**46.6**	42.5	50.8	1,394	**48.2**	43.9	52.5	-	.	.		-	.	.
2005-2009	1	**51.8**	44.6	59.0	554	**51.0**	43.7	58.2	89	**30.8**	19.4	42.2	-	.	.
Ecuador (Quito)															
1995-1999	1	**34.5**	21.1	47.9	181	**35.0**	21.5	48.6	-	.	.		-	.	.
2000-2004	1	**46.9**	35.6	58.2	202	**46.7**	35.3	58.2	-	.	.		-	.	.
2005-2009	1	**46.6**	30.2	63.1	260	**42.5**	24.0	61.0	24	***51.7***	*27.3*	*76.1*	-	.	.
Puerto Rico*															
1995-1999	-	.	.		-	.	.		-	.	.		-	.	.
2000-2004	1	**35.4**	29.8	41.0	622	**34.3**	28.5	40.1	-	.	.		-	.	.
2005-2009	1	**41.2**	32.8	49.6	662	**41.9**	33.4	50.5	52	***55.6***	*40.7*	*70.6*	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI
AMERICA (NORTH)															
Canada*															
1995-1999	13	**37.1**	35.9	38.4	10,292	**37.1**	35.9	38.4	74	**36.3**	24.1	48.6	-	.	.
2000-2004	13	**38.1**	36.9	39.3	11,263	**38.2**	37.0	39.5	84	***22.0***	*12.4*	*31.5*	-	.	.
2005-2009	12	**41.9**	39.3	44.5	12,105	**42.0**	39.4	44.6	91	**30.1**	21.7	38.5	-	.	.
US registries															
1995-1999	34	**39.8**	39.3	40.3	76,288	**39.9**	39.4	40.3	805	**33.2**	28.2	38.2	-	.	.
2000-2004	38	**40.6**	40.2	41.1	89,319	**40.8**	40.3	41.2	1,108	**30.0**	26.4	33.6	-	.	.
2005-2009	38	**42.2**	40.7	43.6	93,582	**42.4**	40.9	43.8	1,120	**29.8**	22.1	37.5	-	.	.
ASIA															
Chinese registries															
1995-1999	3	**42.3**	31.3	53.4	115	**41.6**	29.8	53.3	-	.	.		-	.	.
2000-2004	18	**48.3**	42.0	54.6	1,024	**48.7**	42.1	55.3	115	**44.6**	34.7	54.5	-	.	.
2005-2009	19	**46.8**	41.2	52.4	2,991	**47.2**	40.9	53.5	175	**35.2**	21.6	48.7	-	.	.
Cyprus*															
1995-1999	-	.	.		-	.	.		-	.	.		-	.	.
2000-2004	-	.	.		-	.	.		-	.	.		-	.	.
2005-2009	1	**44.2**	28.7	59.7	254	**44.2**	28.7	59.7	-	.	.		-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

	No. of registries	All tumours NS (%)	95% CI			Specific morphology No. of patients[c]	NS (%)	95% CI			Non-specific morphology No. of patients[c]	NS (%)	95% CI			Missing morphology No. of patients[c]	NS (%)	95% CI		
Hong Kong*																				
1995-1999	1	**41.9**	34.3	-	49.4	527	**41.9**	34.3	-	49.4	-	.	.			-	.	.		
2000-2004	1	**46.6**	41.2	-	52.0	1,012	**46.6**	41.2	-	52.0	-	.	.			-	.	.		
2005-2009	1	**66.6**	59.2	-	74.1	437	**66.6**	59.2	-	74.1	-	.	.			-	.	.		
Indian registries																				
1995-1999	2	**22.2**	14.7	-	29.7	338	**24.2**	15.4	-	33.0	-	.	.			-	.	.		
2000-2004	-	.		.		-	.		.		-	.		.		-	.	.		
2005-2009	2	**17.3**	10.2	-	24.4	72	**20.1**	11.8	-	28.4	68	***14.2***	*3.7*	-	*24.7*	-	.	.		
Indonesia (Jakarta)																				
1995-1999	-	.		.		-	.		.		-	.		.		-	.	.		
2000-2004	-	.		.		-	.		.		-	.		.		-	.	.		
2005-2009	1	***59.9***	*44.3*	-	*75.5*	173	***59.9***	*44.3*	-	*75.5*	-	.		.		-	.	.		
Israel*																				
1995-1999	1	**40.1**	36.4	-	43.8	1,633	**40.1**	36.2	-	43.9	57	***42.3***	*28.4*	-	*56.3*	-	.	.		
2000-2004	1	**41.0**	37.6	-	44.4	1,860	**40.8**	37.3	-	44.4	61	***44.4***	*30.4*	-	*58.3*	-	.	.		
2005-2009	1	**28.8**	11.6	-	45.9	1,895	**29.2**	11.7	-	46.6	62	***20.1***	*3.1*	-	*37.1*	-	.	.		

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Japanese registries													
1995-1999	2	**30.3**	26.5 -	34.1	1,641	**31.9**	27.8 - 36.0	149	**18.2**	10.7 - 25.8	-	.	.
2000-2004	6	**37.0**	34.3 -	39.7	2,989	**38.4**	35.6 - 41.2	135	**16.0**	7.9 - 24.2	-	.	.
2005-2009	8	**42.2**	35.7 -	48.7	3,514	**42.9**	36.2 - 49.5	133	**27.2**	15.4 - 39.0	-	.	.
Jordan*													
1995-1999	-	.	.		-	.	.	-	.	.	-	.	.
2000-2004	1	**17.2**	6.8 -	27.6	298	***17.8***	*7.1* - *28.6*	-	.	.	-	.	.
2005-2009	1	***0.0***	*0.0* -	*0.0*	372	***0.0***	*0.0* - *0.0*	17	.	.	-	.	.
Korea*													
1995-1999	1	**48.2**	44.4 -	52.0	4,430	**48.6**	44.8 - 52.4	96	**44.3**	29.5 - 59.0	-	.	.
2000-2004	1	**48.4**	45.2 -	51.5	5,933	**48.8**	45.6 - 52.0	103	**35.4**	24.2 - 46.6	-	.	.
2005-2009	1	**47.4**	42.6 -	52.2	7,725	**48.0**	43.3 - 52.8	134	**25.0**	21.5 - 28.5	-	.	.
Malaysia (Penang)													
1995-1999	1	**56.5**	43.8 -	69.3	142	**56.5**	43.8 - 69.3	-	.	.	-	.	.
2000-2004	1	**45.4**	35.0 -	55.7	216	**45.4**	35.0 - 55.7	-	.	.	-	.	.
2005-2009	1	**53.5**	38.9 -	68.1	278	**53.5**	38.9 - 68.1	-	.	.	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours				Specific morphology					Non-specific morphology					Missing morphology				
	No. of registries	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI			No. of patients[c]	NS (%)	95% CI		
Mongolia*																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***55.5***	*41.5*	-	*69.5*	52	***68.3***	*51.2*	-	*85.3*	-	.	.			98	**48.2**	30.0	-	66.3
Qatar*																				
1995-1999	-	.	.			-	.	.			-	.	.			-	.	.		
2000-2004	-	.	.			-	.	.			-	.	.			-	.	.		
2005-2009	1	***31.9***	*6.7*	-	*57.1*	22	***31.9***	*6.7*	-	*57.1*	-	.	.			-	.	.		
Saudi Arabia*																				
1995-1999	1	**49.7**	31.2	-	68.2	384	**50.9**	32.1	-	69.8	-	.	.			-	.	.		
2000-2004	1	**42.4**	28.8	-	56.1	546	**42.4**	28.7	-	56.0	15	***70.4***	*43.3*	-	*97.5*	-	.	.		
2005-2009	-	.	.			-	.	.			-	.	.			-	.	.		
Taiwan*																				
1995-1999	1	**45.6**	41.4	-	49.8	2,738	**45.6**	41.3	-	49.9	-	.	.			-	.	.		
2000-2004	1	**45.3**	42.2	-	48.5	3,947	**45.2**	42.0	-	48.5	-	.	.			-	.	.		
2005-2009	1	**43.4**	29.3	-	57.4	5,138	**43.4**	29.4	-	57.4	108	**42.1**	28.1	-	56.2	-	.	.		

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Thai registries													
1995-1999	1	**46.3**	31.0	61.6	170	**46.6**	31.2 - 62.1	-	.	.	-	.	.
2000-2004	3	**39.2**	25.8	52.6	467	**40.1**	26.5 - 53.7	-	.	.	-	.	.
2005-2009	3	**47.3**	39.0	55.5	537	**48.5**	40.1 - 56.9	24	***20.2***	*0.2* - *40.3*	-	.	.
Turkey (Izmir)													
1995-1999	1	**41.0**	23.4	58.6	379	**41.4**	23.7 - 59.2	-	.	.	-	.	.
2000-2004	1	**47.5**	38.5	56.5	508	**47.5**	38.0 - 57.1	-	.	.	-	.	.
2005-2009	1	**36.6**	20.2	52.9	667	**36.8**	20.3 - 53.3	62	**42.8**	27.4 - 58.3	-	.	.
EUROPE													
Austria*													
1995-1999	2	**42.5**	40.3	44.7	4,202	**42.8**	40.5 - 45.0	129	**31.6**	21.0 - 42.1	-	.	.
2000-2004	2	**40.7**	38.6	42.7	3,969	**40.7**	38.6 - 42.9	211	**41.7**	31.6 - 51.9	-	.	.
2005-2009	2	**43.3**	39.5	47.0	3,500	**43.7**	39.9 - 47.6	153	**45.5**	37.5 - 53.6	-	.	.
Belgium*													
1995-1999	-	.	.		-	.	.	-	.	.	-	.	.
2000-2004	1	**42.8**	38.6	47.0	936	**43.1**	38.9 - 47.4	-	.	.	-	.	.
2005-2009	1	**42.5**	38.6	46.4	4,676	**42.6**	38.7 - 46.5	56	***17.4***	*4.7* - *30.1*	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Bulgaria*													
1995-1999	1	**33.3**	29.4 -	37.3	2,755	**34.0**	30.0 - 38.0	-	.	.	-	.	.
2000-2004	1	**38.5**	35.4 -	41.5	3,305	**39.2**	36.2 - 42.3	63	***11.6***	*3.8 - 19.4*	-	.	.
2005-2009	1	**36.0**	30.2 -	41.8	3,878	**36.6**	30.7 - 42.6	92	***0.2***	*0.0 - 0.8*	-	.	.
Croatia*													
1995-1999	1	**38.4**	32.0 -	44.8	764	**38.7**	32.3 - 45.1	-	.	.	-	.	.
2000-2004	1	**38.5**	35.0 -	42.1	1,990	**38.4**	34.8 - 42.0	-	.	.	-	.	.
2005-2009	1	**33.6**	26.8 -	40.4	1,919	**33.5**	26.6 - 40.4	26	***31.4***	*11.7 - 51.0*	-	.	.
Czech Republic*													
1995-1999	1	**34.8**	32.5 -	37.2	5,085	**35.5**	33.1 - 38.0	138	**10.8**	4.1 - 17.5	-	.	.
2000-2004	1	**36.8**	34.8 -	38.9	5,344	**37.5**	35.5 - 39.6	158	**16.8**	8.1 - 25.5	-	.	.
2005-2009	1	**43.2**	40.0 -	46.4	5,060	**44.2**	40.9 - 47.5	160	**15.2**	10.4 - 20.1	-	.	.
Denmark*													
1995-1999	1	**31.8**	29.5 -	34.1	3,045	**31.9**	29.6 - 34.2	-	.	.	-	.	.
2000-2004	1	**33.8**	31.3 -	36.2	2,953	**33.9**	31.4 - 36.4	38	***13.0***	*0.8 - 25.3*	-	.	.
2005-2009	1	**37.5**	31.5 -	43.5	2,903	**37.9**	31.8 - 43.9	117	***29.2***	*17.1 - 41.3*	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

	No. of registries	All tumours NS (%)	95% CI		Specific morphology No. of patients[c]	NS (%)	95% CI		Non-specific morphology No. of patients[c]	NS (%)	95% CI		Missing morphology No. of patients[c]	NS (%)	95% CI	
Estonia*																
1995-1999	1	**28.6**	22.0	35.3	712	**30.7**	23.7	37.8	80	**11.4**	1.0	21.8	-	.	.	
2000-2004	1	**33.3**	27.8	38.8	658	**35.9**	30.0	41.7	-	.	.		-	.	.	
2005-2009	1	**36.5**	28.3	44.6	581	**37.8**	29.4	46.3	84	**10.5**	1.3	19.8	-	.	.	
Finland*																
1995-1999	1	**40.2**	37.1	43.4	2,242	**41.4**	38.2	44.6	83	***5.5***	*0.4*	*10.7*	-	.	.	
2000-2004	1	**42.3**	39.3	45.2	2,408	**43.3**	40.2	46.3	104	***12.9***	*5.7*	*20.2*	-	.	.	
2005-2009	1	**51.6**	47.5	55.7	2,367	**53.4**	49.1	57.6	118	.	.		-	.	.	
French registries																
1995-1999	10	**34.3**	31.4	37.1	2,470	**34.4**	31.6	37.3	-	.	.		-	.	.	
2000-2004	10	**40.4**	38.0	42.9	2,837	**40.6**	38.1	43.1	-	.	.		-	.	.	
2005-2009	8	**29.9**	10.9	48.8	241	**29.9**	10.9	48.8	59	***15.7***	*5.7*	*25.7*	-	.	.	
German registries																
1995-1999	4	**38.0**	36.2	39.8	5,193	**38.2**	36.3	40.0	102	***29.9***	*20.2*	*39.6*	-	.	.	
2000-2004	8	**40.7**	39.4	42.1	8,922	**40.9**	39.6	42.3	125	***22.6***	*14.8*	*30.5*	-	.	.	
2005-2009	8	**38.3**	35.3	41.3	10,463	**38.3**	35.2	41.4	103	***25.2***	*14.3*	*36.2*	-	.	.	

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Iceland*														
1995-1999	1	**25.7**	12.7 -	38.8	108	**25.7**	12.7 -	38.8	-	.	.	-	.	.
2000-2004	1	**34.6**	17.8 -	51.5	124	**34.6**	17.8 -	51.5	-	.	.	-	.	.
2005-2009	1	**42.9**	27.9 -	58.0	117	**42.9**	27.9 -	58.0	-	.	.	-	.	.
Ireland*														
1995-1999	1	**29.4**	25.6 -	33.3	1,317	**29.7**	25.8 -	33.6	-	.	.	-	.	.
2000-2004	1	**30.9**	27.3 -	34.6	1,461	**31.1**	27.5 -	34.8	-	.	.	-	.	.
2005-2009	1	**32.3**	17.2 -	47.5	1,595	**32.5**	17.3 -	47.7	43	***8.5***	*0.0* -	*17.1*	-	.	.
Italian registries														
1995-1999	25	**38.3**	36.6 -	39.9	6,561	**38.7**	37.0 -	40.4	211	**29.4**	17.3 -	41.4	-	.	.
2000-2004	30	**40.0**	38.6 -	41.5	8,085	**40.8**	39.3 -	42.4	309	**20.4**	14.2 -	26.6	-	.	.
2005-2009	29	**43.6**	40.0 -	47.3	4,893	**44.3**	40.6 -	48.0	194	**25.1**	18.9 -	31.4	12	***8.6***	*0.0* -	*21.8*
Latvia*														
1995-1999	1	**32.8**	27.7 -	37.8	1,219	**36.1**	30.6 -	41.6	-	.	.	133	**9.1**	6.2 -	12.0
2000-2004	1	**36.7**	31.9 -	41.4	1,196	**39.1**	34.2 -	44.1	-	.	.	81	**14.6**	8.3 -	20.9
2005-2009	1	**35.9**	28.9 -	42.9	1,223	**37.2**	29.9 -	44.5	19	***27.8***	*7.2* -	*48.4*	57	**17.9**	4.5 -	31.4

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

	No. of registries	All tumours NS (%)	95% CI		Specific morphology No. of patients[c]	NS (%)	95% CI		Non-specific morphology No. of patients[c]	NS (%)	95% CI		Missing morphology No. of patients[c]	NS (%)	95% CI	
Lithuania*																
1995-1999	1	**31.3**	27.7	34.8	1,593	**33.7**	29.8	37.6	-	.	.		204	**22.9**	13.1	32.6
2000-2004	1	**33.0**	29.7	36.3	1,755	**33.3**	29.9	36.7	-	.	.		-	.	.	
2005-2009	1	**31.5**	24.0	39.1	1,764	**31.5**	23.5	39.6	79	***18.3***	*9.1*	*27.4*	94	**33.4**	18.1	48.7
Malta*																
1995-1999	1	**33.3**	17.5	49.1	145	**33.6**	17.6	49.5	-	.	.		-	.	.	
2000-2004	1	**38.0**	28.2	47.9	180	**41.3**	30.9	51.8	-	.	.		-	.	.	
2005-2009	1	**36.0**	27.8	44.2	178	**38.0**	29.5	46.5	27	***4.1***	*0.0*	*10.5*	-	.	.	
Netherlands*																
1995-1999	1	**35.0**	33.3	36.7	6,616	**35.1**	33.4	36.8	-	.	.		-	.	.	
2000-2004	1	**36.7**	35.0	38.3	6,280	**36.7**	35.1	38.3	-	.	.		-	.	.	
2005-2009	1	**34.6**	23.7	45.5	6,395	**34.6**	23.7	45.6	25	.	.		-	.	.	
Norway*																
1995-1999	1	**37.6**	34.8	40.4	2,340	**37.3**	34.6	40.1	-	.	.		-	.	.	
2000-2004	1	**41.3**	38.8	43.9	2,477	**41.3**	38.7	43.9	-	.	.		-	.	.	
2005-2009	1	**38.1**	32.9	43.3	2,379	**38.2**	33.0	43.4	84	***39.7***	*25.4*	*54.1*	-	.	.	

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Poland*													
1995-1999	4	**35.1**	31.5 -	38.7	3,094	**35.5**	31.8 - 39.2	64	***21.9***	*11.4 - 32.5*	-	.	.
2000-2004	5	**35.5**	33.8 -	37.1	12,861	**35.8**	34.1 - 37.4	253	**21.9**	14.9 - 28.9	-	.	.
2005-2009	5	**36.9**	34.2 -	39.5	14,566	**37.2**	34.5 - 39.9	271	**22.9**	15.8 - 30.0	-	.	.
Portugal*													
1995-1999	1	**35.9**	30.5 -	41.3	574	**35.9**	30.5 - 41.3	-	.	.	-	.	.
2000-2004	4	**40.4**	37.3 -	43.5	2,128	**40.6**	37.5 - 43.7	-	.	.	-	.	.
2005-2009	4	**43.1**	36.5 -	49.7	1,958	**43.2**	36.6 - 49.8	45	***35.2***	*20.6 - 49.9*	-	.	.
Romania (Cluj)													
1995-1999	-	.	.		-	.	.	-	.	.	-	.	.
2000-2004	-	.	.		-	.	.	-	.	.	-	.	.
2005-2009	1	.	.		176	**54.6**	40.7 - 68.5	-	.	.	-	.	.
Russia (Arkhangelsk)													
1995-1999	-	.	.		-	.	.	-	.	.	-	.	.
2000-2004	1	**33.2**	23.0 -	43.5	401	**33.9**	21.8 - 46.1	-	.	.	-	.	.
2005-2009	1	**35.3**	23.0 -	47.6	331	**43.0**	29.3 - 56.8	107	**14.5**	5.4 - 23.6	12	***33.0***	*5.1 - 61.0*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Slovakia*													
1995-1999	-	.	.		-	.	.	-	.	.	-	.	.
2000-2004	1	**35.8**	32.4	39.3	1,958	**36.3**	32.8 - 39.8	-	.	.	-	.	.
2005-2009	1	**35.7**	30.7	40.8	1,329	**35.9**	30.7 - 41.0	35	***9.2***	*0.0* - *18.9*	-	.	.
Slovenia*													
1995-1999	1	**34.3**	29.5	39.1	820	**34.4**	29.6 - 39.2	-	.	.	-	.	.
2000-2004	1	**38.9**	34.3	43.6	905	**39.2**	34.5 - 43.9	-	.	.	-	.	.
2005-2009	1	**35.5**	27.3	43.8	985	**35.6**	27.3 - 43.8	11	***9.8***	*0.0* - *24.1*	-	.	.
Spanish registries													
1995-1999	10	**36.9**	34.3	39.6	2,695	**37.0**	34.3 - 39.7	-	.	.	-	.	.
2000-2004	10	**39.9**	37.3	42.6	2,832	**40.1**	37.4 - 42.8	-	.	.	-	.	.
2005-2009	10	**39.8**	35.7	44.0	2,531	**40.1**	35.9 - 44.3	85	***22.1***	*12.5* - *31.6*	-	.	.
Sweden*													
1995-1999	1	**40.9**	39.0	42.8	4,096	**40.1**	38.1 - 42.0	373	**48.9**	40.1 - 57.7	-	.	.
2000-2004	1	**42.8**	40.9	44.7	3,963	**41.0**	39.0 - 43.1	408	**59.6**	52.9 - 66.2	-	.	.
2005-2009	1	**38.4**	31.5	45.3	3,746	**35.0**	26.7 - 43.3	380	**57.4**	52.8 - 62.0	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

		All tumours			Specific morphology			Non-specific morphology			Missing morphology		
	No. of registries	NS (%)	95% CI		No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI	No. of patients[c]	NS (%)	95% CI
Swiss registries													
1995-1999	7	**35.7**	32.0	39.3	1,409	**35.6**	31.9 - 39.3	-	.	.	-	.	.
2000-2004	7	**36.8**	33.6	40.1	1,371	**37.0**	33.7 - 40.2	-	.	.	-	.	.
2005-2009	8	**43.7**	38.5	48.9	1,577	**43.8**	38.5 - 49.0	13	***19.3***	*0.0* - *40.5*	-	.	.
UK*													
1995-1999	12	**28.6**	27.8	29.3	27,828	**28.6**	27.8 - 29.3	242	**31.0**	21.5 - 40.4	-	.	.
2000-2004	12	**30.1**	29.3	30.8	29,684	**30.1**	29.4 - 30.8	266	**25.9**	18.2 - 33.6	-	.	.
2005-2009	12	**32.3**	30.8	33.8	29,399	**32.3**	30.8 - 33.8	301	**28.6**	22.5 - 34.8	-	.	.
OCEANIA													
Australian registries											-	.	.
1995-1999	6	**36.5**	34.7	38.4	5,263	**36.6**	34.7 - 38.4	-	.	.	-	.	.
2000-2004	6	**37.2**	35.5	38.9	5,860	**37.2**	35.5 - 39.0	-	.	.	-	.	.
2005-2009	6	**39.4**	35.5	43.2	4,912	**39.5**	35.7 - 43.4	95	***22.4***	*12.4* - *32.4*			
New Zealand*													
1995-1999	1	**32.6**	28.9	36.4	1,217	**32.4**	28.5 - 36.2	-	.	.	-	.	.
2000-2004	1	**35.6**	31.9	39.3	1,235	**35.7**	32.0 - 39.4	-	.	.	-	.	.
2005-2009	1	**27.8**	20.1	35.5	1,404	**28.7**	20.7 - 36.7	74	***34.7***	*22.8* - *46.6*	-	.	.

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included in the analysis. [b] Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included. [c] Number of patients included in the analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from some registries. The number of patients in each time period may differ from the number shown in Tables 5.3 and 5.4 due to merging of calendar periods.

could be estimated for all three calendar periods, survival increased over time from 9.1% (6.2-12.0%) to 17.9% (4.5-31.4%).

5.3.2 Histological group by sub-site

Tumours of the anatomic ovary were the most common sub-site (628,582, 90.3%) compared to peritoneal tumours (41,333, 5.9%) and fallopian tube tumours (26,017, 3.7%). Survival for each histological group varied with the different topographical sub-sites. Survival by histological group for each sub-site was estimated for the UK and the US separately. The mean age at diagnosis for women with peritoneal cancer was 66 years, while the mean age at diagnosis for women with a tumour of the ovary itself was 63 years, and 65 years for women with fallopian tube cancer. For type I and type II epithelial tumours, women diagnosed with peritoneal cancer had lower survival than women diagnosed with a tumour of the ovary or fallopian tube in both countries [Table 5.6]. During 2005-2009, five-year age-standardised net survival for type I epithelial tumours was only 38.3% (28.5-48.2%) for peritoneal cancer, but as high as 66.5% (64.3-68.6%) for tumours of the anatomic ovary and 70.8% (62.3-79.3%) for tumours of the fallopian tube in the US. In the UK, survival from type I epithelial tumours of the fallopian tube diagnosed during 2005-2009 was lower than that for tumours of the ovary (52.6% (31.8-73.4%) versus 60.1% (55.8-64.4%)). A similar pattern was seen for type II epithelial tumours in both countries, with survival ranging from 14.7% (10.4-19.0%) for peritoneal cancer during 2005-2009 to 53.3% (44.2-62.4%) for fallopian tube tumours during the same time period in the UK, and from 31.9% (28.8-35.1%) for peritoneal tumours to 53.6% (48.2-59.0%) for fallopian tube tumours in the US.

For germ cell tumours, occurrence in the fallopian tube was extremely rare and survival could not be age-standardised for either country. Unstandardised survival was high in both countries. For germ cell tumours of the peritoneum, age-standardised survival during 2005-2009 in the US was 73.4% (58.8-88.0%). The survival estimate for peritoneal

Continued on page 203

Table 5.6 Five-year age-standardised net survival (NS, %) (95% CI) by sub-site, histological group, country and calendar period, United Kingdom and United States, 1995-2009

	Fallopian tube			Peritoneum			Ovary		
	No	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI
Type I epithelial									
United Kingdom									
1995-1999	97	**45.0**	30.8 - 59.3	-	.	-	6,414	**48.9**	47.1 - 50.7
2000-2004	97	**51.1**	36.7 - 65.5	58	**20.2**	12.9 - 27.5	6,246	**54.5**	52.7 - 56.3
2005-2009	129	**52.6**	31.8 - 73.4	73	***40.1***	*23.0 - 57.2*	5,581	**60.1**	55.8 - 64.4
United States									
1995-1999	387	**63.4**	55.7 - 71.1	164	**36.6**	27.0 - 46.2	17,404	**58.5**	57.3 - 59.7
2000-2004	533	**65.9**	59.6 - 72.1	217	**35.8**	26.9 - 44.8	18,470	**62.0**	60.9 - 63.2
2005-2009	613	**70.8**	62.3 - 79.3	277	**38.3**	28.5 - 48.2	17,144	**66.5**	64.3 - 68.6
Type II epithelial									
United Kingdom									
1995-1999	427	**43.2**	36.5 - 49.9	323	**15.9**	11.1 - 20.6	19,523	**21.2**	20.5 - 22.0
2000-2004	450	**44.3**	38.6 - 50.0	842	**17.6**	14.1 - 21.0	20,941	**22.4**	21.7 - 23.2
2005-2009	766	**53.3**	44.2 - 62.4	1,559	**14.7**	10.4 - 19.0	20,181	**24.7**	23.3 - 26.2
United States									
1995-1999	1,978	**52.5**	49.7 - 55.4	2,392	**26.6**	24.5 - 28.6	49,204	**33.0**	32.5 - 33.6
2000-2004	2,430	**55.3**	52.6 - 58.0	4,981	**28.8**	27.3 - 30.3	57,163	**34.0**	33.5 - 34.5
2005-2009	3,467	**53.6**	48.2 - 59.0	6,370	**31.9**	28.8 - 35.1	59,476	**35.5**	33.6 - 37.3

Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code are included.

	Fallopian tube					Peritoneum					Ovary				
	No	NS (%)	95% CI			N	NS (%)	95% CI			N	NS (%)	95% CI		
Germ cell															
United Kingdom															
1995-1999	-	.		-		-	.		-		289	**53.3**	37.5	-	69.0
2000-2004	-	.		-		-	.		-		306	**61.2**	47.5	-	75.0
2005-2009	18	***83.1***	*63.9*	-	*100.0*	43	***33.5***	*17.2*	-	*49.9*	357	**74.9**	64.2	-	85.6
United States															
1995-1999	-	.		-		58	***58.7***	*44.3*	-	*73.0*	1,293	**67.3**	59.2	-	75.3
2000-2004	-	.		-		75	**55.7**	41.0	-	70.3	1,604	**73.4**	66.0	-	80.8
2005-2009	62	***86.7***	*76.5*	-	*96.9*	94	**73.4**	58.8	-	88.0	1,786	**76.0**	65.0	-	87.1
Sex cord-stromal															
United Kingdom															
1995-1999	-	.		-		-	.		-		304	**77.2**	68.9	-	85.6
2000-2004	-	.		-		-	.		-		284	**81.2**	73.2	-	89.3
2005-2009	3	.		-		14	***41.9***	*16.2*	-	*67.6*	284	**78.0**	60.5	-	95.5
United States															
1995-1999	-	.		-		-	.		-		1,200	**81.0**	75.9	-	86.0
2000-2004	-	.		-		-	.		-		1,317	**84.4**	79.6	-	89.2
2005-2009	14	***100.0***	*84.6*	-	*100.0*	59	**56.8**	42.3	-	71.3	1,505	**85.3**	78.1	-	92.4

Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code are included.

	Fallopian tube					Peritoneum					Ovary				
	No	NS (%)	95% CI			N	NS (%)	95% CI			N	NS (%)	95% CI		
Other specific non-epithelial															
United Kingdom															
1995-1999	-	.		-		300	**30.9**	23.0	-	38.9	76	**27.2**	15.2	-	39.1
2000-2004	-	.		-		358	**30.6**	24.2	-	36.9	77	**22.2**	5.1	-	39.3
2005-2009	67	**28.1**	12.2	-	43.9	362	**40.0**	31.0	-	49.1	62	***28.9***	*10.2*	-	*47.5*
United States															
1995-1999	66	***55.7***	*41.8*	-	*69.6*	1,886	**41.1**	38.2	-	44.0	210	**30.9**	22.7	-	39.1
2000-2004	80	**44.8**	28.8	-	60.7	2,196	**43.2**	40.3	-	46.0	211	**30.3**	21.5	-	39.0
2005-2009	93	**60.3**	49.1	-	71.6	2,488	**47.9**	43.2	-	52.6	222	**21.3**	9.9	-	32.6
Non-specific															
United Kingdom															
1995-1999	-	.		-		-	.		-		190	**28.1**	18.1	-	38.1
2000-2004	-	.		-		-	.		-		244	**24.1**	16.1	-	32.0
2005-2009	55	***59.6***	*44.9*	-	*74.4*	56	***22.5***	*8.8*	-	*36.2*	264	**34.5**	24.8	-	44.3
United States															
1995-1999	-	.		-		73	**25.2**	13.4	-	36.9	695	**33.6**	28.3	-	39.0
2000-2004	80	**44.6**	27.2	-	62.1	106	**28.9**	18.4	-	39.3	959	**29.6**	25.7	-	33.5
2005-2009	52	***35.3***	*10.4*	-	*60.1*	89	**36.0**	21.4	-	50.7	979	**28.2**	18.5	-	37.9

Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. Countries with fewer than 10 women for any histological group (all calendar periods combined) were not included. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code are included.

germ cell tumours could not be age-standardised for the UK. For ovarian germ cell tumours, age-standardised survival was similar in both countries during 2005-2009 (74.9% (64.2-85.6%) in the UK and 76.0% (65.0-87.1%) in the US).

Sex cord-stromal tumours of the fallopian tube were also rare. Age-standardised survival was generally higher for tumours of the ovary than for tumours of the peritoneum (85.3% (78.1-92.4%) versus 56.8% (42.3-71.3%) in the US from 2005 to 2009).

Survival from other specific non-epithelial tumours, which was the most common histological group for peritoneal tumours, was generally higher for tumours of the peritoneum than for tumours of the ovary (47.9% (43.2-52.6%) versus 21.3% (9.9-32.6%) in the US during 2005-2009).

For peritoneal and fallopian tube cancers, tumours with non-specific morphology were rare. No obvious pattern in survival can been seen for these tumours. Survival for non-specific tumours of the ovary increased over time in the UK (from 28.1% (18.1-38.1%) to 34.5% (24.8-44.3%)), but decreased for the US (from 33.6% (28.3-39.0%) to 28.2% (18.5-37.9%)). Survival from non-specific tumours of the peritoneum, however, increased over time in the US (from 25.2%, 13.4-36.9% to 36.0%, 21.4-50.7%).

5.3.3 Survival for histological subtypes

Within the type I and type II epithelial groups, survival for each histological subtype varied [Table 5.7]. Estimates for each epithelial subtype were calculated for each calendar period of diagnosis for the US and the UK. During 2005-2009, five-year age-standardised net survival was highest for endometrioid (UK: 64.8%, US: 76.2%) and transitional cell (US: 69.6%) tumours. Survival from clear cell and mucinous tumours was moderate – 57.0-59.1% and 51.3-55.8%, respectively. Survival from squamous tumours was moderate in the UK (51.9%), but poor in the US (37.2%).

Table 5.7 Five-year age-standardised net survival (NS, %) (95% CI) by histological subtype, country and calendar period, United Kingdom and United States, 1995-2009

	United Kingdom			United States		
	N	NS (%)	95% CI	N	NS (%)	95% CI
TYPE I						
Clear cell						
1995-1999	1,065	**45.7**	41.3 - 50.2	2,924	**57.7**	54.6 - 60.9
2000-2004	1,330	**52.5**	48.7 - 56.4	3,636	**61.4**	58.5 - 64.2
2005-2009	1,440	**57.0**	51.1 - 62.8	3,975	**59.1**	54.6 - 63.5
Endometrioid						
1995-1999	2,632	**51.4**	48.5 - 54.3	8,354	**65.2**	63.5 - 66.9
2000-2004	2,578	**59.6**	56.6 - 62.6	9,313	**70.2**	68.6 - 71.8
2005-2009	2,071	**64.8**	58.6 - 71.1	8,408	**76.2**	72.8 - 79.5
Mucinous						
1995-1999	2,653	**47.5**	44.8 - 50.3	6,021	**50.7**	48.7 - 52.6
2000-2004	2,259	**50.7**	47.8 - 53.7	5,474	**50.1**	48.0 - 52.1
2005-2009	2,080	**51.3**	34.0 - 68.6	4,768	**55.8**	52.6 - 59.0
Squamous						
1995-1999	117	**29.5**	18.2 - 40.7	293	**31.9**	24.4 - 39.4
2000-2004	137	**35.6**	24.7 - 46.5	362	**37.8**	30.8 - 44.7
2005-2009	140	**51.9**	40.0 - 63.8	418	**37.2**	27.3 - 47.2
Transitional cell (Brenner)						
1995-1999	74	**54.9**	40.5 - 69.3	363	**64.6**	58.0 - 71.2
2000-2004	67	**62.1**	48.1 - 76.0	435	**69.2**	63.0 - 75.4
2005-2009	52	***53.7***	*38.3 - 69.1*	465	**69.6**	60.2 - 79.1
TYPE II						
Serous						
1995-1999	7,579	**30.8**	29.4 - 32.2	30,691	**38.3**	37.6 - 39.0
2000-2004	9,179	**31.2**	29.9 - 32.5	39,311	**38.6**	38.0 - 39.2
2005-2009	10,923	**32.9**	30.4 - 35.4	43,649	**39.5**	37.4 - 41.6
Mixed epithelial-stromal carcinoma						
1995-1999	619	**17.5**	13.9 - 21.1	2,364	**32.6**	30.2 - 34.9
2000-2004	804	**24.7**	20.9 - 28.4	3,960	**39.1**	37.1 - 41.0
2005-2009	943	**32.5**	25.7 - 39.3	6,235	**44.4**	41.3 - 47.6
Undifferentiated or other specific epithelial carcinoma						
1995-1999	12,075	**16.4**	15.5 - 17.3	20,519	**26.9**	26.1 - 27.6
2000-2004	12,250	**16.3**	15.4 - 17.2	21,303	**26.6**	25.9 - 27.4
2005-2009	10,640	**16.4**	14.8 - 18.1	19,429	**27.3**	25.7 - 28.9

Italics denote net survival estimates that are not age-standardised. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included.

For subtypes grouped as type II, survival from mixed-epithelial stromal tumours was the highest during 2005-2009 (44.4%) in the US, while undifferentiated carcinoma had the lowest (16.4%) in the UK. Survival from serous tumours was 39.5% in the US and 32.9% in the UK during the same time period. Survival for all type II subtypes was lower than that for type I subtypes, except for squamous tumours in the US, which was closer to that of mixed epithelial-stromal and serous carcinoma than mucinous – the second lowest survival for type I epithelial tumours. Survival for each subtype increased or remained stable over time in both countries.

5.4 Discussion

There are few international comparisons of survival for the various histological groups of ovarian cancer. The results from this large study show the importance of histology in comparisons of survival from ovarian cancer between countries.

The distribution of histological groups may explain some of the wide international variation in ovarian cancer survival, which is most frequently reported for epithelial tumours for all histological groups combined. In Asia, for example, type I epithelial tumours are more common than in other regions, in part due to a higher percentage of clear cell tumours. Because survival for type I epithelial tumours is generally higher than that of type II epithelial tumours, survival for all histological groups combined would be expected to be higher in Asian countries with this larger proportion of more favourable tumours. As shown in the results, survival for all histological groups combined was generally higher in Asian countries than other regions. It is therefore important to examine survival from ovarian cancer for each histological group separately, at least in international comparisons, because survival for all histological groups combined may be influenced by a higher proportion of tumours with a more favourable outcome.

The results also confirm that survival is higher for type I epithelial, germ cell and sex cord-stromal tumours than for the more aggressive type II epithelial tumours. Survival from tumours with a non-specific morphology is much lower than for tumours in any of these specific morphology groups, and generally decreased over time. This decrease is likely due to fewer tumours being coded as non-specific morphology over time and a corresponding increase in the number of tumours classified as type II epithelial. The decrease in the proportion of and survival for tumours of non-specific morphology suggests that improvements in the pathological examination of these tumours has led to more tumours being classified appropriately as type II epithelial (with slightly higher survival). Thus, the survival estimates for tumours coded as non-specific morphology were no longer inflated by the inappropriately classified type II epithelial tumours. Survival from tumours of non-specific morphology is expected to be even lower than that of type II tumours, because most women diagnosed with ovarian cancer for whom a specific morphology is not recorded are likely to have been too sick to undergo surgery, which is required for pathological examination and histological classification of the tumour. However, tumours recorded with missing or non-specific morphology may be recorded as such due to lack of or incomplete pathological information reported to registries.

Tumours of the peritoneum and fallopian tube have, more recently, been included in studies of tumours of the ovary. Cancers at all three sub-sites are treated clinically in the same manner, and are thought to have similar aetiology[17]. Since 2000, peritoneal and fallopian tube tumours have been included in clinical trials of tumours of the ovary. The results for this analysis show that survival varies greatly between the three sub-sites within each histological group. Survival was generally higher for tumours of the fallopian tube, and lower for tumours of the peritoneum and the anatomical ovary. Fallopian tube tumours may be diagnosed at an early stage, because of the restrictive guidelines for assigning “fallopian tube” as the sub-site for a pelvic tumour. In order for a tumour to be

considered a primary fallopian tube carcinoma, the majority of the tumour has to be within the fallopian tube rather than the ovary, and there must be evidence of an intraepithelial tubal carcinoma. Additionally, there must be a clear transition from benign to malignant epithelium[21].

Survival for each of the eight epithelial histological subtypes was only estimated separately for the UK and the US, because of the relatively small numbers of women available for analysis in other countries for some of the rarer subtypes. Data from the UK and the US comprised over 50% of all the data included in the analysis. Grouping epithelial subtypes into "type I" and "type II" may have masked some of the differences in survival between histological subtypes. Survival for tumours classified as type I ranged from 37.2% (squamous in the US) to 76.2% (endometrioid in the US). Squamous tumours are rare and are not typically included in epithelial ovarian cancer clinical trials. There is a striking difference in survival between endometrioid (76.2% in the US) and clear cell tumours (59.1% in the US). Clear cell tumours are known to be chemo-resistant, women with clear cell tumours have been shown to have lower survival than women with serous tumours[225]. However, the results from this analysis show that women diagnosed with clear cell tumours have higher survival than women with serous tumours (58.1% versus 39.5% in the US). This contrasting result may be due to women with clear cell tumours being diagnosed at an earlier stage than women with serous tumours. While survival increased or remained stable over time for all histological subtypes, increases in survival for most of type II subtypes were small, while larger increases over time were seen for most type I subtypes. This suggests that improvements in treatment and cancer care may have more influence on type I epithelial subtypes than type II epithelial subtypes.

Some cancer registries do not routinely collect data on tumour grade, and no information on grade was available for this study. Therefore, some serous tumours may have been

misclassified, because grade is required to classify these tumours appropriately. Only high-grade serous tumours are considered as type II epithelial, but all serous tumours were included in the definition of type II epithelial, because grade was not available. The effect on survival should be small, because only a small proportion (5%) of serous tumours are of low grade[2].

All endometrioid tumours were classified as type I epithelial, despite this subtype being previously sub-divided into type I and type II epithelial tumours[12]. If grade had been available, only low-grade endometrioid tumours would have been classified as type I epithelial while high-grade endometrioid tumours would have been classified as type II epithelial based on previous definitions of type I and type II epithelial tumours[12.] As with low-grade serous tumours, however, high-grade endometrioid tumours are rare, so the inclusion of these tumours in the type I epithelial group should not greatly affect the survival estimate by histological group[2]. An update in 2016 to the classification of endometrioid tumours into type I and type II epithelial tumours now classifies all endometrioid tumours as type I, regardless of tumour grade[10]. A sensitivity analysis was conducted to determine how the survival estimates varied between the two possible classifications for endometrioid tumours. Survival for both type I and type II epithelial generally increased by around 3 percentage points on average when endometrioid tumours were included in each group separately (appendix C). Because survival from endometrioid tumours was generally high when examined separately, including these tumours with the less-aggressive type I epithelial subtypes is preferable.

The quality and comparability of histology data between countries may be limited for several reasons, including differences in diagnostic techniques, histological classification and transfer of data to the cancer registry, or even to the CONCORD-2 study. For example, almost all tumours submitted by Sweden were coded as type II epithelial subtypes, the

majority of which were unspecified epithelial carcinomas. Given that previous studies show a wider distribution of histological subtypes[120], it is unlikely that almost all tumours from Sweden included in the analysis would have been true type II epithelial tumours. Additionally, Hong Kong only submitted epithelial ovarian cancers for the CONCORD-2 study. Therefore, the survival comparison is limited to type I and type II epithelial tumours for Hong Kong.

The analysis was limited to tumours that had been reported by the registry as morphologically verified, though tumours with specific ICD-O-3 morphology codes were also included even if the basis of diagnosis was clinical or missing. Morphological verification requires a tumour biopsy, and it may not be performed if the woman presents with advanced-stage disease, or is very elderly or has a high number of comorbidities. Additionally, morphological verification may be difficult to achieve in low resource settings, where survival may also be lower. Therefore, limiting the analysis to morphologically verified tumours may overestimate survival. However, given that 90.8% of tumours (before any exclusions) were reported as morphologically verified, the bias would be small.

This is the largest international population-based study of survival for ovarian cancer by histological subtype. The large number of women included allowed for comparison of survival from epithelial and non-epithelial tumours: these are usually studied separately, complicating comparison between different populations and time periods. The difference in survival between the histological groups emphasises the need to focus future international comparisons of ovarian cancer survival on the various subtypes, rather than simply analysing survival from “ovarian cancer” as if it were a single homogenous group of tumours.

The results from this analysis also emphasise the need for further development of high-quality population-based cancer registries in low-income countries, and the continued improvement of the quality and completeness of cancer registry data in all countries.

Chapter 6: Ovarian cancer survival by stage at diagnosis

6.1 Introduction

While most women with ovarian cancer are diagnosed at an advanced stage, stage-specific survival differs widely between countries[3]. In a comparison of one-year net survival between six high-income countries, the highest percentage of women with advanced disease and the second lowest survival for all stages combined was seen in Denmark[3]. Thus, the international variation in ovarian cancer survival for all stages combined may be partially explained by the distribution of stage at diagnosis.

The distribution of stage has also been shown to vary between histological groups. Type I epithelial tumours tend to be early-stage, while type II epithelial tumours tend to be more advanced. Among type I epithelial tumours, stage I and II are the most common stages at diagnosis for endometrioid, clear cell, mucinous and transitional cell tumours[2,9]. Around 60-70% of germ cell tumours are stage I or II at diagnosis, while 30-40% are stage III; stage IV germ cell tumours are extremely rare[36]. Sex cord-stromal tumours are usually unilateral and confined to the ovaries at diagnosis[2].

6.2 Material and methods

The CONCORD-2 study was based on data for over 25.7 million patients diagnosed with one of 10 common cancers, contributed by 279 population-based cancer registries in 67 countries. The data included 779,302 women diagnosed with ovarian cancer in 61 countries during the 15-year period of 1995 to 2009. The CONCORD-2 protocol, ethical approvals, and quality control procedures have been described elsewhere[188] and in

Chapter 3[a].

Information on stage at diagnosis was requested for only women diagnosed between 2001 and 2009, because the quality and completeness of data on stage at diagnosis in most registries prior to this would be inadequate for survival analysis; therefore, the stage-specific analysis only includes women diagnosed between 2001 and 2009.

Data were available for 517,586 women (aged 15-99 years) diagnosed from 2001 to 2009 with a cancer of the ovary, fallopian tube, uterine ligaments and adnexa, other specified and unspecified female genital organs, peritoneum and retroperitoneum in 245 registries in 61 countries [Figure 6.1]. Survival was estimated for each registry for two calendar periods: 2001-2003 and 2004-2009, when possible. Country-level survival estimates were derived by pooling data for registries that were included in the registry-specific analysis by stage at diagnosis. Borderline tumours and those coded with haematological morphology were excluded from the analysis. Registries for which net survival estimates were considered as less reliable in the main CONCORD-2 analysis[188] were excluded. Registries with fewer than 10 women available for analysis in each stage for any given time period were excluded. Registries were only included if less than 30% of tumours were missing stage at diagnosis during 2004-2009. The majority of the exclusions were because of this requirement. If fewer than 50 women were available for survival analysis by stage at diagnosis in a given calendar period, the data for that registry were merged for the two calendar periods.

Recent evidence suggests that high-grade serous carcinoma, the most common type of ovarian cancer, originates in the fallopian tube. Therefore, cancers of the fallopian tube

[a] The material in Chapters 4-7 is based on examination of the distribution of and ovarian from cancer survival histology, stage at diagnosis and race/ethnicity. A few paragraphs of material and methods are repeated in each of these chapters for ease of reference and to ensure consistency of the descriptions. A detailed definition and description of the data and methods can be found in Chapter 3.

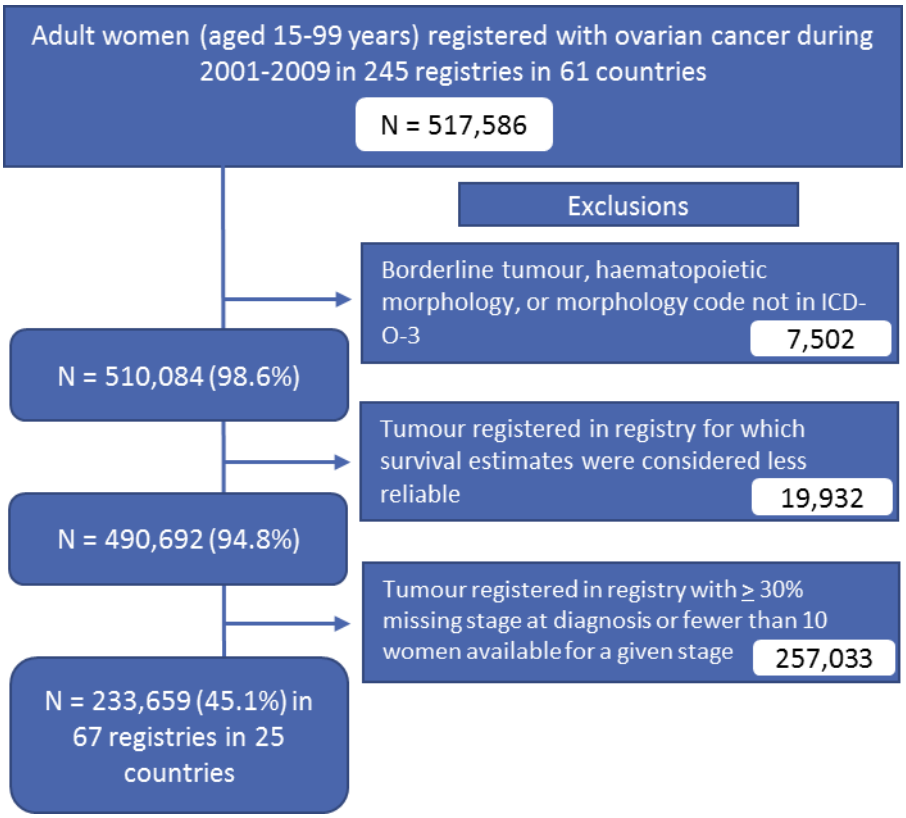


Figure 6.1 Data exclusion flow chart for net survival analysis by stage at diagnosis, 2001-2009

and other specified and unspecified female genital organs were included in a broader definition of ovarian cancer[12]. Similarly, primary peritoneal and retroperitoneal carcinomas are managed in the same way as advanced-stage epithelial ovarian cancer, and they are also included[12]. The term "ovarian" in this chapter refers to tumours at all these sub-sites, unless the context makes clear that it refers to tumours of the anatomic ovary.

Follow-up until 31 December 2009 for vital status was available. Women diagnosed with ovarian cancer as a second or higher-order primary tumour are included in the analysis, in addition to those for whom ovarian cancer was their first cancer. Women whose cancer registration was from a death certificate or autopsy only were excluded, because their true survival time was unknown.

Stage at diagnosis was categorised as "localised" or "advanced". Registries submitted stage data coded to one of several classifications: the UICC's TNM staging system (7th edition), the FIGO system or SEER Summary Stage 2000. Data were received on pathological and/or clinical T, N and M, as well as tumour size (in millimetres) and the number of positive lymph nodes. These data were used to create a final stage at diagnosis variable, prioritising pathological TNM information, supplemented with clinical TNM information where missing. Information on FIGO stage and SEER Summary Stage 2000 was used to supplement missing TNM information when both pathological and clinical TNM were missing, and if no data on tumour size or number of positive lymph nodes were available. Tumours with TNM Stage I are those confined to the ovaries at diagnosis; and these tumours were defined as "localised". Stage II tumours are rare and have spread beyond the ovaries. Stage III tumours have spread to regional lymph nodes, and Stage IV tumours have metastasised to other organs. TNM Stage II, Stage III and Stage IV tumours were defined as "advanced". Where there was no information available on stage, the

tumours were classified as missing stage at diagnosis; net survival was estimated separately for these tumours. Survival was analysed by stage at diagnosis in each country, and where possible, for registry separately.

Net survival is defined as the probability of survival for cancer patients up to a given point in time after diagnosis (for example, 5 years) if death from cancer were to be the only cause of death. Net survival controls for the background mortality of competing causes of death in a population. Life tables of all-cause mortality rates by single year of age (0-99 years), region, sex, calendar year and, where possible, race were used to control for variations in background mortality. The Pohar Perme estimator of net survival[224], which allows for the fact that competing risks of death increase with age, was used to estimate net survival. The Pohar Perme estimator was implemented using *stns*[208] in Stata version 14[207]. Standard errors were calculated using the Greenwood method[209].

Net survival is reported for each country and/or registry and stage at diagnosis with 95% confidence intervals (CI). Survival by stage at diagnosis was estimated for two calendar periods of diagnosis: 2001-2003 and 2004-2009. The cohort approach was used for 2001-2003 because five or more years of follow-up were available for all patients, while the complete approach was used for 2004-2009[a].

Survival by stage at diagnosis for each histological group (see Chapters 4 and 5) was also analysed for the US only (n=169,832). Data from the US comprised over 70% of the data available for the analysis by stage at diagnosis. Only microscopically verified tumours or tumours that were clinically diagnosed but for which a specific morphology code was available were included in this analysis (94.5%; n=160,560). The larger number of women

[a] See Chapter 3 for a more detailed explanation of these methods.

from the US included in the analysis allowed for a more detailed analysis than for other countries.

Survival estimates for all ages combined were age-standardised, where possible, with the International Cancer Standard Survival (ICSS) weights[206]. Age at diagnosis was categorised into five age groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. If an age-specific estimate could not be produced, or fewer than 10 women were available for analysis in an age group, data for adjacent age groups were pooled and the re-estimated survival was used for both of the original age groups. If two or more age-specific estimates could not be produced, or fewer than 10 women were available for analysis in two or more age groups, only the unstandardised estimate is reported.

6.3 Results

6.3.1 Stage at diagnosis

Data for 233,659 women were available from 67 registries in 25 countries for analysis of survival by stage [Figure 6.1]. Only two out of 19 Central and South American registries provided enough information on stage at diagnosis to be included in this analysis. In North America, one out of 13 Canadian registries and 36 out of 37 US registries provided adequate stage data. In Asia and Europe, only 12 (out of 48) and 13 (out of 115) registries, respectively, provided adequate stage data to be included in the analysis. No data from African registries were available for analysis by stage at diagnosis.

Overall, 38,033 (16.3%) of these 233,659 women were diagnosed with localised ovarian cancer, and 169,033 (72.3%) with advanced disease. Stage at diagnosis was missing for 26,593 women (11.4%). Women diagnosed with localised ovarian cancer were the youngest (mean age 56 years), while women with a missing stage at diagnosis were the oldest (mean age 68 years). The mean age at diagnosis for women diagnosed with advanced disease was 65 years [Table 6.1].

Table 6.1 Worldwide distribution (%) of stage at diagnosis and mean age at diagnosis, 2001-2009, 25 countries

Stage at diagnosis	No.	%	Mean age(SD)[a] (years)
Localised	38,033	16.3	56 (16)
Advanced	169,033	72.3	65 (14)
Missing	26,593	11.4	68 (16)
Total	233,659	100.0	64 (15)

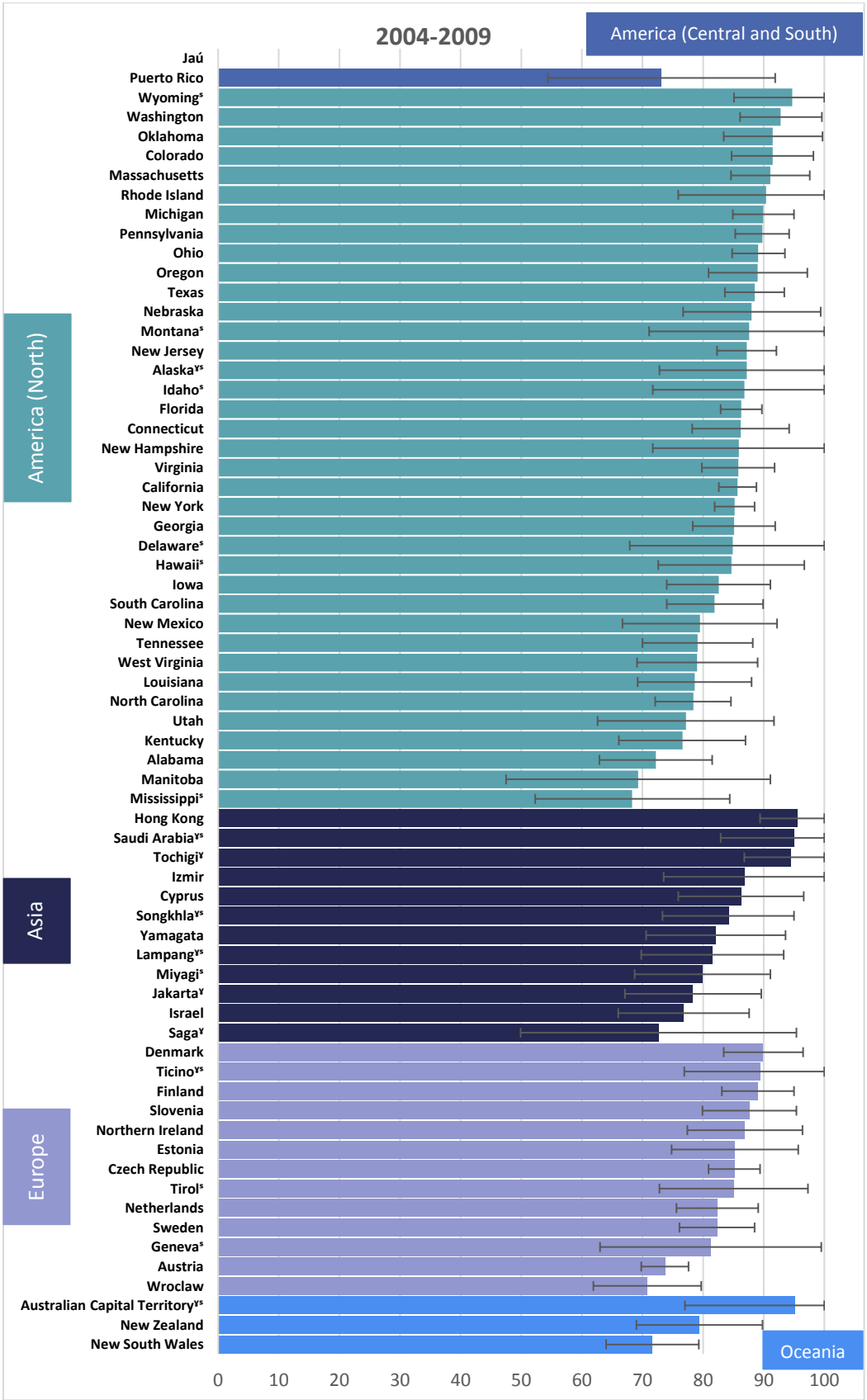
[a] Standard deviation.

Overall, 5-year age-standardised net survival for localised ovarian cancer was much higher than that for advanced disease, or tumours with a missing stage at diagnosis [Figures 6.2-6.4]. For women diagnosed with localised ovarian cancer during 2004-2009, survival in all registries was much higher than for women diagnosed with advanced disease. In some registries, 5-year age-standardised survival was over 90% for localised tumours, with the highest survival in Hong Kong (95.5%, 95% CI: 89.4-100.0%) [Table 6.2]. The lowest age-standardised survival from localised tumours was seen in Mississippi (US) (68.3%, 52.3-84.4%). This is still much higher, however, than the highest survival for advanced-stage tumours during the same time period.

Over time, age-standardised survival for localised tumours increased or remained stable in 21 of the 37 registries for which age-standardised estimates could be produced for both calendar periods. The largest increase was seen in Oklahoma (US) where survival increased from 80.6% (68.3-92.9%) in 2001-2003 to 91.5% (83.4-99.7%) in 2004-2009. In Tennessee (US), survival decreased from 84.3% (71.3-97.3%) to 79.1% (70.0-88.2%), whereas in New South Wales (Australia) survival decreased from 76.8% (68.1-85.5%) to 71.6% (64.0-79.3%), two of the largest decreases seen during 2001-2009.

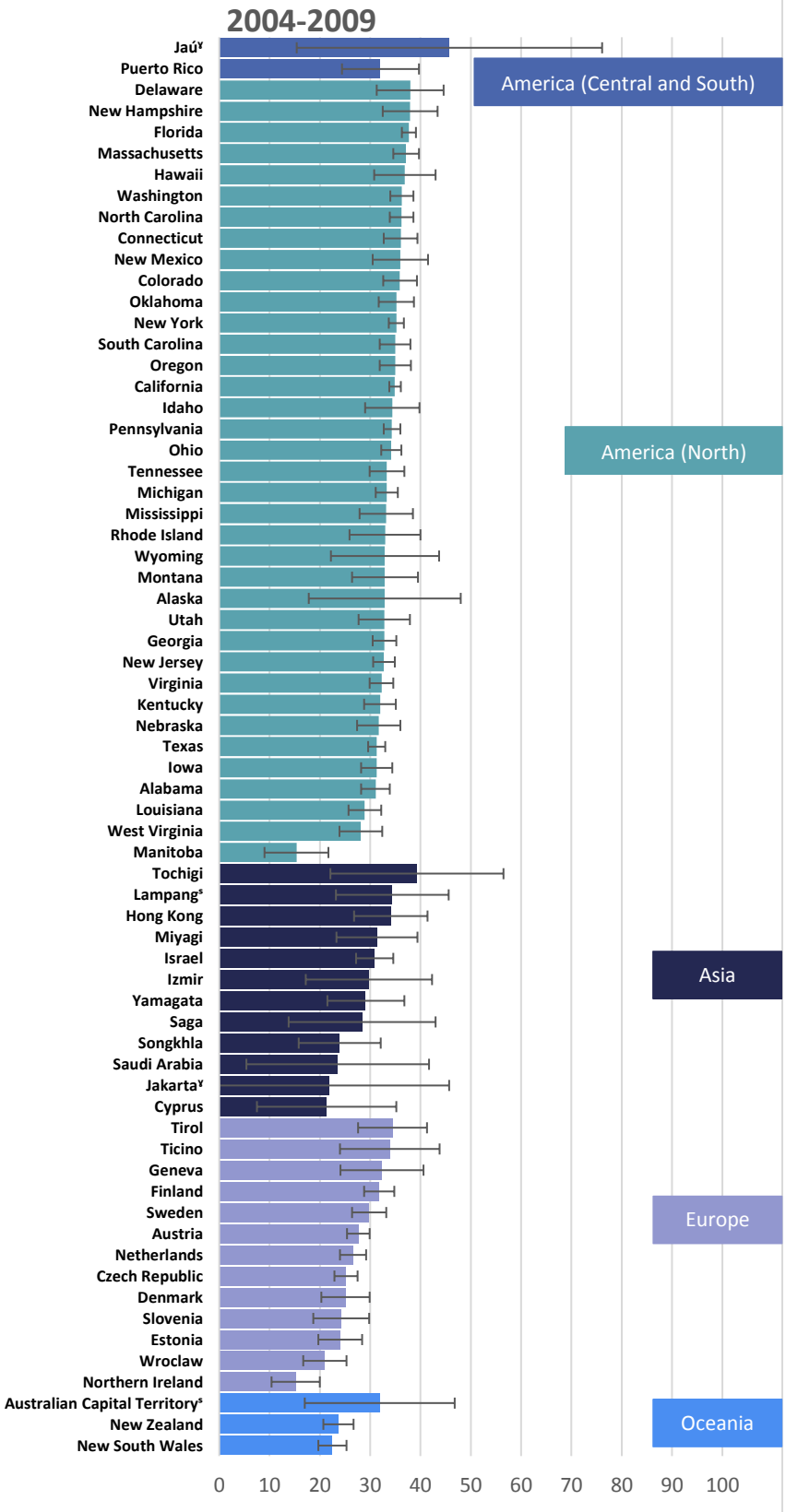
For advanced-stage ovarian cancer, survival was generally around 30%. Age-standardised survival from advanced-stage disease diagnosed during 2004-2009 was highest in Tochigi (Japan; 39.3%, 22.1-56.5%), while the lowest survival was in Northern Ireland (UK; 15.2%, 10.4-20.0%). The between-registry variation in survival for advanced-stage disease was not as wide as that for localised disease. Survival increased or remained stable over time in 47 of the 62 registries for which age-standardised survival estimates could be produced for both time periods. The largest increase in survival was seen in Songkhla (Thailand; from 14.0% (4.7-23.4%) to 23.9% (15.8-32.1%)). Decreases in survival over time were

Continued on page 232



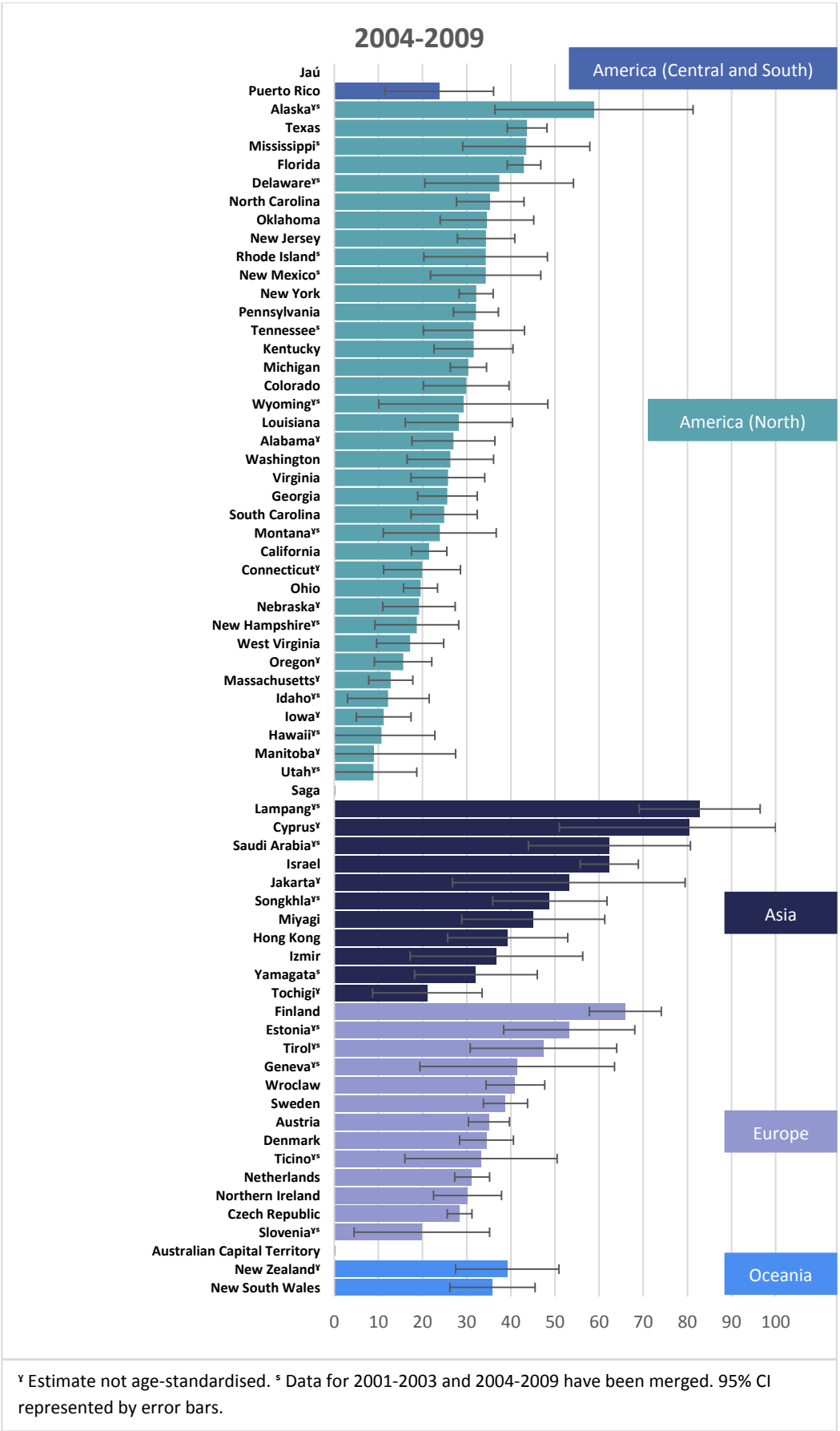
[Y] Estimate not age-standardised. [s] Data for 2001-2003 and 2004-2009 have been merged. 95% CI represented by error bars.

Figure 6.2 Five-year age-standardised net survival (%) for localised tumours, 2004-2009



¥ Estimate not age-standardised. $ Data for 2001-2003 and 2004-2009 have been merged. 95% CI represented by error bars.

Figure 6.3 Five-year age-standardised net survival (%) for advanced tumours, 2004-2009



[ɣ] Estimate not age-standardised. [s] Data for 2001-2003 and 2004-2009 have been merged. 95% CI represented by error bars.

Figure 6.4 Five-year age-standardised net survival (%) for tumours with missing stage, 2004-2009

Table 6.2 Five-year age-standardised net survival (NS, %) (95% CI) by country, registry, calendar period and stage at diagnosis, 1995-2009, 25 countries

	Calendar period	Localised				Advanced				Missing			
		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
AMERICA (CENTRAL AND SOUTH)													
Brazil													
Jaú	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	-	.	.		18	***45.7***	*15.4*	*76.1*	-	.	.	
Puerto Rico													
Puerto Rico	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	187	**73.1**	54.4	91.9	535	**32.0**	24.4	39.7	122	**23.8**	11.5	36.1
AMERICA (NORTH)													
Canada*													
Manitoba	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	88	**69.3**	47.5	91.1	501	**15.4**	9.0	21.7	21	***9.0***	*0.0*	*27.5*
United States	2001-2003	8,957	**84.8**	83.3	86.4	40,928	**32.4**	31.8	33.0	5,467	**31.6**	29.9	33.3
	2004-2009	16,612	**85.5**	84.4	86.7	88,747	**34.2**	33.8	34.7	9,121	**30.9**	29.7	32.2
Alabama	2001-2003	188	**69.3**	54.6	83.9	806	**31.0**	27.0	34.9	82	***26.3***	*15.7*	*36.8*
	2004-2009	326	**72.2**	62.9	81.5	1,814	**31.1**	28.2	33.9	133	***27.0***	*17.6*	*36.4*
Alaska	2001-2003	-	.	.		71	**27.6**	12.9	42.2	-	.	.	
	2004-2009	61	***87.2***	*72.8*	*100.0*	171	**32.9**	17.8	48.0	23	***58.9***	*36.4*	*81.3*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
California	2001-2003	1,142	**90.2**	86.0	94.5	6,188	**34.1**	32.5	35.7	455	**23.3**	17.1	29.4
	2004-2009	2,393	**85.7**	82.6	88.8	12,921	**34.9**	33.8	36.1	965	**21.5**	17.5	25.5
Colorado	2001-2003	176	**94.4**	85.5	100.0	719	**33.6**	28.9	38.4	75	**24.8**	13.5	36.1
	2004-2009	328	**91.5**	84.7	98.2	1,768	**35.9**	32.6	39.3	107	**29.9**	20.2	39.6
Connecticut	2001-2003	139	**87.7**	76.4	99.0	771	**34.4**	30.0	38.8	54	***20.8***	*8.8*	*32.9*
	2004-2009	266	**86.2**	78.2	94.2	1,572	**36.1**	32.7	39.4	80	***19.9***	*11.2*	*28.6*
Delaware	2001-2003	-	.	.		153	**37.1**	27.5	46.7	-	.	.	
	2004-2009	75	**84.9**	67.9	100.0	368	**38.0**	31.3	44.6	45	***37.4***	*20.5*	*54.2*
Florida	2001-2003	714	**84.9**	80.1	89.6	3,615	**33.5**	31.6	35.4	560	**39.9**	34.6	45.1
	2004-2009	1,244	**86.3**	82.9	89.7	7,613	**37.7**	36.3	39.1	909	**43.0**	39.2	46.8
Georgia	2001-2003	267	**86.8**	76.5	97.2	1,385	**33.7**	30.3	37.0	176	**27.9**	18.4	37.4
	2004-2009	600	**85.1**	78.3	91.9	3,100	**32.8**	30.5	35.2	263	**25.6**	18.9	32.4
Hawaii	2001-2003	-	.	.		209	**37.7**	29.1	46.3	-	.	.	
	2004-2009	114	**84.7**	72.6	96.7	467	**36.9**	30.8	43.0	32	***10.7***	*0.0*	*22.8*
Idaho	2001-2003	-	.	.		217	**33.1**	23.9	42.2	-	.	.	
	2004-2009	128	**86.8**	71.7	100.0	519	**34.4**	29.0	39.8	58	***12.2***	*3.0*	*21.5*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Iowa	2001-2003	123	**83.6**	71.4	95.9	670	**33.6**	29.2	37.9	69	***9.0***	*1.6*	*16.5*
	2004-2009	233	**82.6**	74.0	91.1	1,333	**31.3**	28.2	34.4	116	***11.2***	*5.0*	*17.4*
Kentucky	2001-2003	130	**78.5**	63.0	94.0	753	**32.2**	27.8	36.7	104	**28.7**	18.5	38.9
	2004-2009	334	**76.6**	66.1	87.0	1,597	**32.0**	28.8	35.1	160	**31.6**	22.6	40.5
Louisiana	2001-2003	122	**78.9**	64.9	92.9	758	**29.6**	25.2	34.0	70	***25.5***	*12.9*	*38.0*
	2004-2009	235	**78.6**	69.2	88.0	1,416	**28.9**	25.7	32.2	97	**28.2**	16.1	40.4
Massachusetts	2001-2003	256	**87.6**	79.1	96.2	1,456	**34.8**	31.3	38.2	124	***16.4***	*8.6*	*24.1*
	2004-2009	526	**91.1**	84.6	97.6	2,863	**37.1**	34.6	39.7	213	***12.8***	*7.8*	*17.8*
Michigan	2001-2003	425	**88.8**	82.0	95.7	1,823	**31.7**	28.8	34.5	292	**31.4**	24.7	38.1
	2004-2009	737	**89.9**	84.9	95.0	3,449	**33.3**	31.1	35.5	842	**30.4**	26.3	34.5
Mississippi	2001-2003	-	.	.		123	**26.7**	15.4	38.0	-	.	.	
	2004-2009	197	**68.3**	52.3	84.4	894	**33.2**	27.9	38.5	109	**43.5**	29.1	57.9
Montana	2001-2003	-	.	.		189	**33.2**	24.1	42.4	-	.	.	
	2004-2009	101	**87.6**	71.1	100.0	448	**32.9**	26.4	39.5	61	***23.9***	*11.1*	*36.7*
Nebraska	2001-2003	80	**85.8**	70.2	100.0	342	**29.7**	23.8	35.7	51	***18.1***	*7.6*	*28.6*
	2004-2009	121	**88.0**	76.7	99.4	753	**31.7**	27.4	36.0	82	***19.2***	*11.0*	*27.4*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
New Hampshire	2001-2003	61	***87.8***	*75.7*	*99.9*	213	**40.1**	32.0	48.3	-	.	.	
	2004-2009	108	**85.9**	71.7	100.0	553	**37.9**	32.5	43.4	94	***18.7***	*9.2*	*28.2*
New Jersey	2001-2003	407	**87.4**	79.8	94.9	1,914	**31.5**	28.6	34.5	236	**35.6**	26.4	44.9
	2004-2009	727	**87.2**	82.3	92.1	3,648	**32.7**	30.6	34.9	399	**34.4**	27.9	40.9
New Mexico	2001-2003	51	***83.9***	*71.8*	*96.1*	317	**34.4**	26.2	42.7	-	.	.	
	2004-2009	126	**79.5**	66.7	92.2	636	**36.0**	30.5	41.5	128	**34.3**	21.8	46.8
New York	2001-2003	918	**82.0**	77.1	86.9	3,670	**34.0**	31.9	36.1	735	**26.8**	22.4	31.1
	2004-2009	1,671	**85.2**	81.9	88.5	8,001	**35.2**	33.7	36.7	791	**32.2**	28.3	36.0
North Carolina	2001-2003	396	**75.2**	66.9	83.6	1,373	**31.1**	27.8	34.5	170	**43.2**	32.6	53.8
	2004-2009	602	**78.4**	72.1	84.6	3,298	**36.2**	33.9	38.6	277	**35.3**	27.7	43.0
Ohio	2001-2003	539	**86.6**	80.4	92.8	1,804	**31.6**	28.8	34.3	440	**25.1**	19.9	30.3
	2004-2009	851	**89.1**	84.8	93.5	4,283	**34.2**	32.2	36.2	572	**19.6**	15.7	23.4
Oklahoma	2001-2003	147	**80.6**	68.3	92.9	663	**34.7**	29.9	39.5	103	**28.6**	16.9	40.4
	2004-2009	224	**91.5**	83.4	99.7	1,286	**35.2**	31.7	38.7	193	**34.6**	24.0	45.2
Oregon	2001-2003	148	**86.1**	74.4	97.9	778	**34.0**	29.8	38.3	77	***24.8***	*13.5*	*36.1*
	2004-2009	263	**89.0**	80.9	97.2	1,672	**35.0**	31.9	38.1	126	***15.6***	*9.1*	*22.1*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Pennsylvania	2001-2003	658	**89.7**	84.0	95.4	2,737	**32.5**	30.2	34.8	355	**32.6**	25.8	39.5
	2004-2009	1,044	**89.8**	85.3	94.2	5,900	**34.3**	32.7	36.0	509	**32.1**	27.0	37.2
Rhode Island	2001-2003	60	***87.2***	*75.3*	*99.0*	177	**29.9**	21.5	38.2	-	.	.	
	2004-2009	113	**90.4**	75.9	100.0	266	**33.0**	25.9	40.0	97	**34.3**	20.3	48.3
South Carolina	2001-2003	176	**83.7**	73.1	94.3	695	**32.8**	28.5	37.1	119	**31.8**	20.7	42.8
	2004-2009	307	**81.9**	74.0	89.9	1,478	**35.0**	31.9	38.0	159	**24.9**	17.4	32.4
Tennessee	2001-2003	70	**84.3**	71.3	97.3	308	**28.3**	21.7	34.8	-	.	.	
	2004-2009	468	**79.1**	70.0	88.2	2,048	**33.3**	29.9	36.8	217	**31.6**	20.2	43.1
Texas	2001-2003	645	**89.0**	82.7	95.3	2,608	**28.7**	26.4	31.0	576	**48.4**	42.3	54.4
	2004-2009	1,146	**88.5**	83.6	93.4	6,053	**31.3**	29.6	33.0	932	**43.7**	39.2	48.2
Utah	2001-2003	72	**70.0**	56.9	83.1	354	**31.3**	24.8	37.7	-	.	.	
	2004-2009	137	**77.2**	62.6	91.7	695	**32.8**	27.7	37.9	47	***8.9***	*0.0*	*18.7*
Virginia	2001-2003	296	**79.9**	71.5	88.3	1,201	**24.8**	21.7	27.9	112	**23.8**	10.9	36.7
	2004-2009	494	**85.8**	79.8	91.8	2,692	**32.3**	29.9	34.6	231	**25.8**	17.4	34.1
Washington	2001-2003	228	**93.3**	83.9	100.0	1,398	**35.6**	32.4	38.7	85	***17.1***	*7.7*	*26.4*
	2004-2009	351	**92.8**	86.1	99.6	2,245	**36.3**	34.0	38.6	190	**26.3**	16.5	36.1

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
West Virginia	2001-2003	104	**77.3**	64.1	90.6	383	**25.8**	20.4	31.1	76	***16.8***	*7.7*	*25.9*
	2004-2009	124	**79.0**	69.1	89.0	740	**28.1**	23.9	32.4	110	**17.2**	9.6	24.8
Wyoming	2001-2003	-	.	.		87	**30.9**	18.0	43.8	-	.	.	
	2004-2009	56	**94.7**	85.1	100.0	187	**32.9**	22.2	43.7	25	***29.3***	*10.1*	*48.4*
ASIA													
Cyprus													
Cyprus	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	81	**86.3**	75.9	96.6	166	**21.4**	7.5	35.2	18	***80.5***	*51.0*	*100.0*
Hong Kong													
Hong Kong	2001-2003	226	**93.8**	85.6	100.0	322	**25.2**	15.4	35.0	67	***54.7***	*41.9*	*67.5*
	2004-2009	239	**95.5**	89.4	100.0	322	**34.1**	26.8	41.4	92	**39.3**	25.7	52.9
Indonesia													
Jakarta	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	144	***78.3***	*67.1*	*89.6*	49	***21.8***	*0.0*	*45.7*	42	***53.2***	*26.8*	*79.5*
Israel*													
Israel	2001-2003	110	**81.6**	68.2	95.0	831	**30.6**	26.0	35.2	288	**61.4**	52.8	70.0
	2004-2009	279	**76.8**	66.0	87.6	1,698	**30.9**	27.2	34.6	438	**62.3**	55.7	68.9
Japan	2001-2003	107	**80.8**	70.9	90.8	419	**30.5**	22.5	38.5	137	**44.2**	29.7	58.7
	2004-2009	326	**80.4**	69.0	91.8	920	**30.7**	25.3	36.0	233	**39.1**	29.9	48.3

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Miyagi	2001-2003	-	.	.		282	**32.2**	21.9	42.4	106	**47.2**	29.7	64.7
	2004-2009	88	**79.9**	68.7	91.1	171	**31.4**	23.3	39.4	85	**45.1**	28.9	61.3
Saga	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	14	***72.7***	*49.9*	*95.4*	80	**28.4**	13.8	43.0	-	.	.	
Tochigi	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	126	***94.5***	*86.8*	*100.0*	365	**39.3**	22.1	56.5	71	***21.1***	*8.7*	*33.5*
Yamagata	2001-2003	58	***87.3***	*77.8*	*96.8*	137	**26.5**	15.6	37.5	-	.	.	
	2004-2009	147	**82.1**	70.6	93.6	304	**29.1**	21.5	36.8	108	**32.1**	18.2	46.0
Saudi Arabia*													
Saudi Arabia	2001-2003	-	.	.		211	***31.4***	*21.4*	*41.4*	-	.	.	
	2004-2009	103	***95.0***	*82.9*	*100.0*	78	**23.5**	5.4	41.7	65	***62.4***	*44.0*	*80.7*
Thailand	2001-2003	-	.	.		96	**19.0**	10.3	27.7	-	.	.	
	2004-2009	150	**83.8**	72.7	94.8	260	**41.1**	22.0	60.3	126	**51.7**	34.4	69.0
Lampang	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	73	***81.5***	*69.8*	*93.3*	145	**34.4**	23.2	45.6	56	***82.8***	*69.1*	*96.5*
Songkhla	2001-2003	-	.	.		55	**14.0**	4.7	23.4	-	.	.	
	2004-2009	77	***84.2***	*73.3*	*95.0*	156	**23.9**	15.8	32.1	70	***48.8***	*35.9*	*61.8*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

	Calendar period	Localised				Advanced				Missing			
		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Turkey													
Izmir	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	200	**86.9**	73.5	100.0	559	**29.7**	17.2	42.3	137	**36.8**	17.2	56.3
EUROPE													
Austria*	2001-2003	679	**75.4**	70.2	80.5	1,427	**26.6**	23.6	29.6	420	**35.5**	29.1	41.9
	2004-2009	1,163	**74.5**	70.9	78.2	2,589	**28.3**	26.2	30.5	848	**35.8**	31.1	40.4
Austria	2001-2003	635	**74.8**	69.5	80.2	1,276	**26.4**	23.2	29.6	405	**35.0**	28.5	41.5
	2004-2009	1,080	**73.7**	69.8	77.6	2,317	**27.7**	25.4	29.9	816	**35.1**	30.4	39.7
Tirol	2001-2003	-	.	.		151	**29.0**	19.9	38.1	-	.	.	
	2004-2009	127	**85.1**	72.8	97.3	272	**34.5**	27.6	41.3	47	***47.4***	*30.8*	*64.0*
Czech Republic*													
Czech Republic	2001-2003	683	**84.0**	77.9	90.1	1,916	**22.0**	19.1	24.8	1,011	**32.0**	27.9	36.2
	2004-2009	1,336	**85.2**	80.9	89.4	4,426	**25.2**	22.9	27.5	1,433	**28.4**	25.6	31.2
Denmark*													
Denmark	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	716	**89.9**	83.4	96.5	2,067	**25.1**	20.3	29.9	813	**34.5**	28.4	40.6
Estonia*													
Estonia	2001-2003	88	**86.0**	72.2	99.8	378	**22.5**	16.7	28.2	-	.	.	
	2004-2009	176	**85.2**	74.8	95.7	620	**24.0**	19.7	28.4	58	***53.3***	*38.4*	*68.1*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Finland*													
Finland	2001-2003	234	**81.1**	71.3	90.9	1,181	**30.6**	26.5	34.7	201	**60.2**	45.7	74.8
	2004-2009	455	**89.0**	83.1	95.0	2,314	**31.8**	28.8	34.8	420	**66.0**	57.8	74.1
Netherlands*													
Netherlands	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	1,340	**82.4**	75.6	89.1	4,444	**26.6**	24.0	29.2	2,152	**31.2**	27.3	35.2
Poland*													
Wroclaw	2001-2003	165	**65.9**	47.7	84.1	494	**20.9**	15.5	26.3	273	**45.9**	35.3	56.5
	2004-2009	307	**70.8**	61.9	79.7	989	**21.0**	16.7	25.3	447	**41.0**	34.4	47.7
Slovenia													
Slovenia	2001-2003	140	**89.1**	78.3	99.9	416	**23.2**	17.0	29.5	-	.	.	
	2004-2009	279	**87.6**	79.9	95.4	904	**24.2**	18.7	29.8	44	***19.9***	*4.5*	*35.2*
Sweden*													
Sweden	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	1,026	**82.3**	76.1	88.5	2,790	**29.8**	26.4	33.2	1,160	**38.8**	33.8	43.8
Switzerland	2001-2003	-	.	.		188	**34.2**	25.6	42.9	-	.	.	
	2004-2009	111	**81.0**	67.2	94.9	341	**34.7**	27.8	41.5	61	***36.3***	*22.4*	*50.2*
Geneva	2001-2003	-	.	.		114	**34.0**	24.0	44.0	-	.	.	
	2004-2009	60	**81.3**	63.0	99.5	199	**32.4**	24.1	40.6	20	***41.5***	*19.4*	*63.5*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

		Localised				Advanced				Missing			
	Calendar period	No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI		No. of patients[b]	NS (%)	95% CI	
Ticino	2001-2003	-	.	.		74	***36.1***	*24.3*	*47.9*	-	.	.	
	2004-2009	51	***89.4***	*76.9*	*100.0*	142	**33.9**	24.0	43.8	41	***33.3***	*16.0*	*50.5*
United Kingdom*													
Northern Ireland	2001-2003	132	**85.8**	71.8	99.9	255	**12.9**	10.0	15.9	130	**32.2**	21.0	43.4
	2004-2009	221	**86.9**	77.4	96.4	592	**15.2**	10.4	20.0	235	**30.2**	22.5	37.9
OCEANIA													
Australia	2001-2003	255	**77.3**	68.8	85.8	914	**27.6**	24.0	31.1	175	**37.1**	24.8	49.5
	2004-2009	288	**72.3**	64.8	79.8	1,078	**23.0**	20.2	25.8	154	**35.8**	26.2	45.5
Australian Capital Territory	2001-2003	-	.	.		-	.	.		-	.	.	
	2004-2009	20	***95.2***	*77.0*	*100.0*	107	**31.9**	17.0	46.8	-	.	.	
New South Wales	2001-2003	245	**76.8**	68.1	85.5	872	**27.0**	23.4	30.6	175	**37.1**	24.8	49.5
	2004-2009	278	**71.6**	64.0	79.3	1,013	**22.5**	19.7	25.3	154	**35.8**	26.2	45.5
New Zealand*													
New Zealand	2001-2003	166	**81.1**	69.0	93.1	584	**24.0**	19.7	28.4	51	**24.6**	12.1	37.1
	2004-2009	264	**79.4**	69.0	89.8	1,466	**23.7**	20.7	26.7	133	***39.2***	*27.5*	*50.9*

*Data with 100% coverage of the national population. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. [a] Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis. [b] Number of patients included in analysis for a given calendar period. The number of women per registry may differ from the main CONCORD-2 analysis due to the exclusion of borderline tumours and updates from registries. The total number of women for a country in a given calendar period may not equal the sum of the number per registry for that period due to merging of calendar periods to produce the registry-level estimates.

small; the largest decrease (from 27.0% (23.4-30.6%) to 22.5% (19.7-25.3%)) was seen in New South Wales (Australia).

Survival from tumours with a missing stage at diagnosis was similar to or lower than that for advanced disease in most registries in Central and South America and North America during 2005-2009. In North America, survival for tumours with a missing stage at diagnosis was 43.7% (39.2-48.2%) in Texas but only 31.3% (29.6-33.0%) for advanced-stage tumours. In Florida and Mississippi, survival for tumours with a missing stage was also higher than that of advanced-stage disease. In contrast to registries in Central and South America and North America, age-standardised survival from tumours with a missing stage at diagnosis was higher than for advanced stage disease in Asia, Europe and Oceania registries for which age-standardised estimates were available.

No obvious trend in survival over time was evident for tumours with missing stage at diagnosis: survival increased in 12 registries and decreased in 14 registries for which age-standardised estimates were available for both calendar periods. Changes over time were generally small, and the largest increase was seen in Oklahoma (US; from 28.6%, 16.9-40.4% to 34.6%, 24.0-45.2%). The largest decrease was seeing in South Carolina (US) where survival decreased from 31.8% (20.7-42.8%) in 2001-2003 to 24.9% (17.4-32.4%) in 2004-2009.

6.3.2 Stage at diagnosis and histology

Survival for each histological group by stage at diagnosis was estimated for the US. Data from registries included in the analysis for stage at diagnosis were pooled to estimate survival at the national level, as numbers were too small to estimate survival for each stage at diagnosis within each histological group for each registry.

The distribution of stage at diagnosis varied by histological group. For type I and type II epithelial tumours, advanced-stage tumours were more common than localised tumours.

For women diagnosed from 2004 to 2009, 60.4% were diagnosed with advanced-stage type I epithelial tumours, while only 37.0% were diagnosed with localised type I epithelial tumours. Only 2.6% of type I epithelial tumours were missing stage at diagnosis. The stage distribution for type II epithelial tumours was even more skewed toward advanced-stage disease: during 2004-2009, 87.7% of women were diagnosed with advanced tumours versus only 7.0% diagnosed with localised-stage tumours, with 5.3% of tumours missing stage at diagnosis [Table 6.3].

For non-epithelial tumours, localised tumours were more common than advanced-stage tumours for germ cell and sex cord-stromal tumours. For germ cell tumours, 55.2% were diagnosed at a localised stage and 39.7% were diagnosed at an advanced stage. Similarly, 55.2% of sex cord-stromal tumours were localised at diagnosis and 38.2% were advanced. The stage distribution for other specific non-epithelial tumours favoured advanced stage at diagnosis (61.1% of tumours were advanced versus 30.1% localised).

Non-specific tumours were rarely localised at diagnosis (7.7%) during 2004-2009. Most tumours of non-specific morphology were either advanced-stage disease at diagnosis (44.9%) or tumours with a missing stage (47.5%).

For all histological groups – type I epithelial, type II epithelial, germ cell, sex cord-stromal, other specific non-epithelial and tumours of non-specific morphology – survival from tumours that were localised at diagnosis was much higher than for tumours that were advanced [Table 6.4, Figure 6.5].

For type I tumours, 5-year age-standardised survival for localised tumours was 92.9% (91.3-94.5%) during 2004-2009, while survival from advanced tumours was only 49.1% (47.8-50.4%). Similarly, for type II tumours, survival was much higher for localised tumours (82.7%, 80.9-84.4%) than for advanced tumours (31.9%, 31.5-32.4%). Survival from tumours with a missing stage at diagnosis was similar to that of advanced tumours

Continued on page 237

Table 6.3 Distribution (%) of stage at diagnosis by histological group and calendar period, United States, 2001-2009

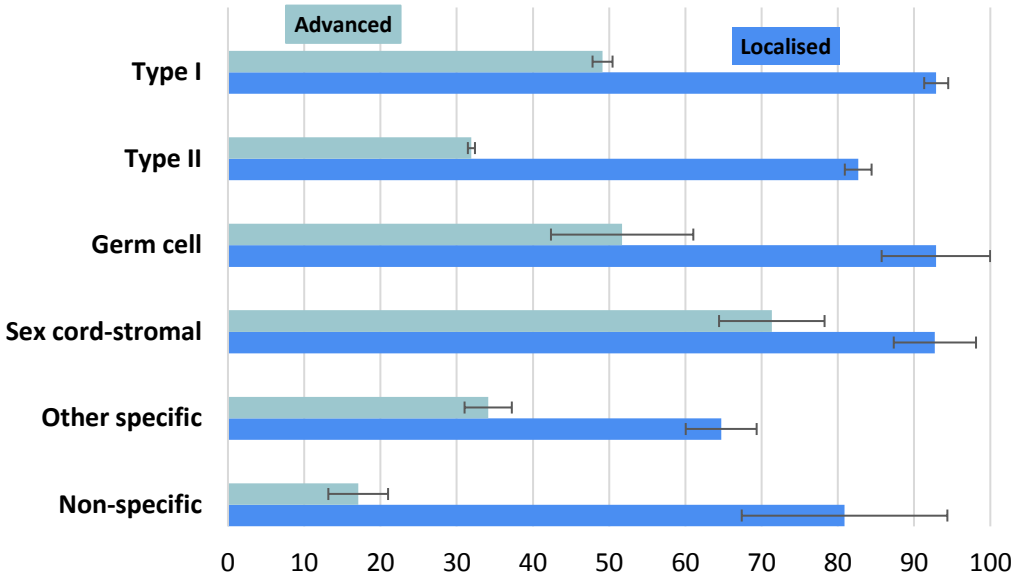
	Localised		Advanced		Missing	
	N	%	N	%	N	%
Type I						
2001-03	4,348	**39.0**	6,383	**57.3**	414	**3.7**
2004-09	7,727	**37.0**	12,626	**60.4**	542	**2.6**
Type II						
2001-03	3,010	**8.1**	31,656	**84.8**	2,677	**7.2**
2004-09	5,487	**7.0**	69,301	**87.7**	4,198	**5.3**
Germ cell						
2001-03	597	**60.0**	326	**32.7**	73	**7.3**
2004-09	1,192	**55.2**	857	**39.7**	110	**5.1**
Sex cord-stromal						
2001-03	429	**54.8**	270	**34.5**	84	**10.7**
2004-09	930	**55.2**	644	**38.2**	111	**6.6**
Other specific						
2001-03	443	**29.7**	846	**56.7**	202	**13.6**
2004-09	945	**30.1**	1,917	**61.1**	274	**8.7**
Non-specific						
2001-03	-	-	277	**47.3**	309	**52.7**
2004-09	104	**7.7**	608	**44.9**	643	**47.5**

Registries with fewer than 10 women for any stage (both calendar periods combined) were not included in the distribution. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included in the distribution.

Table 6.4 Five-year age-standardised net survival (NS, %) by histological group, stage at diagnosis and calendar period, United States, 2001-2009

	Localised			Advanced			Missing		
	NS (%)	95% CI		NS (%)	95% CI		NS (%)	95% CI	
Type I									
2001-03	**92.5**	90.3	94.7	**45.2**	43.4	47.1	**47.0**	39.3	54.6
2004-09	**92.9**	91.3	94.5	**49.1**	47.8	50.4	**49.4**	43.7	55.0
Type II									
2001-03	**81.0**	78.6	83.5	**30.3**	29.7	30.9	**30.4**	28.2	32.7
2004-09	**82.7**	80.9	84.4	**31.9**	31.5	32.4	**30.0**	28.3	31.6
Germ cell									
2001-03	**97.1**	88.4	100.0	**45.0**	32.4	57.7	**84.6**	75.0	94.3
2004-09	**92.9**	85.7	100.0	**51.7**	42.4	61.0	**88.3**	79.1	97.4
Sex cord-stromal									
2001-03	**90.2**	82.4	97.9	**69.0**	59.5	78.4	**92.0**	81.9	100.0
2004-09	**92.7**	87.3	98.1	**71.3**	64.4	78.3	**86.3**	72.7	99.9
Other specific									
2001-03	**63.7**	57.2	70.2	**33.3**	28.9	37.7	**33.7**	25.2	42.2
2004-09	**64.7**	60.0	69.3	**34.1**	31.0	37.2	**36.7**	30.3	43.2
Non-specific									
2001-03	-		-	**14.7**	9.9	19.6	**32.8**	25.9	39.8
2004-09	**80.9**	67.4	94.4	**17.1**	13.2	21.0	**34.1**	29.3	38.9

When data for the two calendar periods of diagnosis were merged, the net survival estimates are underlined. Registries with fewer than 10 women for any stage (both calendar periods combined) were not included in the analysis. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included in the analysis.



Registries with fewer than 10 women for any stage (both calendar periods combined) were not included in the analysis. Only microscopically verified tumours or tumours with a clinical diagnosis and a specific morphology code were included in the analysis. 95% CI represented by error bars.

Figure 6.5 Five-year age-standardised net survival (%) for ovarian cancer by stage at diagnosis and histological group, United States, 2004-2009

for both epithelial histological groups. Survival remained stable over time for each stage for both histological groups.

For non-epithelial tumours, survival was highest for localised germ cell tumours during 2004-2009 (92.9%, 85.7-100.0%), though survival from localised sex cord-stromal tumours was only slightly lower (92.7%, 87.3-98.1%). Survival from localised germ cell and sex cord-stromal tumours was similar to that of localised type I epithelial tumours. Survival from localised other specific non-epithelial tumours was still relatively high (64.7%, 60.0-69.3%), though it was the lowest survival for localised tumours among the histological groups. Survival from localised sex cord-stromal and other specific non-epithelial tumours increased slightly over time, while survival decreased from 97.1% (82.4-97.9%) to 92.9% (85.7-100.0%) for localised germ cell tumours.

For advanced-stage non-epithelial tumours during 2004-2009, survival was highest for sex cord-stromal tumours (71.3%, 64.4-78.3%) and lowest for other specific non-epithelial tumours (34.1%, 31.0-37.2%). Survival from advanced-stage tumours increased over time for all non-epithelial histological groups. Survival from tumours with missing stage was higher than that for advanced non-epithelial tumours for each histological group, but lower than that for localised non-epithelial tumours.

For tumours of non-specific morphology, survival was 80.9% (67.4-94.4%) for localised tumours, but only 17.1% (13.2-21.0%) for advanced tumours. Survival from non-specific tumours with a missing stage was 34.1% (29.3-38.9%) during 2004-2009, which was similar to that for type II epithelial tumours with a missing stage at diagnosis.

6.4 Discussion

Survival for stage at diagnosis could only be estimated for 25 of 61 eligible countries. The majority of the data exclusions were because more than 30% of cancer registrations were missing stage at diagnosis for a majority of the registries.

Survival for localised tumours was much higher than for either advanced tumours or tumours with missing stage, and this result supports previous evidence of poorer survival for advanced-stage tumours[3]. Early diagnosis of ovarian cancer is thus important for improved survival.

The poorer survival for tumours of with a missing stage at diagnosis is not surprising, because accurate staging can only be achieved if a woman has undergone surgery. Women with significantly advanced disease are less likely to have surgery, and are therefore less likely to be staged appropriately at diagnosis. Furthermore, women with higher comorbidity, some of whom will also have advanced-stage disease, may not be healthy enough for surgery and their tumours may also not be staged appropriately.

In some countries, however, survival from tumours of with a missing stage was higher than that for advanced-stage tumours. In these countries, it seems more likely that if stage data are reported missing, it may be due to lack of reporting stage to the registry than to higher survival for tumours with missing stage. Thus, stage at diagnosis is missing at random for these registries and missingness of stage at diagnosis is not due to the stage itself.

Tumour stage is not routinely collected by cancer all registries; therefore, the analysis by stage at diagnosis could only include data from 25 of 61 countries. Additionally, changes in coding of stage at diagnosis in the US (72.7% of women included in the analysis) from the Summary Staging Guide 1977 to SEER Summary Stage 2000 meant that only data from 2001 forward could be included from the US. Thus, survival was estimated for only two calendar periods: 2001-2003 and 2004-2009. The method in which registries in the US collected and reported stage changed from 2004. Prior to 1 January 2004, some US registries manually coded stage data, while others derived SEER Summary Stage 2000 using the Extent of Disease classification system. From 1 January 2004, all US registries

derived SEER Summary Stage using the Collaborative Staging System. The calendar periods were chosen taking into account this change in recording of stage at diagnosis. The decrease in survival from 31.8% to 24.9% over time in South Carolina (US) for tumours with missing stage may be partly because of this change in stage coding. The cancer registry in South Carolina was one of the registries in the US for which stage was manually coded using stage data from patient records. Thus, the adoption of a standard process for coding stage at diagnosis may have increased the accuracy of the recorded stage at diagnosis for women diagnosed in South Carolina. Because stage at diagnosis may be missing because of the stage of the tumour – when the disease is too advanced to be properly surgically staged a woman may be reported as having a missing stage at diagnosis – accurately recording stage at diagnosis may result in a decrease in survival for tumours with missing stage at diagnosis.

International variations in survival within each stage were wider for localised tumours than for advanced tumours, suggesting that other factors, such as access to optimal treatment for or histology of localised tumours, may vary between countries more than for advanced-stage disease.

Survival by stage at diagnosis also varied in the US between histological groups, though the range was smaller for localised tumours than for advanced-stage tumours or tumours with a missing stage. The results from this analysis suggest that survival can be improved for all histological groups if the tumour is diagnosed at an early stage. However, is it clear that most type II epithelial tumours are diagnosed at advanced stages, which may partly explain the lower survival for this histological group. Thus, it appears that survival from ovarian cancer is affected by a combination of factors including histology and stage at diagnosis, along with treatment.

International comparisons of survival within each stage at diagnosis were limited due to the quality and completeness of stage data available worldwide. Only 25 of 61 eligible countries could be included in by stage at diagnosis, and only for one country (US) could survival by estimated for each stage within each histological group. International comparisons of survival within each stage are essential to identify inequalities in survival that are not because of the stage at diagnosis, but may be due to other factors such as access to treatment or the management of cancer services. Without the availability of high-quality stage data in more countries worldwide, efforts to narrow the gap in stage-specific survival will be limited, and progress will be difficult to measure and evaluate over time. Improvements in the availability and quality of stage data, therefore, are needed crucially worldwide.

Chapter 7: Ovarian cancer survival by race/ethnicity

7.1 Introduction

Ovarian cancer survival has been shown to vary by race and ethnicity, particularly for black and white women in the US. Minority groups generally have worse health outcomes than the majority race or ethnicity, and this is also evident in cancer survival. It is unclear whether race or ethnicity influences the histology of ovarian tumours, but given the higher proportion of type I epithelial tumour subtypes in most East Asian countries, genetic factors may influence the histology of the tumour. In order to understand more fully the impact of race and histology on survival, survival by race for each histological group was estimated for blacks and whites in the US and Māori and non-Māori in New Zealand. Survival for all ovarian cancers combined was also estimated by race for Israel, New Zealand and the US.

7.2 Material and methods

Data from the CONCORD-2 study were used for this analysis[188]. Data for adult women (aged 15-99 years) diagnosed during the period of 1995 to 2009 with ovarian cancer were included. Follow-up for vital status was available until 31 December 2009. Women diagnosed with ovarian cancer as a second or higher-order primary tumour were included, in addition to those for whom ovarian cancer was their first cancer. Women whose cancer registration was from a death certificate or autopsy only were excluded, because their true survival time was unknown. The CONCORD-2 protocol, ethical approvals, and quality control procedures have been described elsewhere[188] and in Chapter 3[a].

[a] The material in Chapters 4-7 is based on examination of the distribution of and survival from ovarian cancer histology, stage at diagnosis and race/ethnicity. A few paragraphs of material and methods are repeated in each of these chapters for ease of reference and to ensure consistency of the descriptions. A detailed definition and description of the data and methods can be found in Chapter 3.

Recent evidence suggests that high-grade serous carcinoma, the most common type of ovarian cancer, originates in the fallopian tube. Therefore, cancers of the fallopian tube and other specified and unspecified female genital organs were included in a broader definition of ovarian cancer[12]. Similarly, primary peritoneal and retroperitoneal carcinomas are managed in the same way as advanced-stage epithelial ovarian cancer, and they are also included[12]. The term "ovarian" in this chapter refers to tumours at all these sub-sites, unless the context makes clear that it refers to tumours of the anatomic ovary.

Data on race or ethnicity were reported for only four countries in the CONCORD-2 study: Israel, Malaysia (Penang), New Zealand and the United States. This analysis included black and white women from the US, Māori and non-Māori women from New Zealand and Jewish and non-Jewish women from Israel. Survival was not estimated for Malaysia (Penang) because there were not enough women in each age-race group to provide age-standardised estimates.

Net survival was estimated by race for all ovarian cancers combined for Israel, New Zealand and the US. Survival was also estimated by race for each of the six histological groups [Table 7.1], where possible, for the US and New Zealand. Survival by race for each histological group was not estimated for Israel because most of the survival estimates would have been unstandardised due to small numbers, and thus could not be compared appropriately.

Net survival is defined as the probability of survival for cancer patients up to a given point in time after diagnosis (for example, 5 years) if death from cancer were to be the only cause of death. Net survival controls for the hazard of death from competing causes of death (background mortality) in a population. Life tables of all-cause mortality rates by single year of age (0-99 years), region, sex, calendar year and race were used to control

Table 7.1 Ovarian cancer histological groups and subtypes

Histological group[a]	Histological subtype	ICD-O-3 morphology code
Type I epithelial	Clear cell carcinoma	8005, 8310, 8443, 9110
	Endometrioid carcinoma[b]	8380, 8382-8383, 8560, 8570
	Mucinous carcinoma	8470-8471, 8480-8482, 8490
	Squamous carcinoma	8051-8084
	Transitional cell or Brenner carcinoma	8120-8131, 9000
Type II epithelial	Serous carcinoma[c]	8050, 8441, 8450, 8460-8461
	Mixed epithelial-stromal carcinoma	8313, 8323, 8381, 8930-8991, 9010-9030
	Undifferentiated or other epithelial	8010-8015, 8020-8046, 8090-8110, 8140-8231, 8246-8300, 8311-8312, 8314-8322, 8324-8325, 8336-8337, 8341-8375, 8384-8440, 8452-8454, 8500-8551, 8561-8562, 8571-8589
Germ cell	Germ cell	8240-8245, 8330-8335, 8340, 9060-9105, 9380-9523
Sex cord-stromal	Sex cord-stromal	8590-8671, 8810
Other specific non-epithelial	Other specific non-epithelial	8680-8806, 8811-8921, 9040-9055, 9120-9373, 9530-9589
Non-specific	Non-specific	8000-8004

Table presented here for ease of reference (originally presented in Chapter 4, page 81).
[a] Borderline tumours (ICD-O-3 codes: 8442, 8444, 8451, 8462, 8463, 8472, 8473) were excluded from the analysis of survival by histological group. Tumours with missing morphology codes were analysed separately (see text). [b] No information on grade was available; therefore, all endometrioid tumours were classified as type I epithelial. [c] No information on grade was available; therefore, all serous tumours were classified as type II epithelial.

for variations in background mortality. The Pohar Perme estimator of net survival[224], which allows for the fact that competing risks of death increase with age, was used to estimate net survival. This estimator was implemented using *stns*[208] in Stata version 14[207]. Standard errors were calculated using the Greenwood method[209].

Net survival is reported for each country, race and histological group, with 95% confidence intervals (CI). Survival by race and histological group for the US was estimated for three calendar periods of diagnosis: 1995-1999, 2000-2004 and 2005-2009. The cohort approach was used for 1995-1999 and 2000-2004, because five or more years of follow-up were available for all patients, while the period approach was used for 2005-2009. Survival was estimated for all 15 years combined for Israel and New Zealand, using the complete approach[a].

Survival estimates for all ages combined were age-standardised with the International Cancer Standard Survival (ICSS) weights[206]. Age at diagnosis was categorised into five age groups: 15-44, 45-54, 55-64, 65-74 and 75-99 years. If an age-specific estimate could not be produced, or fewer than 10 women were available for analysis in an age group, data for adjacent age groups were pooled and the re-estimated survival was used for both of the original age groups. Only epithelial tumours were included in the analysis for New Zealand because there were not enough in each race-age-histological group category to allow for age standardisation.

7.3 Results

Type II epithelial tumours were the most common histological group for each race in each country. Jewish women had a higher proportion (74.9%) of type II epithelial tumours than

[a] See Chapter 3 for a more detailed explanation of these methods.

non-Jewish women (64.2%). The distribution of histological groups was similar Māori and non-Māori women in New Zealand and for white and black women in the US.

Survival for all ovarian tumour histological groups combined was estimated by race for Israel (all years combined), New Zealand (all years combined) and in the United States (for each calendar period: 1995-1999, 2000-2004 and 2005-2009) [Table 7.2]. Survival from ovarian cancer was higher in all countries for the majority race (Jewish, non-Māori or white). In Israel, survival from ovarian cancer from 1995 to 2009 was 41.5% (39.1-43.9%) for Jewish women, but only 34.5% (18.9-50.0%) for non-Jewish women. In New Zealand, survival from ovarian cancer was only slightly higher for non-Māori women (34.6%) than for Māori women (33.5%). In the US, survival was much higher for white women than for black women throughout the 15-year period of 1995-2009. Survival increased slightly over time for both races.

In the US, 5-year age-standardised survival for most histological groups and periods of diagnosis, was higher for white women than for black women [Table 7.3]. For type I epithelial tumours diagnosed from 2005 to 2009, five-year age-standardised survival was 67.0% (64.9-69.1%) for white women, but only 50.9% (44.1-57.7%) for black women. Survival for black women for type I epithelial tumours was lower than that for white women in all three calendar periods. Survival from type I tumours increased steadily over time from 58.9% (57.7-60.1%) to 67.0% (64.9-69.1%) for white women. Though survival was higher during 2005-2009 than 1995-1999 for black women, survival decreased from 1995-1999 to 2000-2004 (44.9% to 40.9%) before increasing to 50.9%. Over time, the gap in survival between white and black women widened.

For type II epithelial tumours, survival was higher for white than black women during all three calendar periods. Survival increased over time from 33.8% to 36.6% for white

Table 7.2 Five-year age-standardised net survival (NS, %) by race, country and calendar period, 1995-2009

Country	Years of diagnosis	Race	NS (%)	95% CI	
Israel	1995-2009	Jews	**41.5**	39.1	- 43.9
		Non-Jews	**34.5**	18.9	- 50.0
New Zealand	1995-2009	Māori	**33.5**	21.5	- 45.6
		Non-Māori	**34.6**	32.1	- 37.1
United States	1995-1999	White	**40.1**	39.6	- 40.6
		Black	**31.8**	29.9	- 33.7
	2000-2004	White	**41.2**	40.7	- 41.6
		Black	**30.6**	28.9	- 32.2
	2005-2009	White	**42.7**	41.2	- 44.2
		Black	**33.1**	30.4	- 35.8

Table 7.3 Five-year age-standardised net survival (NS, %) by race, histological group and period of diagnosis, United States, 1995-2009

	Whites				Blacks			
	N	NS (%)	95% CI		N	NS (%)	95% CI	
Type I								
1995-1999	16,136	**58.9**	57.7	60.1	963	**44.9**	40.3	49.6
2000-2004	16,932	**62.8**	61.6	64.0	1,164	**40.9**	36.4	45.5
2005-2009	15,673	**67.0**	64.9	69.1	1,150	**50.9**	44.1	57.7
Type II								
1995-1999	48,565	**33.8**	33.2	34.3	3,488	**26.1**	24.1	28.2
2000-2004	57,836	**34.9**	34.5	35.4	4,603	**25.0**	23.2	26.7
2005-2009	61,149	**36.6**	34.9	38.2	5,353	**26.6**	23.7	29.6
Germ cell								
1995-1999	1,087	**63.7**	55.5	71.9	176	**71.5**	58.1	84.9
2000-2004	1,323	**71.5**	64.6	78.4	243	**61.0**	46.3	75.7
2005-2009	1,459	**80.5**	71.8	89.1	287	**65.0**	46.5	83.5
Sex cord-stromal								
1995-1999	955	**79.9**	74.6	85.3	228	**71.9**	56.1	87.6
2000-2004	970	**82.0**	76.9	87.2	314	**90.6**	78.8	100.0
2005-2009	1,088	**86.8**	79.3	94.2	359	**77.5**	58.7	96.4
Other non-epithelial								
1995-1999	1,866	**40.6**	37.7	43.5	219	**35.3**	26.1	44.6
2000-2004	2,050	**43.2**	40.4	46.1	308	**31.5**	19.6	43.5
2005-2009	2,290	**45.9**	41.0	50.8	369	**44.9**	30.5	59.4
Non-specific								
1995-1999	700	**34.4**	29.0	39.7	78	**21.0**	8.4	33.6
2000-2004	975	**30.6**	26.7	34.4	99	**25.2**	14.4	36.1
2005-2009	955	**29.3**	21.5	37.2	106	**22.8**	5.8	39.7

women, but remained relatively stable for black women (26.1% during 1995-1999 and 26.6% during 2005-2009).

For non-epithelial tumours, survival was highest for white women diagnosed with sex cord-stromal tumours (86.8%, 79.3-94.2%) during 2005-2009. Survival for this histological group was only 77.5% (58.7-96.4%) for black women during the same time period. Survival for sex cord-stromal tumours increased over time for both races. For germ cell tumours, survival was 80.5% (71.8-89.1%) for white women, but only 65.0% (46.5-83.5%) for black women. While survival increased over time for white women diagnosed with germ cell tumours, survival fell from 71.5% (58.1-84.9%) during 1995-1999 to 65.0% (46.5-83.5%) during 2005-2009 for black women. Survival from other specific non-epithelial tumours was similar for white and black women (45.9% vs. 44.9%) during 2005-2009, respectively.

For tumours of non-specific morphology, survival was lower for both races than for other histological groups, but was still lower among black women (22.8%) than white women (29.3%). Survival for white women decreased over time from 34.4% (29.0-37.2%) to 29.3% (5.8-39.7%), while survival was relatively stable for black women (21.0%, 8.4-33.6% during 1995-1999 versus 22.8%, 5.8-39.7% during 2005-2009).

In New Zealand, Māori women had higher survival (68.7%) than non-Māori women (58.3%) for type I epithelial tumours [Table 7.4]. Trends over time could not be assessed, because data were merged for the entire period 1995-2009 in order to for enough women to be available in each race-histological group combination to produce estimates. Survival from type II tumours, however, was higher for non-Māori women (25.0%, 22.4-27.6%) than for Māori women (20.4%, 13.0-27.9%). Estimates for non-epithelial histological groups could not be age-standardised, therefore comparison between race groups was not possible due to potential differences in the age structure of the cancer patient populations.

Table 7.4 Five-year age-standardised net survival (NS, %) for epithelial ovarian cancer by race and histological group, New Zealand, 1995-2009

	N	NS (%)	95% CI		
Type I					
Māori	92	**68.7**	51.9	-	85.5
Non-Māori	208	**58.3**	52.3	-	64.2
Type II					
Māori	854	**20.4**	13.0	-	27.9
Non-Māori	2,446	**25.0**	22.4	-	27.6

7.4 Discussion

Survival from ovarian cancer varied by race in the three countries included in these analyses. Survival was generally higher for the majority racial group, which is similar to results from studies of survival by race for other cancers. The minority racial groups may experience more barriers to accessing cancer care.

Survival by race could only be estimated for each histological group for the US and New Zealand, due to the limited number of woman for each race available in each histological group in Israel and Malaysia. Survival from all histological groups of ovarian cancer was higher for white women than for black women in the US. This suggests that the impact of race on survival may not vary by histological group. The persistently lower survival for black women than for white women in each of the histological groups, suggests that other factors such as stage at diagnosis or treatment may explain variations in survival more than histology. Racial disparities in ovarian cancer survival among women in the US first appeared in the 1980s with the emergence of debulking surgery, thus suggesting a lack of access to optimal treatment for black women. While insurance status may influence a woman's access to cancer care, black women diagnosed with advanced-stage epithelial ovarian cancer and enrolled in Medicare in the US were less likely to receive guideline-adherent care than white women, suggesting that access to treatment may not be the only barrier to receiving optimal care for black women[87].

There is some evidence that racial inequalities in ovarian cancer survival may be eliminated when black and white women receive equal treatment. Results from clinical trial results[85] and data on women treated in the same hospital[88] suggest that when black and white women with advanced-stage epithelial ovarian cancer received similar treatment, inequalities in survival are non-existent. When the likelihood of receiving treatment is controlled for among white and black women, differences in ovarian cancer survival between these women are eliminated[89].

In New Zealand, however, Māori women – the minority race – had higher survival for type I epithelial tumours than the majority group, non-Māori women. This is interesting, because minority groups usually have worse outcomes than the majority group. Survival for type I epithelial tumours was much higher for Māori women than for non-Māori women; however, the confidence interval was wide and includes the point estimate for non-Māori women. Thus, the more favourable survival estimate seen for Māori women may be due to smaller numbers rather than an actual higher survival for this tumour type. Estimates for other tumour types were not possible because of small numbers for Māori women. Age-standardisation of survival estimates by race was only possible for epithelial tumours because they are the most common and therefore enough women were available in each age-race-histological group category to include in the analysis. However, even with the most common groups, data for all three time periods had to be combined, and therefore trends over time in survival by histological group could not be satisfactorily examined for Māori and non-Māori in New Zealand.

While the number of women from the US was quite large, more detailed analysis of stage-specific survival by histological group for each race was not possible, because the number of women available in each age-stage-race-histological group category was not always large enough to produce age-specific estimates required for age-standardisation. Future analyses could include multivariable modelling to examine the impact of race on survival, when controlling for age, stage at diagnosis and histology.

In this large study of ovarian cancer survival by race/ethnicity, minority groups generally had lower survival than the majority racial group. Efforts to ensure equal access to optimal, guideline-adherent care for minority women are needed to help minimise inequalities in ovarian cancer survival between racial or ethnic groups.

Chapter 8: Strengths and Limitations

8.1 Strengths

This is the largest international study examining some of the factors that influence ovarian cancer survival worldwide. The data included in this thesis came from over 240 population-based cancer registries in 60 countries, which are home to over two-thirds of the world's population. A common protocol and strict, centralised quality control measures were used to collect and clean the data to ensure the highest standard and completeness of data for analysis. Individual data for women diagnosed between 1995 and 2009 were used to produce robust and comparable estimates of survival for each country.

Due to the scope of the data collected, survival by various histological groups was estimated using the same methods, allowing for direct comparison of survival between the various histological groups of ovarian cancer. Previous research has focused on only a few countries when comparing survival from different histological groups.

While the data quality and availability varies worldwide, it is generally high, and the inclusion of data from low- and middle-income countries is an essential first step to understanding the cancer burden in these countries. Improvements in data quality are needed before the quality of the data will allow more detailed analyses.

8.2 Limitations

The proportion of women lost to follow-up as reported by the registries was only 0.5% overall. The proportions were highest in Switzerland (1.8%), France (4.9%), Hong Kong (7.2%), Mongolia (11.5%), India (32.4%) and Jordan (57.5%). The proportion was less than 1% in the 54 other countries. Women who were lost to follow-up were presumed still to be alive at the date of last known vital status or at the end of the follow-up period (31 December 2009). Thus, if the women who are lost to follow-up are different with respect

to their (unknown) survival from those who were not lost to follow-up and were known to be alive at the end of the study, the survival estimates may be biased. If being lost to follow-up is associated with risk of dying from ovarian cancer, then survival may be overestimated because women with poor survival, who were lost to follow-up, were in fact presumed to be alive. While for most countries the proportion lost to follow up was 0.0% (36 countries) or less than 1.0% (18 countries) and this bias would thus be non-existent or extremely small, the bias would be larger for the countries where a higher proportion of women are lost to follow-up (India and Jordan).

When registries use passive follow-up only, it is impossible to distinguish women who are lost to follow-up from those who are actually alive at the end of follow-up. Because of the reliance on death registration systems, deaths are ascertained only if they occur and are then registered. Thus, passive follow-up will capture accurately all deaths that have occurred and been registered, and it will also identify accurately women who are still alive because they were not matched to a death record, but it will not identify women who have been lost to follow-up, regardless of whether they are alive or dead. Women who are lost to follow-up are, therefore, identical in this respect to women who are actually alive at the end of follow-up. Thus, those who are lost to follow-up must be presumed to be alive at the end of follow-up. Because it is impossible to distinguish the women lost to follow-up from women who are, in fact, alive at the end of follow-up, it is also impossible to quantify the amount of bias the presumed alive assumption may have on survival estimates. Thus, for some registries using passive follow-up only, survival estimates may be overestimated if a large proportion of women who are unknowingly lost to follow-up have actually died. However, if the quality of the national death index is high, then passive follow-up is less biased[193,226].

The proportion of women excluded because their tumour was registered through a death certificate or autopsy only was 3.7% for all countries combined. This proportion was greater than 10% of the eligible cases for analysis for Brazil (11.3%), Argentina (11.8%), Japan (12.4%), Germany (18.2%) and Romania (18.7%). Survival for patients whose tumours are death-certificate-initiated tend to have lower survival than patients who are registered while alive. Therefore, if efforts to trace back death-certificate-initiated patients to obtain a date of diagnosis are not effective, a higher proportion of patients will be registered through a death certificate only. A higher proportion of DCO may result in an overestimation of survival because these patients must be excluded from survival analysis because their survival time is not known and they tend to have lower survival than patients who are registered while alive.

Tumours coded as not morphologically verified but with a specific ICD-O-3 morphology code (any valid code except 8000-8004) were included in survival analyses by histological group. Registries reported the basis of diagnosis for each tumour record: clinical, morphologically verified or unknown whether clinical or morphologically verified. A specific morphology code was given priority over codes reported as clinically diagnosed, since it was assumed that reporting a specific morphology implied that morphological verification had, in fact, been conducted. Thus, the error was assumed to be in the coding of the basis of diagnosis rather than in the coding of morphology, since it seems improbable that the basis of diagnosis could correctly be coded as “clinical” if the morphology code was specific as, for example, mucinous cystadenocarcinoma (8470). This may be a limitation of the analyses by histological group if the morphology code was reported in error and the basis of diagnosis was, in fact, correct as reported by the registry.

A surgical procedure is required to obtain a sample of an ovarian tumour for morphological verification, and women with advanced disease or comorbidity may not

receive surgery as part of their treatment. Survival for these women may thus be lower than for women with morphologically verified tumours who were healthy enough at the time of diagnosis to undergo surgery. Thus, survival estimates may be under-estimated when including the tumours that were reported as not morphologically verified but had been assigned a specific morphology, because survival from these tumours may be lower if the basis of diagnosis had in fact been solely clinical. However, given that these tumours represented only 2.2% of the data, the bias in survival estimation would be small. The proportion of these tumours was highest in Germany (4.6%), Australia (5.5%), the UK (11.6%) and Qatar (13.6%). The proportion was less than 2.1% in all other countries included in the analyses.

Chapter 9: Conclusion

The aim of this thesis was to examine how and why ovarian cancer survival differs between and within countries. There were four objectives: (1) to determine if the distribution of histology varied by country or geographic region, or over time, (2) to determine if survival varied between histological groups, (3) to determine if survival varied by stage at diagnosis, and (4) to determine if survival varied by race/ethnicity.

9.1 Distribution of histology

Type II epithelial tumours were the most common histology worldwide (69.9%), followed by type I epithelial (22.4%). Germ cell, sex cord-stromal, other specific non-epithelial and non-specific tumours were all rare by comparison, comprising only 8% of tumours worldwide; the distribution of these groups remained relatively stable over the 15-year period 1995 to 2009. The proportion of type II epithelial tumours increased slightly from 68.6% to 71.1%, and there was a corresponding decrease in type I epithelial tumours (from 23.8% to 21.2%).

During 2005-2009, type II ovarian cancer was the most common histological group in all continents, although the proportion was much higher in Oceania (73.1%), North America (73.0%) and Europe (72.6%) than in Central and South America (65.7%) and Asia (56.1%). The range at the national level, however, was much wider. There was little between-country variation in the proportion of type II tumours in Central and South America, North America and Oceania. However, the proportion varied widely in Asia, where the proportion of type II tumours was lower than that of type I epithelial tumours in Hong Kong and Thailand. There was also variation in the proportion of type II tumours in Europe, where they accounted for over 70% of tumours in 15 countries, 60% in 11 countries and only 50.2% in Russia.

9.2 Survival by histological group

Net survival for women diagnosed with type I epithelial tumours five years after diagnosis was fairly high, generally 40-60%. During 2005 to 2009, age-standardised 5-year survival for type I epithelial tumours varied widely, with the highest survival in Hong Kong (82.9%, 95% CI: 72.4-93.4%) and the lowest in Argentina (30.8%, 16.3-45.2%).

Survival from type II epithelial tumours five years after diagnosis was lower than that of type I epithelial tumours, around only 20-40%. For women diagnosed between 2005 and 2009, the highest age-standardised survival was again seen in Hong Kong (61.5%, 54.8-68.2%), compared with only 18.1% (6.3-29.9%) for women in Chile (Los Rios).

Survival from germ cell tumours was generally higher than that for type II epithelial tumours, though it varied widely between countries. Considering the age-standardised estimates for all 15 years combined, the highest survival was seen in Australia (76.0%, 57.6-94.5%) and the lowest in China (41.5%, 23.6-59.4%).

During 2005-2009, age-standardised net survival was over 90% at 5 years after diagnosis in Korea and Portugal for women diagnosed with sex cord-stromal tumours. However, survival varied widely between countries, and the lowest survival during the same period (Japan: 58.9%) was almost half that seen in Korea.

Survival from other specific non-epithelial tumours was generally around 30-60%, slightly higher than that of type II epithelial tumours. The variation in age-standardised survival was very wide, ranging from only 0.3% (0.0-0.8%) in Bulgaria to 60.0% (48.4-71.5%) in Cuba.

Age-standardised net survival for tumours of non-specific morphology (ICD-O-3 codes 8000-8004) was generally lower than that for all specific histological groups combined, and generally decreased over time. This suggests pathological examination of ovarian

tumours is improving and that tumours previously coded as non-specific morphology are increasingly being pathologically examined and coded as a specific morphology.

9.3 Survival by stage at diagnosis

Overall, 5-year age-standardised net survival for localised ovarian cancer was much higher than that for advanced disease, or tumours with a missing stage at diagnosis. In some countries, 5-year age-standardised survival was over 90% for localised tumours, whereas for advanced-stage ovarian cancer, survival was generally around 30%. The highest age-standardised five-year survival from advanced-stage disease diagnosed during 2004 to 2009 was seen in Tochigi (Japan), but it was still only 39.3%.

Survival from tumours with a missing stage at diagnosis was similar to or lower than that of advanced disease in most registries in Central and South America and North America during 2005-2009, but age-standardised survival was higher for missing stage at diagnosis than for advanced stage disease in all registries in Asia, Europe and Oceania for which age-standardised estimates were available.

Survival also varied by stage at diagnosis within each histological group. Survival from localised tumours was higher in all histological groups, and was as high as 81% in the US for localised type II epithelial tumours, which are thought to have a poor prognosis when survival is estimated for all stages combined. Survival was much lower for advanced-stage type II epithelial tumours (32%). Survival from localised type I epithelial tumours was around 90% and around 49% for advanced-stage tumours. Thus, the variation in survival between type I and type II epithelial tumours is not completely explained by stage at diagnosis.

9.4 Survival by race/ethnicity

Differences in survival by race could only be examined in detail for three countries. For all histological groups and stages combined, minority racial groups had lower survival than

the majority group. In the US, survival for black women was lower than for white women for each histological group. Thus, the impact of race on survival does not appear to differ by histological group.

9.5 Future directions

Data on treatment were not available for these analyses. International differences in ovarian cancer survival may be explained in part or even largely by differences in access to and the quality of care. Differences in survival between racial groups have been shown to be eliminated when both groups receive equal treatment. Future analyses could examine how much variation between countries in survival for each histological group of ovarian cancer could be explained by differences in treatment. CONCORD-3 will include data on the type and date of the first course of treatment received by each patient, and it will examine differences in treatment between countries and their impact on variations in survival.

The Pohar Perme estimator used throughout the thesis is a non-parametric approach to estimating net survival. Future analyses could examine excess mortality using various model-based methods. This would allow for more detailed analyses of the data, particularly when numbers are small. Modelling approaches could also explore how much of the variation in survival between countries can be explained by the factors that influence survival, such as histology, stage, race/ethnicity and treatment.

Age-standardised 5-year net survival was the main outcome for the analyses in this thesis. Other approaches could examine differences in age-standardised one-year net survival or 5-year survival conditional on surviving the first year after diagnosis. One-year net survival may be of particular interest to help identify the reasons for disparities in 5-year survival seen in this thesis.

One could also examine whether the international differences in short-term survival widen (or narrow) over time, perhaps focusing on the survival from just one histological group of ovarian cancer for a certain region of the world.

The focus of most comparisons in this thesis is the between-country variation in survival. Survival was also compared between histological groups and over time, but examining the differences between countries was given priority. The data in this thesis could have been visualised in other ways. An emphasis on the improvements, or lack thereof, over time would require focusing on fewer countries at one time, but allow for a clearer picture of the trends in ovarian cancer survival. Additionally, the differences between histological groups could have also been emphasised by focusing on fewer countries and time periods. The analysis by stage at diagnosis also focused on the variations in survival within each stage between countries. The focus could have been, however, comparing survival between stages within a country.

9.6 Conclusion

Ovarian cancer survival for all histological groups and stages combined varies widely between countries. This variation appears to be explained in part by the variation between countries in the distribution of histological groups, which have varying levels of survival. Previous work in ovarian cancer survival has shown that the different histological subtypes have varying levels of survival, but such work has been limited to a few countries and histological groups. This is the largest ever study of the distribution of – and survival from – the various ovarian cancer histological groups, including rare subtypes such as sex cord-stromal and germ cell tumours.

Stage at diagnosis also has a strong influence survival and thus on international comparisons of survival. However, more than half of the data eligible for analysis by stage at diagnosis was excluded because of the quality of the stage data. This lack of quality and

completeness of stage data in several registries worldwide severely limits the examination of international variations in survival by stage at diagnosis. While this is the largest ever study on survival from ovarian cancer by stage at diagnosis, only 25 of the eligible 61 countries could be included.

Race and/or ethnicity impacts ovarian cancer survival greatly. In each of the three countries for which survival could be estimated by race or ethnicity, the minority race/ethnicity had consistently lower survival than the majority race or ethnic group – except for Māori women in New Zealand diagnosed with type I epithelial tumours. Race or ethnicity is not routinely collected by cancer registries, and may even be illegal to report to the registry in some jurisdictions. Thus, data for race or ethnicity were only available for four of 61 countries, and ovarian cancer survival by race could only be estimated for three of the countries for which data on race were available.

There is increasing interest in the prevention of cancer, in addition to earlier diagnosis and improvements in treatment, and all three are key factors in improving the healthcare system's management of the cancer burden. Treatment for ovarian cancer has not changed greatly over the past few decades, despite numerous clinical trials and drug combinations for chemotherapy.

Early diagnosis, particularly for epithelial ovarian cancer, remains elusive. Previous efforts to increase early diagnosis have focused on finding tumours while they are confined to the ovary. However, given the recent discovery of serous tubal intraepithelial carcinoma as a potential precursor to ovarian epithelial carcinoma, future efforts should focus on identifying any potential precursor lesions outside the ovary.

Prevention of ovarian cancer is difficult, because the development of the various histological subtypes of ovarian cancer is still poorly understood. The primary prevention strategy currently in use is risk-reducing salpingo-oophorectomy for high-risk women

(women with either a BRCA mutation and/or a strong family history of ovarian cancer). While this decreases a woman's risk of developing ovarian cancer, it does not eliminate it completely, and no routine prevention strategies are available for women who are not at a higher risk of ovarian cancer.

International comparisons of cancer survival depend inherently on the availability and reliability of high-quality cancer data. Information on the cancer patient's age at diagnosis, date of diagnosis, vital status and type of cancer are required for survival analysis. Additional variables such as stage at diagnosis, histological subtype of the tumour, the patient's race or ethnicity, the patient's socioeconomic status and the patient's residence are useful in understanding why survival may vary between countries. The availability and quality of these data varies worldwide. In some countries with high-quality data, detailed analysis such as stage-specific survival for each histological group is possible. However, in countries with fewer resources, collecting such information is difficult and often impossible. In this thesis, survival from ovarian cancer could only be estimated in five African countries. The comparisons for African countries were limited as none of the estimates could be age-standardised. Additionally, only for one country (Algeria) were the numbers of women large enough to produce estimates for histological groups other than type II epithelial tumours.

The majority of the analyses by histology in this thesis are by histological group using a classification for epithelial tumours, which was introduced in 2004[16] and recently updated in 2016[10]. The use of this classification system may mask differences in survival between epithelial subtypes grouped as either type I or type II. However, because most of the histological subtypes classified as type I epithelial are quite rare, survival by histological subtype could be estimated only for the US. Thus, in order to compare survival by histology worldwide, a grouping of histological subtypes of epithelial tumours is required.

International cancer survival comparisons are useful to establish benchmarks in order to monitor progress in the management of the cancer burden. However, without the high-quality data needed to produce robust survival estimates, it is extremely difficult, if not impossible, to understand the variations in survival, in order to design strategies to reduce them. Efforts to increase the quality of cancer registration data in low resource settings are needed.

Given the high-quality data, centralised protocol and rigorous methods used to produce ovarian cancer survival estimates for women diagnosed over the 15-year period of 1995 to 2009 in 61 countries, the results presented in this thesis may be taken as a comprehensive overview of the trends and variations in ovarian cancer survival among women diagnosed up to 2009 worldwide. The results presented in this thesis provide a valuable contribution to the understanding of variations in ovarian cancer survival, which may thus be used to inform health care policies and plans to reduce disparities in survival.

The burden of ovarian cancer will increase for the foreseeable future, particularly in low- and middle-income countries with aging populations. To achieve the highest survival possible, women will need access to optimal ovarian cancer care. The global surveillance of ovarian cancer, which monitors trends and variations in survival, is thus essential, because unless the inequalities in survival are measured, efforts to reduce them will be limited, or even non-existent.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 18 May 2016].
2. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2014.
3. Maringe C, Walters S, Butler J, Coleman MP, Hacker N, Hanna L, et al. Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership. Gynecol Oncol. 2012 Oct;127(1):75-82
4. Bryzski RG, Knudston J. Female Reproductive Endocrinology. 2013. In: MSD Manual [Internet]. Kenilworth, NJ, USA: Merck and Co., Inc.
5. Drake RL, Vogl W, Mitchell AWM. Gray's Anatomy for Students. 3rd ed. Philadelphia, PA: Churchill Livingston/Elsevier; 2015.
6. Salvador S, Gilks B, Kobel M, Huntsman D, Rosen B, Miller D. The fallopian tube: primary site of most pelvic high-grade serous carcinomas. Int J Gynecol Cancer. 2009 Jan;19(1):58-64
7. Blaustein A, Kurman R. Blaustein's pathology of the female genital tract. 5th ed. Kurman R, editor. New York: Springer; 2002.
8. Taylor H. Malignant and semi-malignant tumours of the ovary. Surg Gynecol Obsts. 1929 (48):204-30
9. Aslam Sohaib S, Husband J, Reznek R. Ovarian Cancer. In: Husband J, Reznek R, editors. Imaging in oncology. 2nd ed. London: Taylor & Francis; 2004.
10. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis revisited, revised, and expanded. American Journal of Pathology. 2016 01 Apr;186(4):733-47
11. Kurman RJ, Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Human pathology. 2011 Jul;42(7):918-31
12. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. The American journal of surgical pathology. 2010 Mar;34:433-43
13. McCluggage WG. My approach to and thoughts on the typing of ovarian carcinomas. Journal of clinical pathology. 2008 Feb;61(2):152-63
14. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011 Aug;43(5):420-32
15. Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013 Mar 1;19(5):961-8
16. Shih Ie M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004 May;164(5):1511-8
17. PDQ Adult Treatment Editorial Board. PDQ Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment Bethesda, MD: National Cancer Institute; 2016 [updated 12 August 2016; cited 15 August 2016]. Available from: http://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq.
18. Goodman MT, Shvetsov YB. Incidence of ovarian, peritoneal, and fallopian tube carcinomas in the United States, 1995-2004. Cancer Epidemiol Biomarkers Prev. 2009 Jan;18(1):132-9
19. Tavassoli FAD, P., editor. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003.
20. Bloss JD, Liao SY, Buller RE, Manetta A, Berman ML, McMeekin S, et al. Extraovarian peritoneal serous papillary carcinoma: a case-control retrospective comparison to papillary adenocarcinoma of the ovary. Gynecol Oncol. 1993 Sep;50(3):347-51
21. Eken M, Temizkan O, Kaygusuz EI, Herkiloglu D, Cogendez E, Karateke A. Primary carcinoma of the fallopian tubes: Analysis of sixteen patients. Turk Jinekoloji ve Obstetrik Dernegi Dergisi. 2015 01 Jun;12(2):83-8

22. Jordan SJ, Green AC, Whiteman DC, Moore SP, Bain CJ, Gertig DM, et al. Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis. Int J Cancer. 2008 Apr 1;122(7):1598-603
23. Harrison ML, Jameson C, Gore ME. Mucinous ovarian cancer. Int J Gynecol Cancer. 2008 Mar-Apr;18(2):209-14
24. Nasioudis D, Sisti G, Kanninen TT, Holcomb K, Di Tommaso M, Fambrini M, et al. Epidemiology and outcomes of squamous ovarian carcinoma; A population-based study. Gynecol Oncol. 2016 01 Apr;141(1):128-33
25. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009 Oct 17;374(9698):1371-82
26. Hankinson SE, Danforth KN. Ovarian Cancer. In: Schottenfelt D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Third ed. Oxford: Oxford University Press; 2006.
27. Rosenthal AN, Fraser L, Manchanda R, Badman P, Philpott S, Mozersky J, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol. 2013 Jan 1;31(1):49-57
28. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? Lancet. 1971 Jul 17;2(7716):163
29. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. Journal of the National Cancer Institute. 1983 Oct;71(4):717-21
30. Vang R, Shih Ie M, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol. 2009 Sep;16(5):267-82
31. Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. The American journal of surgical pathology. 2006 Feb;30(2):230-6
32. Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. The Journal of pathology. 2007 Jan;211(1):26-35
33. Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Current opinion in obstetrics & gynecology. 2007 Feb;19(1):3-9
34. Acien P, Velasco I. Endometriosis: a disease that remains enigmatic. ISRN Obstet Gynecol. 2013;2013:242149
35. Prat J. Pathology of cancers of the female genital tract. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2012 Oct;119 Suppl 2:S137-50
36. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev. 2008 Aug;34(5):427-41
37. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol. 2005 Feb;18 Suppl 2:S61-79
38. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynaecol. 2012 Jun;26(3):347-55
39. PDQ Adult Treatment Editorial Board. PDQ Ovarian Germ Cell Tumors Bethesda, MD: National Cancer Institute; 2016 [updated 12 February 2016; cited 15 August 2016]. Available from: http://www.cancer.gov/types/ovarian/hp/ovarian-germ-cell-treatment-pdq.
40. Wilkinson N, Osborn S, Young RH. Sex cord-stromal tumours of the ovary: a review highlighting recent advances. Diagnostic Histopathology. 2008;14(8):388-400
41. Sigismondi C, Gadducci A, Lorusso D, Candiani M, Breda E, Raspagliesi F, et al. Ovarian Sertoli-Leydig cell tumors. a retrospective MITO study. Gynecol Oncol. 2012 Jun;125(3):673-6
42. Colombo N, Peiretti M, Garbi A, Carinelli S, Marini C, Sessa C, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii20-6
43. Boyce EA, Costaggini I, Vitonis A, Feltmate C, Muto M, Berkowitz R, et al. The epidemiology of ovarian granulosa cell tumors: A case-control study. Gynecol Oncol. 2009 Nov;115(2):221-5

44. Pectasides D, Pectasides E, Psyrri A. Granulosa cell tumor of the ovary. Cancer Treat Rev. 2008 Feb;34(1):1-12
45. Willemsen W, Kruitwagen R, Bastiaans B, Hanselaar T, Rolland R. Ovarian stimulation and granulosa-cell tumour. Lancet. 1993 Apr 17;341(8851):986-8
46. Meisel JL, Hyman DM, Jotwani A, Zhou Q, Abu-Rustum NR, Iasonos A, et al. The role of systemic chemotherapy in the management of granulosa cell tumors. Gynecol Oncol. 2015 Mar;136(3):505-11
47. Colombo N, Peiretti M, Castiglione M, Group EGW. Non-epithelial ovarian cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May;20 Suppl 4:24-6
48. Fritz AG, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, et al., editors. International Classification of Diseases for Oncology (ICD-O). 3rd ed. Geneva: World Health Organization; 2000.
49. Prat J, Oncology FCoG. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2014 Jan;124(1):1-5
50. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010 Jun;17(6):1471-4
51. Young JL, Roffers SD, Ries LAG. SEER Summary Staging Manual - 2000: Codes and Coding Instructions. Bethesda: 2001.
52. Walters S, Maringe C, Butler J, Brierley JD, Rachet B, Coleman MP. Comparability of stage data in cancer registries in six countries: lessons from the International Cancer Benchmarking Partnership. Int J Cancer. 2013 Feb 1;132(3):676-85
53. Wilson JM, Jungner YG. Principles and practice of screening for disease. Geneva: WHO; 1968.
54. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008 Apr;86(4):317-9
55. Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. PLoS Med. 2009 Jul;6(7):e1000114
56. Menon U, Griffin M, Gentry-Maharaj A. Ovarian cancer screening-Current status, future directions. Gynecol Oncol. 2014 Feb;132(2):490-5
57. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016 Mar 5;387(10022):945-56
58. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011 Jun 8;305(22):2295-303
59. Chan JK, Zhang M, Hu JM, Shin JY, Osann K, Kapp DS. Racial disparities in surgical treatment and survival of epithelial ovarian cancer in United States. Journal of Surgical Oncology. 2008 01 Jan;97(2):103-7
60. Braicu EI, Sehouli J, Richter R, Pietzner K, Denkert C, Fotopoulou C. Role of histological type on surgical outcome and survival following radical primary tumour debulking of epithelial ovarian, fallopian tube and peritoneal cancers. British Journal of Cancer. 2011 Dec 6;105(12):1818-24
61. Kalapotharakos G, Hogberg T, Bergfeldt K, Borgfeldt C. Long-term survival in women with borderline ovarian tumors: A population-based survey of borderline ovarian tumors in Sweden 1960-2007. Acta Obstetricia et Gynecologica Scandinavica. 2016 01 Apr;95(4):473-9
62. Solheim O, Gershenson DM, Trope CG, Rokkones E, Sun CC, Weedon-Fekjaer H, et al. Prognostic factors in malignant ovarian germ cell tumours (The Surveillance, Epidemiology and End Results experience 1978-2010). European Journal of Cancer. 2014 Jul;50(11):1942-50
63. Bhagyalakshmi A, Sreelekha A, Srideva S, Chandralekha J, Parvathi G, A V. Prospective study of histopathological patterns of ovarian tumours in a tertiary care centre. International Journal of Research in Medical Sciences. 2014 May 2014;2(2):448-56
64. Arab M, Khayamzadeh M, Hashemi M, Hosseini M, Tabatabaeefar M, Anbiaee R, et al. Crude and age-specific incidence rate patterns for histopathologic subtypes of ovarian cancer in Iran. Archives of Iranian Medicine. 2010;13(3):203-8

65. Sorensen RD, Schnack TH, Karlsen MA, Hogdall CK. Serous ovarian, fallopian tube and primary peritoneal cancers: a common disease or separate entities - a systematic review. Gynecol Oncol. 2015 Mar;136(3):571-81
66. Usach I, Blansit K, Chen LM, Ueda S, Brooks R, Kapp DS, et al. Survival differences in women with serous tubal, ovarian, peritoneal, and uterine carcinomas. Am J Obstet Gynecol. 2015 Feb;212(2):188.e1-6
67. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. British Journal of Cancer. 2015 Mar 31;112 Suppl 1:S108-15
68. Praestegaard C, Kjaer SK, Nielsen TS, Jensen SM, Webb PM, Nagle CM, et al. The association between socioeconomic status and tumour stage at diagnosis of ovarian cancer: A pooled analysis of 18 case-control studies. Cancer Epidemiol. 2016 Apr;41:71-9
69. Merrill RM, Sloan A, Anderson AE, Ryker K. Unstaged cancer in the United States: a population-based study. BMC Cancer. 2011;11:402
70. Forbes LJL, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation: a survey of cancer patients. British Journal of Cancer. 2014 Jul 29;111(3):581-8
71. Devlin SM, Diehr PH, Andersen MR, Goff BA, Tyree PT, Lafferty WE. Identification of ovarian cancer symptoms in health insurance claims data. Journal of Women's Health. 2010 01 Mar;19(3):381-9
72. Ryerson AB, Eheman C, Burton J, McCall N, Blackman D, Subramanian S, et al. Symptoms, diagnoses, and time to key diagnostic procedures among older U.S. women with ovarian cancer. Obstetrics & Gynecology. 2007;109(5):1053-61
73. MacLeod U, Mitchell ED, Burgess C, MacDonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: Evidence for common cancers. British Journal of Cancer. 2009 December;101(SUPPL. 2):S92-S101
74. Evans J, Ziebland S, McPherson A. Minimizing delays in ovarian cancer diagnosis: An expansion of Andersen's model of 'total patient delay'. Family Practice. 2007 February;24(1):48-55
75. Low EL, Simon AE, Waller J, Wardle J, Menon U. Experience of symptoms indicative of gynaecological cancers in UK women. British Journal of Cancer. 2013 Aug 20;109(4):882-7
76. Boxell EM, Smith SG, Morris M, Kummer S, Rowlands G, Waller J, et al. Increasing awareness of gynecological cancer symptoms and reducing barriers to medical help seeking: does health literacy play a role? Journal of health communication. 2012;17 Suppl 3:265-79
77. Carter RR, DiFeo A, Bogie K, Zhang GQ, Sun J. Crowdsourcing awareness: Exploration of the ovarian cancer knowledge gap through amazon mechanical turk. PLoS ONE. 2014 22 Jan;9(1)
78. Parham G, Phillips JL, Hicks ML, Andrews N, Jones WB, Shingleton HM, et al. The National Cancer Data Base report on malignant epithelial ovarian carcinoma in African-American women. Cancer. 1997;80(4):816-26
79. Tammemagi CM. Racial/ethnic disparities in breast and gynecologic cancer treatment and outcomes. Current Opinion in Obstetrics and Gynecology. 2007 February;19(1):31-6
80. Terplan M, Schluterman N, McNamara EJ, Tracy JK, Temkin SM. Have racial disparities in ovarian cancer increased over time? An analysis of SEER data. Gynecol Oncol. 2012 April;125(1):19-24
81. Kim S, Dolecek TA, Davis FG. Racial differences in stage at diagnosis and survival from epithelial ovarian cancer: A fundamental cause of disease approach. Social Science and Medicine. 2010 July;71(2):274-81
82. Du XL, Lin CC, Johnson NJ, Altekruse S. Effects of individual-level socioeconomic factors on racial disparities in cancer treatment and survival. Cancer. 2011 15 Jul;117(14):3242-51
83. Bristow RE, Ueda S, Gerardi MA, Ajiboye OB, Ibeanu OA. Analysis of racial disparities in stage IIIC epithelial ovarian cancer care and outcomes in a Tertiary Gynecologic Oncology Referral Center. Gynecol Oncol. 2011 August;122(2):319-23
84. Du XL, Sun CC, Milam MR, Bodurka DC, Fang S. Ethnic differences in socioeconomic status, diagnosis, treatment, and survival among older women with epithelial ovarian cancer. International Journal of Gynecological Cancer. 2008 July/August;18(4):660-9
85. Farley JH, Tian C, Rose GS, Brown CL, Birrer M, Maxwell GL. Race does not impact outcome for advanced ovarian cancer patients treated with cisplatin/paclitaxel: Analysis of Gynecologic Oncology Group Trials. Cancer. 2009 15 Sep;115(18):4210-7

86. Collins Y, Holcomb K, Chapman-Davis E, Khabele D, Farley JH. Gynecologic cancer disparities: A report from the Health Disparities Taskforce of the Society of Gynecologic Oncology. Gynecol Oncol. 2014 May;133(2):353-61
87. Howell EA, Egorova N, Hayes MP, Wisnivesky J, Franco R, Bickell N. Racial disparities in the treatment of advanced epithelial ovarian cancer. Obstetrics and Gynecology. 2013 November;122(5):1025-32
88. Terplan M, Temkin S, Tergas A, Lengyel E. Does equal treatment yield equal outcomes? The impact of race on survival in epithelial ovarian cancer. Gynecol Oncol. 2008 November;111(2):173-8
89. Bristow RE, Chang J, Ziogas A, Campos B, Chavez LR, Anton-Culver H. Sociodemographic disparities in advanced ovarian cancer survival and adherence to treatment guidelines. Obstetrics & Gynecology. 2015 Apr;125(4):833-42
90. Albain KS, Unger JM, Crowley JJ, Coltman CA, Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the southwest oncology group. Journal of the National Cancer Institute. 2009 July;101(14):984-92
91. McGuire V, Herrinton L, Whittemore AS. Race, epithelial ovarian cancer survival, and membership in a large health maintenance organization. Epidemiology. 2002;13(2):231-4
92. Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al. A multi-center population-based case-control study of ovarian cancer in African-American women: the African American Cancer Epidemiology Study (AACES). Bmc Cancer. 2014 Sep 22;14
93. Averette HE, Janicek MF, Menck HR. The National Cancer Data Base report on ovarian cancer. American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer. 1995;76(6):1096-103
94. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. Lancet Oncology. 2008 Mar;9(3):222-31
95. Merrill RM, Anderson AE, Merrill JG. Racial/ethnic differences in the use of surgery for ovarian cancer in the United States. Advances in Medical Sciences. 2010 Jun;55(1):93-8
96. Terplan M, Smith EJ, Temkin SM. Race in ovarian cancer treatment and survival: A systematic review with meta-analysis. Cancer Causes and Control. 2009 September;20(7):1139-50
97. Long B, Chang J, Ziogas A, Tewari KS, Anton-Culver H, Bristow RE. Impact of race, socioeconomic status, and the health care system on the treatment of advanced-stage ovarian cancer in California. Am J Obstet Gynecol. 2015 Apr;212(4):468.e1-9
98. Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. Gynecol Oncol. 2013 April;129(1):258-64
99. Javid SH, Varghese TK, Morris AM, Porter MP, He H, Buchwald D, et al. Guideline-Concordant Cancer Care and Survival Among American Indian/Alaskan Native Patients. Cancer. 2014 Jul 15;120(14):2183-90
100. Burnett-Hartman AN, Bensink ME, Berry K, Mummy DG, Warren-Mears V, Korenbrot C, et al. Access to the Indian health service care system is not associated with early enrollment in medicaid for American Indian and alaska natives with cancer. Cancer Epidemiology Biomarkers and Prevention. 2014 February;23(2):362-4
101. Farley J, Risinger JI, Rose GS, Maxwell GL. Racial disparities in Blacks with gynecologic cancers. Cancer. 2007 15 Jul;110(2):234-43
102. Bryant CS, Kumar S, Shah JP, Mahdi H, Ali-Fehmi R, Munkarah AR, et al. Racial disparities in survival among patients with germ cell tumors of the ovary-United States. Gynecol Oncol. 2009 September;114(3):437-41
103. Hinchcliff E, Rauh-Hain JA, Clemmer JT, Diver E, Hall T, Stall J, et al. Racial disparities in survival in malignant germ cell tumors of the ovary. Gynecol Oncol. 2016 01 Mar;140(3):463-9
104. Fuh KC, Shin JY, Kapp DS, Brooks RA, Ueda S, Urban RR, et al. Survival differences of Asian and Caucasian epithelial ovarian cancer patients in the United States. Gynecol Oncol. 2015 Mar;136(3):491-7
105. Dachs GU, Currie MJ, McKenzie F, Jeffreys M, Cox B, Foliaki S, et al. Cancer disparities in indigenous Polynesian populations: Maori, Native Hawaiians, and Pacific people. The Lancet Oncology. 2008 May;9(5):473-84

106. Jeffreys M, Sarfati D, Stevanovic V, Tobias M, Lewis C, Pearce N, et al. Socioeconomic inequalities in cancer survival in New Zealand: The role of extent of disease at diagnosis. Cancer Epidemiology Biomarkers and Prevention. 2009 March;18(3):915-21
107. Firestone RT, Wong KC, Ellison-Loschmann L, Pearce N, Jeffreys M. Characteristics of ovarian cancer in women residing in Aotearoa, New Zealand: 1993-2004. Journal of epidemiology and community health. 2009 Oct;63(10):814-9
108. Baldwin AE, Usher K. Going the distance--experiences of women with gynaecological cancer residing in rural remote north Queensland. International journal of nursing practice. 2008 Aug;14(4):322-8
109. Chirlaque MD, Salmeron D, Ardanaz E, Galceran J, Martinez R, Marcos-Gragera R, et al. Cancer survival in Spain: estimate for nine major cancers. Annals of Oncology. 2010 May;21:iii21-iii9
110. Fairfield KM, Lee Lucas F, Earle CC, Small L, Trimble EL, Warren JL. Regional variation in cancer-directed surgery and mortality among women with epithelial ovarian cancer in the Medicare population. Cancer. 2010;116(20):4840-8
111. Chan JK, Kapp DS, Shin JY, Osann K, Leiserowitz GS, Cress RD, et al. Factors associated with the suboptimal treatment of women less than 55 years of age with early-stage ovarian cancer. Gynecol Oncol. 2008;108(1):95-9
112. Ulanday KT, Ward KK, Macera CA, Ji M, Plaxe SC. Regional variation in surgical assessment of lymph nodes for staging among women with early-stage epithelial ovarian cancer. Gynecol Oncol. 2014 Feb;132(2):411-5
113. O'Malley CD, Cress RD, Campleman SL, Leiserowitz GS. Survival of Californian women with epithelial ovarian cancer, 1994-1996: A population-based study. Gynecol Oncol. 2003 December;91(3):608-15
114. Anuradha S, Webb PM, Blomfield P, Brand AH, Friedlander M, Leung Y, et al. Survival of Australian women with invasive epithelial ovarian cancer: a population-based study. Medical Journal of Australia. 2014 Sep 1;201(5):283-8
115. Szpurek D, Moszynski R, Szubert S, Sajdak S. Urban and rural differences in characteristics of ovarian cancer patients. Annals of Agricultural and Environmental Medicine. 2013 2013;20(2):390-4
116. Jones AP, Haynes R, Sauerzapf V, Crawford SM, Forman D. Geographical access to healthcare in Northern England and post-mortem diagnosis of cancer. Journal of Public Health. 2010 Dec;32(4):532-7
117. Jones AP, Haynes R, Sauerzapf V, Crawford SM, Zhao H, Forman D. Travel times to health care and survival from cancers in Northern England. European Journal of Cancer. 2008 Jan;44(2):269-74
118. Jones AP, Haynes R, Sauerzapf V, Crawford SM, Zhao H, Forman D. Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer. European Journal of Cancer. 2008 May;44(7):992-9
119. Polsky D, Armstrong KA, Randall TC, Ross RN, Even-Shoshan O, Rosenbaum PR, et al. Variation in chemotherapy utilization in ovarian cancer: The relative contribution of geography. Health Services Research. 2006 Dec;41(6):2201-18
120. Oberaigner W, Minicozzi P, Bielska-Lasota M, Allemani C, de Angelis R, Mangone L, et al. Survival for ovarian cancer in Europe: the across-country variation did not shrink in the past decade. Acta oncologica. 2012 Apr;51(4):441-53
121. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011;377(9760):127-38
122. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: Results of EUROCARE-5-a population-based study. The Lancet Oncology. 2014 January;15(1):23-34
123. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Ann Oncol. 2006 Jan;17(1):5-19
124. Kurkure AP, Yeole BB. Social inequalities in cancer with special reference to South Asian countries. Asian Pacific journal of cancer prevention : APJCP. 2006 Jan-Mar;7(1):36-40

125. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. New England Journal of Medicine. 1985;312:1604-8
126. Lyratzopoulos G, Abel GA, Brown CH, Rous BA, Vernon SA, Roland M, et al. Socio-demographic inequalities in stage of cancer diagnosis: evidence from patients with female breast, lung, colon, rectal, prostate, renal, bladder, melanoma, ovarian and endometrial cancer. Annals of Oncology. 2013 Mar;24(3):843-50
127. Shen N, Weiderpass E, Antilla A, Goldberg MS, Vasama-Neuvonen KM, Boffetta P, et al. Epidemiology of occupational and environmental risk factors related to ovarian cancer. Scandinavian Journal of Work, Environment & Health. 1998;24(3):175-82
128. Vagero D, Persson G. Occurrence of cancer in socioeconomic groups in Sweden. An analysis based on the Swedish Cancer Environment Registry. Scandinavian Journal of Social Medicine. 1986;14(3):151-60
129. Menvielle G, Luce D, Geoffroy-Perez B, Chastang JF, Leclerc A. Social inequalities and cancer mortality in France, 1975-1990. Cancer Causes & Control. 2005;16(5):501-13
130. Brain KE, Smits S, Simon AE, Forbes LJ, Roberts C, Robbe IJ, et al. Ovarian cancer symptom awareness and anticipated delayed presentation in a population sample. Bmc Cancer. 2014 Mar 10;14
131. Hvidberg L, Pedersen AF, Wulff CN, Vedsted P. Cancer awareness and socio-economic position: results from a population-based study in Denmark. Bmc Cancer. 2014 Aug 9;14
132. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. IARC scientific publications. 1997 (138):65-176
133. Kiadaliri AA. Social disparity in breast and ovarian cancer incidence in iran, 2003-2009: A time trend province-level study. Journal of Breast Cancer. 2013 December;16(4):372-7
134. Cooper N, Quinn MJ, Rachet B, Mitry E, Coleman MP. Survival from cancer of the ovary in England and Wales up to 2001. British Journal of Cancer. 2008;99 Suppl 1:S70-2
135. Jensen KE, Hannibal CG, Nielsen A, Jensen A, Nohr B, Munk C, et al. Social inequality and incidence of and survival from cancer of the female genital organs in a population-based study in Denmark, 1994-2003. European Journal of Cancer. 2008 September;44(14):2003-17
136. Weiderpass E, Oh J-K, Algeri S, Bellocco R. Socioeconomic status and epithelial ovarian cancer survival in Sweden. Cancer Causes & Control. 2014 Aug;25(8):1063-73
137. Braaten T, Weiderpass E, Lund E. Socioeconomic differences in cancer survival: the Norwegian Women and Cancer Study. BMC public health. 2009;9:178
138. Vercelli M, Lillini R, Capocaccia R, Micheli A, Coebergh JW, Quinn M, et al. Cancer survival in the elderly: effects of socio-economic factors and health care system features (ELDCARE project). European Journal of Cancer. 2006;42(2):234-42
139. Mackillop WJ, ZhangSalomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. Journal of Clinical Oncology. 1997 Apr;15(4):1680-9
140. Schrijvers CT, Mackenbach JP, Lutz JM, Quinn MJ, Coleman MP. Deprivation, stage at diagnosis and cancer survival. International Journal of Cancer. 1995;63(3):324-9
141. Boyd LR, Novetsky AP, Curtin JP. Ovarian Cancer Care for the Underserved: Are Surgical Patterns of Care Different in a Public Hospital Setting? Cancer. 2011 Feb 15;117(4):777-83
142. Chase DM, Rincon A, Deane M, Tewari KS, Brewster WR. Socioeconomic factors may contribute to neoadjuvant chemotherapy use in metastatic epithelial ovarian carcinoma. Gynecol Oncol. 2009 December;115(3):339-42
143. Chan JK, Kapp DS, Shin JY, Husain A, Teng NN, Berek JS, et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. Obstetrics and Gynecology. 2007 June;109(6):1342-50
144. Bristow RE, Palis BE, Chi DS, Cliby WA. The National Cancer Database report on advanced-stage epithelial ovarian cancer: Impact of hospital surgical case volume on overall survival and surgical treatment paradigm. Gynecol Oncol. 2010 September;118(3):262-7
145. Bristow RE, Chang J, Ziogas A, Randall LM, Anton-Culver H. High-volume ovarian cancer care: Survival impact and disparities in access for advanced-stage disease. Gynecol Oncol. 2014 February;132(2):403-10
146. Chase DM, Fedewa S, Chou TS, Chen A, Ward E, Brewster WR. Disparities in the Allocation of Treatment in Advanced Ovarian Cancer Are There Certain Patient Characteristics Associated With Nonstandard Therapy? Obstetrics and Gynecology. 2012 Jan;119(1):68-77

147. Mercado C, Zingmond D, Karlan BY, Sekaris E, Gross J, Maggard-Gibbons M, et al. Quality of care in advanced ovarian cancer: The importance of provider specialty. Gynecol Oncol. 2010 April;117(1):18-22
148. Vernooij F, Heintz AP, Witteveen PO, van der Heiden-van der Loo M, Coebergh JW, van der Graaf Y. Specialized care and survival of ovarian cancer patients in The Netherlands: nationwide cohort study. Journal of the National Cancer Institute. 2008 19 Mar;100(6):399-406
149. Kravdal O. Does place matter for cancer survival in Norway? A multilevel analysis of the importance of hospital affiliation and municipality socio-economic resources. Health and Place. 2006 December;12(4):527-37
150. du Bois A, Rochon J, Pfisterer J, Hoskins WJ. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: A systematic review. Gynecol Oncol. 2009 February;112(2):422-36
151. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer. 2006;106(3):589-98
152. Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. Journal of the National Cancer Institute. 2006;98(3):172-80
153. Elit LM, Bondy SJ, Paszat LP, Holowaty EJ, Thomas GM, Stukel TA, et al. Surgical outcomes in women with ovarian cancer. Canadian Journal of Surgery. 2008;51(5):346-54
154. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol. 1992;47(2):203-9
155. Hodeib M, Chang J, Liu F, Ziogas A, Dilley S, Randall LM, et al. Socioeconomic status as a predictor of adherence to treatment guidelines for early-stage ovarian cancer. Gynecol Oncol. 2015 Jul;138(1):121-7
156. Silber JH, Rosenbaum PR, Polsky D, Ross RN, Even-Shoshan O, Schwartz JS, et al. Does ovarian cancer treatment and survival differ by the specialty providing chemotherapy? Journal of Clinical Oncology. 2007 01 Apr;25(10):1169-75
157. Schrag D, Earle C, Xu F, Panageas KS, Yabroff KR, Bristow RE, et al. Associations between hospital and surgeon procedure volumes and patient outcomes after ovarian cancer resection. Journal of the National Cancer Institute. 2006;98(3):163-71
158. Doufekas K, Olaitan A. Clinical epidemiology of epithelial ovarian cancer in the UK. Int J Womens Health. 2014;6:537-45
159. Bristow RE, Powell MA, Al-Hammadi N, Chen L, Miller JP, Roland PY, et al. Disparities in ovarian cancer care quality and survival according to race and socioeconomic status. Journal of the National Cancer Institute. 2013 05 Jun;105(11):823-32
160. Thrall MM, Gray HJ, Symons RG, Weiss NS, Flum DR, Goff BA. Neoadjuvant chemotherapy in the Medicare cohort with advanced ovarian cancer. Gynecol Oncol. 2011;123(3):461-6
161. Goff BA, Matthews BJ, Larson EH, Andrilla CHA, Wynn M, Lishner DM, et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. Cancer. 2007 May 15;109(10):2031-42
162. Fairfield KM, Murray K, Lucas FL, Wierman HR, Earle CC, Trimble EL, et al. Completion of adjuvant chemotherapy and use of health services for older women with epithelial ovarian cancer. J Clin Oncol. 2011 Oct 10;29(29):3921-6
163. Thrall MM, Gray HJ, Symons RG, Weiss NS, Flum DR, Goff BA. Trends in treatment of advanced epithelial ovarian cancer in the Medicare population. Gynecol Oncol. 2011 Jul;122(1):100-6
164. Cress RD, O'Malley CD, Leiserowitz GS, Campleman SL. Patterns of chemotherapy use for women with ovarian cancer: A population-based study. Journal of Clinical Oncology. 2003 Apr 15;21(8):1530-5
165. Bristow RE, Zahurak ML, Ibeanu OA. Racial disparities in ovarian cancer surgical care: A population-based analysis. Gynecol Oncol. 2011 May 1;121(2):364-8
166. Erickson BK, Martin JY, Shah MM, Straughn Jr JM, Leath CA. Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center. Gynecol Oncol. 2014 May;133(2):142-6

167. Liu FW, Randall LM, Tewari KS, Bristow RE. Racial disparities and patterns of ovarian cancer surgical care in California. Gynecol Oncol. 2014 Jan;132(1):221-6
168. Austin S, Martin MY, Kim Y, Funkhouser EM, Partridge EE, Pisu M. Disparities in Use of Gynecologic Oncologists for Women with Ovarian Cancer in the United States. Health Services Research. 2013 Jun;48(3):1135-53
169. Fairfield KM, Murray K, LaChance JA, Wierman HR, Earle CC, Trimble EL, et al. Intraperitoneal chemotherapy among women in the Medicare population with epithelial ovarian cancer. Gynecol Oncol. 2014 Sep;134(3):473-7
170. Quaglia A, Tavilla A, Shack L, Brenner H, Janssen-Heijnen M, Allemani C, et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. European Journal of Cancer. 2009 Apr;45(6):1006-16
171. Lyratzopoulos G, Newsome H, Barbiere J, Bolton K, Wright K, Kitchener H, et al. Trends in the surgical management of epithelial ovarian cancer in East Anglia 1995-2006. Ejso. 2011 May;37(5):435-41
172. Rachet B, Ellis L, Maringe C, Chu T, Nur U, Quaresma M, et al. Socioeconomic inequalities in cancer survival in England after the NHS cancer plan. British Journal of Cancer. 2010 10 Aug;103(4):446-53
173. Ito Y, Nakaya T, Nakayama T, Miyashiro I, Ioka A, Tsukuma H, et al. Socioeconomic inequalities in cancer survival: A population-based study of adult patients diagnosed in Osaka, Japan, during the period 1993-2004. Acta Oncologica. 2014 01 Oct;53(10):1423-33
174. Abdel-Rahman ME, Butler J, Sydes MR, Parmar MKB, Gordon E, Harper P, et al. No socioeconomic inequalities in ovarian cancer survival within two randomised clinical trials. British Journal of Cancer. 2014 Jul 29;111(3):589-97
175. Balli S, Fey MF, Hanggi W, Zwahlen D, Berclaz G, Dreher E, et al. Ovarian cancer: an institutional review of patterns of care, health insurance and prognosis. European Journal of Cancer. 2000 Oct;36(16):2061-8
176. Smith JK, Ng SC, Zhou Z, Carroll JE, McDade TP, Shah SA, et al. Does increasing insurance improve outcomes for US cancer patients? Journal of Surgical Research. 2013;185(1):15-20
177. Morgan MA, Behbakht K, Benjamin I, Berlin M, King SA, Rubin SC. Racial differences in survival from gynecologic cancer. Obstetrics and Gynecology. 1996 December;88(6):914-8
178. Auvinen A, Karjalainen S. Possible explanations for social class differences in cancer patient survival. IARC scientific publications. 1997 (138):377-97
179. Rudan I, Bukovic D, Lesko V, Roguljic D. The comparison of the impacts of psychocultural, socioeconomical, hereditary-constitutional and clinicopathological factors on ovarian cancer prognosis. Collegium Antropologicum. 1995 Dec;19(2):461-70
180. Aizer AA, Chen MH, McCarthy EP, Mendu ML, Koo S, Wilhite TJ, et al. Marital status and survival in patients with cancer. Journal of Clinical Oncology. 2013;31(31):3869-76
181. Mahdi H, Kumar S, Munkarah AR, Abdalamir M, Doherty M, Swensen R. Prognostic impact of marital status on survival of women with epithelial ovarian cancer. Psycho-Oncology. 2013;22(1):83-8
182. Kvikstad A, Vatten LJ. Cancer risk and prognosis in Norway: comparing women in their first marriage with women who have never married. Journal of Epidemiology & Community Health. 1996;50(1):51-5
183. Yeole BB, Kumar AV, Kurkure A, Sunny L. Population-based survival from cancers of breast, cervix and ovary in women in Mumbai, India. Asian Pacific journal of cancer prevention : APJCP. 2004 2004;5(3):308-15
184. Kvikstad A, Vatten LJ, Tretli S. Widowhood and divorce in relation to overall survival among middle-aged Norwegian women with cancer. British Journal of Cancer. 1995;71(6):1343-7
185. Louwman WJ, Aarts MJ, Houterman S, Van Lenthe FJ, Coebergh JWW, Janssen-Heijnen MLG. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. Br J Cancer. 2010 23 Nov;103(11):1742-8
186. Thrall MM, Goff BA, Symons RG, Flum DR, Gray HJ. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. Obstetrics and Gynecology. 2011 September;118(3):537-47
187. O'Malley CD, Shema SJ, Cress RD, Bauer K, Kahn AR, Schymura MJ, et al. The implications of age and comorbidity on survival following epithelial ovarian cancer: Summary and results from

a Centers for Disease Control and Prevention study. Journal of Women's Health. 2012 01 Sep;21(9):887-94
188. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet. 2015 14 March 2015;385:977–1010
189. Commission on Cancer. Facility Oncology Registry Data Standards. Chicago, IL: American College of Surgeons, 2010.
190. Pheby D, Martínez C, Roumagnac M, Schouten L. Recommendations for coding incidence date. European Network of Cancer Registries, 1997.
191. MacLennan R. Chapter 6. Items of patient information which may be collected by registries. In: Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG, editors. Cancer Registration: Principles and Methods. Lyon, France: International Agency for Research on Cancer; 1991.
192. Weir HK, Johnson CJ, Mariotto AB, Turner D, Wilson RJ, Nishri D, et al. Evaluation of North American Association of Central Cancer Registries' (NAACCR) Data for Use in Population-Based Cancer Survival Studies. JNCI Monographs. 2014 November 1, 2014;2014(49):198-209
193. Johnson CJ, Weir HK, Yin D, Niu X. The impact of patient follow-up on population-based survival rates. Journal of Registry Management. 2010;37:86-103
194. Silcocks P. Survival of death certificate initiated registrations: Selection bias, incomplete trace-back or higher mortality? British Journal of Cancer. 2006 Dec 4;95(11):1576-8
195. Ellison LF. Measuring the effect of including multiple cancers in survival analyses using data from the Canadian Cancer Registry. Cancer Epidemiol. 2010 Oct;34(5):550-5
196. Rosso S, De Angelis R, Ciccolallo L, Carrani E, Soerjomataram I, Grande E, et al. Multiple tumours in survival estimates. Eur J Cancer. 2009 Apr;45(6):1080-94
197. Rosso S, Terracini L, Ricceri F, Zanetti R. Multiple primary tumours: incidence estimation in the presence of competing risks. Population health metrics. 2009;7:5
198. Brenner H, Hakulinen T. Patients with previous cancer should not be excluded in international comparative cancer survival studies. Int J Cancer. 2007 Nov 15;121(10):2274-8
199. International Association of Cancer Registries. International rules for multiple primary cancers (ICD-O Third Edition). Lyon, France: International Agency for Research on Cancer: World Health Organization, International Association of Cancer Registries, European Network of Cancer Registries, 2004 2004/02.
200. National Cancer Institute Surveillance Epidemiolgy and End Results Program. Multiple Primary and Histology Coding Rules. Bethesda, MD: National Cancer Institute, 2007.
201. Ellis L, Woods LM, Esteve J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. Int J Cancer. 2014 Oct 15;135(8):1774-82
202. Woods LM, Rachet B, Ellis L, Coleman MP. Full dates (day, month, year) should be used in population-based cancer survival studies. Int J Cancer. 2012 Oct 1;131(7):E1120-4
203. Pohar Perme M, Stare J, Estève J. On estimation in relative survival. Biometrics. 2012;68:113-20
204. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer. 1996 Nov 1;78(9):2004-10
205. Brenner H, Rachet B. Hybrid analysis for up-to-date long-term survival rates in cancer registries with delayed recording of incident cases. Eur J Cancer. 2004 Nov;40(16):2494-501
206. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer. 2004 Oct;40(15):2307-16
207. StataCorp. STATA statistical software. 14 ed. College Station TX: Stata Corporation; 2015.
208. Clerc-Urmès I, Grzebyk M, Hédelin G. Net survival estimation with stns. Stata Journal. 2014;14:87-102
209. Greenwood M. The natural duration of cancer. (Report on Public Health and Medical Subjects No. 33). London: HMSO, 1926.
210. Trent Cancer Registry National Cancer Intelligence Network. Overview of ovarian cancer in England: incidence, mortality and survival. London: Trent Cancer Registry, 2012.
211. Clarke B, Gilks B. Ovarian carcinoma: recent developments in classification of tumour histological subtype. Canadian Journal of Pathology. 2011:33-42

212. Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. Gynecol Oncol. 2011 Mar;120(3):470-3
213. Sung PL, Chang YH, Chao KC, Chuang CM, Task Force on Systematic R, Meta-analysis of Ovarian C. Global distribution pattern of histological subtypes of epithelial ovarian cancer: a database analysis and systematic review. Gynecol Oncol. 2014 May;133(2):147-54
214. Moslehi R, Chu W, Karlan B, Fishman D, Risch H, Fields A, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. American journal of human genetics. 2000 Apr;66(4):1259-72
215. Wang Y, Mang M, Wang Y, Wang L, Klein R, Kong B, et al. Tubal origin of ovarian endometriosis and clear cell and endometrioid carcinoma. American journal of cancer research. 2015;5(3):869-79
216. Jacoby VL, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. Am J Obstet Gynecol. 2010 Jun;202(6):514-21
217. Rahman R, Asombang AW, Ibdah JA. Characteristics of gastric cancer in Asia. World J Gastroenterol. 2014 Apr 28;20(16):4483-90
218. Wang J, El-Bahrawy MA. Expression profile of mucins in ovarian mucinous tumors: distinguishing primary ovarian from metastatic tumors. International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists. 2014 Mar;33(2):166-75
219. Mangili G, Sigismondi C, Gadducci A, Cormio G, Scollo P, Tateo S, et al. Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. Int J Gynecol Cancer. 2011 Nov;21(8):1414-21
220. Holscher G, Anthuber C, Bastert G, Burges A, Mayr D, Oberlechner E, et al. Improvement of survival in sex cord stromal tumors - an observational study with more than 25 years follow-up. Acta obstetricia et gynecologica Scandinavica. 2009;88(4):440-8
221. Servov S, Scully R, Sobin LH. Histological typing of ovarian tumours. Geneva: World Health Organization; 1973.
222. Scully R, Sobin LH. Histological typing of ovarian tumours. 2nd ed. Geneva: World Health Organization; 1999.
223. Seidman JD, Horkayne-Szakaly I, Cosin JA, Ryu HS, Haiba M, Boice CR, et al. Testing of two binary grading systems for FIGO stage III serous carcinoma of the ovary and peritoneum. Gynecol Oncol. 2006 Nov;103(2):703-8
224. Pohar Perme M, Henderson R, Stare J. An approach to estimation in relative survival regression. Biostatistics. 2009;10:136-46
225. Takano M, Tsuda H, Sugiyama T. Clear cell carcinoma of the ovary: is there a role of histology-specific treatment? J Exp Clin Cancer Res. 2012;31:53
226. Johnson CJ, Weir HK, Fink AK, German RR, Finch JL, Rycroft RK, et al. The impact of National Death Index linkages on population-based cancer survival rates in the United States. Cancer Epidemiol. 2013 Feb;37(1):20-8

Appendix A: CONCORD-2 data specification

Annex 3 Data specification **29 November 2012**

1 Introduction

1.1 CONCORD-2 will establish global surveillance of cancer survival. This annex to the main protocol provides a detailed description of the data that each registry is asked to provide. It has been substantially modified in the light of discussion at the CONCORD Working Group meeting in Cork, Ireland, 20-21 September 2012, attended by participants from 48 countries.

1.2 Data for the CONCORD study will be sent to the Cancer Survival Group at the London School of Hygiene and Tropical Medicine. We expect to receive up to 2,000 data files - 200 or more cancer registries may each supply up to 10 data files (one for each cancer). **To manage these files efficiently, we must impose strict rules on data structure.** This annex sets out the rules!

1.3 First, we define 10 **index sites** - the stomach, colon, rectum, liver, lung, breast (women), cervix, ovary and prostate, plus leukaemia.

1.4 Second, for simplicity, we will use "**cancer**" to refer to all invasive, primary, malignant neoplasms, including the haematological malignancies.

1.5 **Index cancers** are those that:

- occur at an **index site**
- were diagnosed in persons who are **normally resident** in the territory covered by the registry
- were diagnosed during the **calendar period** covered by the registry's data submission

1.6 Most participating registries will supply data on all 10 **index cancers**, but that is ***not*** a requirement in order to participate in CONCORD. Some specialised registries only record certain cancers (e.g., breast, colorectal, haematological; childhood cancers). Some registries do not have follow-up data for patients with every type of cancer that they register.

1.7 We will focus on analysing survival for **index cancers** diagnosed during the period **1 January 1995 to 31 December 2009**. You are invited to contribute data for as much of that period as possible, but it is ***not*** a requirement to supply data for the entire period 1995-2009. Some registries only began operation more recently than 1995.

1.8 When identifying the data you propose to submit, however, you should ensure that (a) the *incidence data* are considered to be complete for the years submitted and

(b) the *follow-up* of all patients for their vital status is also considered to be complete, at least up to 31 December of the last year of incidence, and preferably a later year. **More recent data are admissible**, if your data are complete for 2010 or a later year. Some examples follow:

- Example (1): incidence data 1995-2009, follow-up to 31 December 2009
- Example (2): incidence data 1998-2007, follow-up to 31 December 2008
- Example (3): incidence data 2000-2010, follow-up to 31 December 2011

1.9 Some participating **cancer registries** will cover the entire national population; others will only cover part of a country (state, province, region, etc.).

1.10 Survival analyses will focus on **adults** (defined as aged 15-99 years at diagnosis). We will also examine survival from acute lymphoid leukaemia in **children** (0-14 years).

1.11 If your registry collects data on tumours that are benign (behaviour code 0), uncertain (1) or *in situ* (2), such as *in situ* cancers of the cervix, please include records for ***all*** neoplasms diagnosed at an **index site** when submitting your data. This will enable comparison of the intensity of diagnostic activity between participating registries (see variable 22, behaviour, in Section 3). Please note, however, that **survival analyses will be restricted to invasive, primary malignancies (behaviour code 3).**

1.12 During the period 1995-2009, most registries switched to ICD-O-3[1] for coding tumour site, morphology and behaviour, instead of ICD-9[2], ICD-10[3] or ICD-O-2[4]. At the CONCORD Working Group meeting in Cork in September 2012, it was agreed to use ICD-O-3. If your data are not coded to ICD-O-3, ***please discuss this with us*** before submitting your data.

1.13 Full dates (day, month and year) of birth, diagnosis and death are important in international survival analyses. The evidence and the rationale are explained in a recent paper[5]. This is also available on the CONCORD web-site. A brief summary is given with the relevant variables in Section 3 of this document. If you *cannot* send the full dates of birth, diagnosis and death, ***please discuss this with us*** before preparing your data for submission. We may be able to help you obtain ethical approval, or to find an alternative solution.

1.14 **All cancer data files must have the same structure.** The details are set out for each variable in the following pages. First, please note the general points below, which apply to most variables:

- All data files will be tested for adherence to protocol. This is the first step of quality control. Tables of protocol adherence will be sent to you shortly after data submission. Data files that do not meet the protocol cannot be used. If you are in doubt about how to construct your data files, ***please discuss this with us*** before sending them.
- Every tumour record ***must contain a value for every variable***, both <u>core</u> and <u>optional</u> variables (see page 3):
  - *If you do not collect data* for a particular variable, you must still include that variable in every tumour record, whether it is a **core variable** or an **optional variable**. Do

not leave the variable blank. For example, if you do not collect data on race/ethnicity (variable 8), you should assign the value 99 to that variable in every tumour record (see summary list on page 32).

- *If no data are available* for a variable in a particular tumour record, you must still include that variable, whether it is a **core variable** or an **optional variable**. Assign the value 9, 99 or 999, etc., depending on how many digits are specified for that variable (see page 32). For example, if a tumour record contains no data for the core variable 'sex', you should assign the value 9 to that variable in every tumour record. Do not assign an imputed value.
- *If you choose not to supply* an optional variable, you must still include that variable in every tumour record. Do not leave the variable blank. For example, if you choose not to supply the optional variables 23-37 on stage at diagnosis, you should assign the value 9, 99 or 999 (etc.) to these variables, depending on how many digits are specified for each variable (see page 32).

- If it is routine practice in your registry to substitute an imputed value for a missing value (e.g. the month of the year), and some of the variables you submit contain imputed values **please tell us**: *we will request a description* of the imputation procedures.
- If tumour records in your database include a special code ("flag") to indicate when a missing value has been imputed, ***please discuss this with us*** before submitting your data. *We will request a description* of how each flag has been generated.
- If you have modified a standard coding scheme (such as ICD-O-3) by adding special codes for local use in your registry, **please recode your data** to the standard form before submission. If you have any doubts about the appropriate conversion, ***please discuss this with us***.
- The variables on **stage at diagnosis** are optional, but many registries that do collect such data have requested survival analyses by stage. Stage data are only requested for cases **diagnosed in 2001 or later**. For cancers diagnosed during the period 1995-2000, therefore, the stage variables should be set to 9, 99, etc. (see page 32). Data on stage for 2000 or earlier years will not be included in quality control or survival analyses.

2 Variable names and short descriptions

2.1 The sequence of variables to be used in each record is as follows:

Core variables		Optional variables	
Name	**Short description**	**Name**	**Short description**
VAR1	Country	VAR23	SEER Summary Stage 2000
VAR2	Registry	VAR24	Pathological T
VAR3	Person code	VAR25	Pathological N
VAR4	Tumour code	VAR26	Pathological M
VAR5	IARC check flag *	VAR27	Clinical T
VAR6	Sex	VAR28	Clinical N
VAR7	Region *	VAR29	Clinical M
VAR8	Race/ethnicity *	VAR30	Condensed T
VAR9	Day of birth	VAR31	Condensed N
VAR10	Month of birth	VAR32	Condensed M
VAR11	Year of birth	VAR33	Dukes' stage
VAR12	Day of diagnosis	VAR34	FIGO stage
VAR13	Month of diagnosis	VAR35	Tumour size
VAR14	Year of diagnosis	VAR36	No. of lymph nodes examined
VAR15	Last known vital status	VAR37	No. of lymph nodes involved
VAR16	Day of last known vital status		
VAR17	Month of last known vital status		
VAR18	Year of last known vital status		
VAR19	Basis of diagnosis		
VAR20	ICD-O-3 Topography		
VAR21	ICD-O-3 Morphology		
VAR22	Behaviour		

* If your registry does not use these variables, see paragraph 1.14 on page 2

2.2 Details of the content and coding of each variable are given in Section 3.

2.3 Abbreviations

AJCC	American Joint Committee on Cancer
DCO	Death-certificate-only registration
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique; International Federation of Gynecology and Obstetrics
IARC	International Agency for Research on Cancer (WHO)
ICCC	International Classification of Childhood Cancers
ICD	International Classification of Diseases (WHO)
ICD-O	International Classification of Diseases for Oncology (WHO)
LSHTM	London School of Hygiene and Tropical Medicine
NAACCR	North American Association of Central Cancer Registries
SEER	Surveillance, Epidemiology and End Results programme (US National Cancer Institute)
TNM	Tumour Nodes Metastasis (UICC)
UICC	Union for International Cancer Control

3 Description of variables

Variable 1 Country

Numeric variable, four digits.

The value for this variable is assigned centrally (see table below). It comprises a one-digit code for the continent followed by the 3-digit UN code for each country. The 4-digit code for your country in the table below *must be included in each tumour record*.

The names shown for each country in the table are mainly the English names associated with the UN code. We have shortened some of the names for convenience: this does not carry any political significance.

AFRICA	**Eastern Africa**		**North America**		**Northern Europe**
2404	Kenya	1124	Canada	4208	Denmark
2480	Mauritius	1840	United States of America	4233	Estonia
2638	Réunion			4246	Finland
2800	Uganda	**ASIA**	**Eastern Asia**	4352	Iceland
2716	Zimbabwe	3156	China	4372	Ireland
	Northern Africa	3344	China, Hong Kong SAR	4428	Latvia
2012	Algeria	3392	Japan	4440	Lithuania
2818	Egypt	3410	Korea	4578	Norway
2434	Libya	3158	Taiwan	4752	Sweden
2504	Morocco		**Southern Asia**	4826	United Kingdom
2788	Tunisia	3356	India		**Southern Europe**
	Southern Africa	3364	Iran	4191	Croatia
2710	South Africa	3586	Pakistan	4292	Gibraltar
	Western Africa		**South-Eastern Asia**	4380	Italy
2270	Gambia	3360	Indonesia	4470	Malta
2288	Ghana	3458	Malaysia	4620	Portugal
2466	Mali	3608	Philippines	4705	Slovenia
2566	Nigeria	3702	Singapore	4724	Spain

		3764	Thailand		**Western Europe**
AMERICAS	**Caribbean**		**Western Asia**	4040	Austria
5192	Cuba	3196	Cyprus	4056	Belgium
5312	Guadeloupe	3368	Iraq	4250	France
5474	Martinique	3376	Israel	4276	Germany
5630	Puerto Rico	3400	Jordan	4528	Netherlands
	Central America	3414	Kuwait	4756	Switzerland
5188	Costa Rica	3634	Qatar		
5484	Mexico	3792	Turkey	**OCEANIA**	**Australia and NZ**
	South America			9036	Australia
5032	Argentina	**EUROPE**	**Eastern Europe**	9554	New Zealand
5076	Brazil	4100	Bulgaria		**Melanesia**
5152	Chile	4203	Czech Republic	9540	New Caledonia
5170	Colombia	4348	Hungary		**Micronesia**
5218	Ecuador	4616	Poland	9316	Guam
5604	Peru	4642	Romania		**Polynesia**
5858	Uruguay	4643	Russian Federation	9258	French Polynesia
		4703	Slovakia		

If your country is not listed, please contact us for advice.

For reference, the country codes are at the following United Nations web-page, accessed 31 October 2012: http://unstats.un.org/unsd/methods/m49/m49regin.htm

Variable 2 Registry

Numeric variable; one to three digits (range 1-950).

We will provide the code for your registry before you prepare your data. The code for your registry must be included as variable 2 in every tumour record.

Together with the country code (variable 1), this variable will be used to link the data file with the relevant life tables during survival analysis.

Variable 3 Person code

Numeric variable, up to 15 digits; ***or***

Alphanumeric variable, up to 15 characters.

If the **person code** in your registry is numeric, you should not submit 'leading zeros'. For example, if the **person code** has nine digits, submit it as a nine-digit number (e.g. 123456789), and not as 000000123456789 (15 characters).

This is a unique code used in your **cancer registry** to refer to each registered cancer patient.

The **person code** can be any unique string of characters, but ***not*** the person's name, national identity number, social security number or any similarly recognisable code. The **person code** must be included in each tumour record, to enable you to check the record in the event that we identify possible errors during quality control.

The same **person code** must be included in any other tumour records supplied for the same person. Together with the **tumour code** (variable 4), this variable provides a unique identification of each tumour included in the study, for the purposes of quality control, but without compromising patient confidentiality.

Note: A few cancer registries do not routinely use a **person code**. These registries will need to create a unique code for each person included in their data files. The code will be used to identify patients with more than one **index cancer**. It will also enable the registry to identify all tumours for a given person in the event that we identify possible errors during quality control. If you have any doubts about the appropriate procedure, ***please discuss this with us***.

Variable 4 Tumour code

Numeric variable, up to ten digits, ***or***

Alphanumeric variable, up to ten characters.

If the tumour codes in your registry are numeric, you should not submit 'leading zeros'. For example, if your tumour code has six digits, submit it as a six-digit number (e.g. 123456), and not as 0000123456 (10 characters).

This is the code used in your **cancer registry** to refer to each registered tumour. Together with the **person code** (variable 3), this variable will enable persons with more than one **index cancer** to be identified.

The main survival analyses will include all primary, invasive, malignancies at an **index site** for patients diagnosed during the period 1995-2009 (or the calendar period for which your registry provides data – see paragraph 1.8 on page 1).

If your registry has submitted data for all patients diagnosed during 1995-2009, a patient with an invasive primary cancer of the breast diagnosed in 2000, followed by a different invasive primary cancer of the colon diagnosed in 2005, would therefore be included in the survival analyses for each of those cancers.

Variable 5 IARC CHECK flag

Numeric variable, one digit.

We will use this variable to avoid sending you requests to check tumour records that you have already checked and, if necessary, corrected (codes 2, 3 or 4).

Code	Meaning
1 =	Tumour record has not been checked with IARC CHECK
2 =	Tumour record has been checked with IARC CHECK: no error(s) or warning(s)
3 =	Tumour record has been checked with IARC CHECK: any error(s) or warning(s) have been corrected
4 =	Tumour record has been checked with IARC CHECK: no change was made because the registry has confirmed that the original record was correct
9 =	This variable will not be provided

If you choose not to supply the IARC CHECK flag, ***please assign the code 9 to this variable*** in every tumour record.

Variable 6 Sex

Numeric variable, one digit.

Code	Meaning
1	Male
2	Female
9	Sex is ambiguous, or sex was not known

Please do not exclude any records from your data on the basis of this variable, even if the sex of the patient is not known.

Variable 7 Region

Numeric variable, up to five digits.

In some cases, it may be possible to estimate survival for geographic areas within the territory of your registry. For example, if your registry has national coverage, such analyses could be for regions (e.g. provinces, states, etc.) within your country. Alternatively, if your registry covers a province or state, such analyses could be for smaller regions (e.g. counties) within your territory.

The categories for geographic region will be different for each registry that supplies this variable.

If you wish us to provide such analyses, *you will need to include a suitable geographic code* in each tumour record.

You will also need to identify for us the region (province, state, county, etc.) that corresponds to each geographic code.

For example, the counties within some US states are a geographic variable of interest:

Code	**Meaning**
21001 =	Kentucky, Adair
21003 =	Kentucky, Allen
21005 =	Kentucky, Anderson
21007 =	Kentucky, Ballard
21009 =	Kentucky, Barren
21011 =	Kentucky, Bath
21... =	Kentucky, ...
99999 =	Region not known, or you will not supply this variable

We will also need to be able to construct appropriate life tables for each geographic region (province, state, etc.) for which you wish to obtain separate survival estimates: see Annex 6: Life tables).

If you choose not to supply data for separate areas of the territory covered by your registry ("Region"), ***please assign the code 99999 to this variable*** in every tumour record.

Variable 8 Race/ethnicity

Numeric variable, one or two digits.

In some cases, it may be possible to estimate survival separately for each race/ethnicity within a population. Cancer registries in some countries collect information on race and/or ethnicity (USA), race (Australia, Israel and Singapore), ethnicity (New Zealand, UK) or nationality (Dubai, Kuwait).

By contrast, most European registries ***do not*** record information on race or ethnicity. In some countries, it is illegal to do so.

The categories for race/ethnicity will be different for each registry that supplies this variable.

If you wish us to provide such analyses, *you will need to include a suitable code for race/ethnicity in each tumour record*.

You will also need to identify for us the race or ethnic group that corresponds to each code.

The example shown here is for the USA:

Code		Meaning
1	=	White, Hispanic
2	=	White, Non-Hispanic
3	=	White, Hispanic status unknown
4	=	Black, Hispanic
5	=	Black, Non-Hispanic
6	=	Black, Hispanic status unknown
7	=	Asian or Pacific Islander, Hispanic
8	=	Asian or Pacific Islander, Non-Hispanic
9	=	Asian or Pacific Islander, Hispanic status unknown
10	=	American Indian/Alaska Native, Hispanic
11	=	American Indian/Alaska Native, Non-Hispanic

12 = American Indian/Alaska Native, Hispanic status unknown

13 = Other, unspecified or unknown race, Hispanic

14 = Other, unspecified or unknown race, Non-Hispanic

15 = Other, unspecified or unknown race, Hispanic status unknown

99 = Unknown or missing, or variable not supplied

Other race/ethnicity groups may be used, after discussion with the registry concerned, but the extent to which robust life tables can be constructed for each race or ethnic group may limit the scope for such analyses.

If you want us to provide survival analyses by race or ethnicity, we will need to construct appropriate life tables for each race/ethnicity: see Annex 6 (Life tables).

If your registry does not collect data on race/ethnicity, or you choose not to supply such data, ***please assign the code 99 to this variable*** in every tumour record.

Variables 9-11 Date of birth

A full and accurate date of ***birth*** is important because it is used to calculate the exact age at diagnosis. This is used to determine the age group (at diagnosis) into which patients are assigned for age-specific survival estimates, and later for age-standardised survival. It is also used to calculate the exact age at death, and thus to select the appropriate background death rate from the life table for the computation of expected survival.

A few cancer registries do not record the full date of birth. Most registries do record the full date, but some registries may face problems in supplying this information to external researchers, for a range of legal, ethical or regulatory reasons.

A brief explanation of why full dates are important is given in the **main protocol**. We have published a peer-reviewed article setting out the argument in detail, supported by empirical evidence.[5] The article shows the difficulties that arise in quality control when full dates cannot be obtained, and, more importantly, the biases that arise in survival estimation and survival comparisons. The conclusions are based on sensitivity analyses with a large data set. The article is accessible (with your login and password) on the CONCORD web-site.

Data preparation and analyses will be performed at the London School of Hygiene and Tropical Medicine (LSHTM). The Cancer Survival Group at LSHTM has acquired both statutory and ethical approvals from relevant bodies in the UK to receive and analyse individual tumour records with full dates (day, month and year) of birth, diagnosis and death for the CONCORD-2 study (**Annex 12.1: Statutory approval; Annex 12.2: Ethical approval**).

Variable 9 Day of birth

Numeric variable, one or two digits.

1-31 = the day of birth

99 = the day of birth of this patient is not known

Note: please tell us if the day *of the date of birth cannot be provided for* ***any*** *of your patients.*

Note: please see comments below *(variables 12-14) about the imputation of dates.*

Variable 10 Month of birth

Numeric variable, one or two digits.

1-12 = the month of birth

99 = the month of birth of this patient is not known

Note: please tell us if the month *of the date of birth cannot be provided for* ***any*** *of your patients.*

Note: please see comments below *(variables 12-14) about the imputation of dates.*

Variable 11 Year of birth

Numeric variable, four digits.

YYYY = the year of birth, from 1895 (person diagnosed in 1995 aged 99) to the present

9999 = the year of birth of this patient is not known

Variables 12-14 Date of diagnosis

The date of diagnosis should be the date used by the registry for cancer incidence or survival.

A full and accurate date of ***diagnosis*** is important because it is the starting point for the duration of survival.

A few cancer registries only record the month and year of diagnosis. Other registries only began to record the *full* date of diagnosis at some point since 1995.

A brief explanation of why full dates are important is given in the **main protocol**. We have published a peer-reviewed article setting out the argument in detail, supported by empirical evidence.[5] The article shows the difficulties that arise in quality control when full dates cannot be obtained, and, more importantly, the biases that arise in survival estimation and survival comparisons. The conclusions are based on sensitivity analyses with a large data set. The article is accessible (with your login and password) on the CONCORD web-site.

Some registries routinely capture more than one possible date of diagnosis (e.g. date of admission, date of biopsy, date of surgery, etc.). Before you supply your data for CONCORD, **you will need to complete the cancer registry questionnaire** on coding practices in your registry (**Annex 15**). This includes information about any rules that you use to select the date of diagnosis from two or more possible dates.

We kindly request that you do not impute the missing components of any dates while preparing your data for submission. If, however, the day and/or the month of the date of diagnosis for some tumours have *already* been imputed:

- ***Please provide us*** with any rules used to impute the day and/or the month of any dates
- If you routinely add a "flag" to tumour records to show when the day and/or the month of any date has been imputed, ***please discuss this with us*** before submitting your data.

Variable 12 Day of diagnosis

Numeric variable, one or two digits.

1-31 = the day of the date of diagnosis

99 = the day of the date of diagnosis of this patient is not known

***Note: please tell us if the day** of the date of diagnosis cannot be provided for **any** of your patients.*

Variable 13 Month of diagnosis

Numeric variable, one or two digits.

1-12 = the month of the date of diagnosis

99 = the month of the date of diagnosis of this patient is not known

***Note: please tell us if the month** of the date of diagnosis cannot be provided for **any** of your patients.*

Variable 14 Year of diagnosis

Numeric variable, four digits.

YYYY = the year of diagnosis, from 1995 onwards

9999 = the year of diagnosis of this patient is not known

Variable 15 Last known vital status

Numeric variable, one digit.

This variable encodes the patient's **last known vital status**, to the extent that it is known to the **cancer registry**. The ***date*** of the patient's **last known vital status** is recorded in variables 16-18.

Code	**Meaning**
1 =	Alive
2 =	Dead
3 =	Lost to follow-up
9 =	Vital status is not known

Information about vital status is conventionally captured using either **'active'** or **'passive'** procedures, which we discuss below. Some registries use both. Before you submit a data file for CONCORD, **you will need to complete the cancer registry questionnaire (Annex 15)** on routine practices in your registry. If you have any doubts about which procedure is used for follow-up in your registry, ***please contact us before preparing your data***.

'Active' follow-up

Active follow-up refers to the situation in which the registry actively seeks information about the vital status of each cancer patient on a regular basis, e.g. from the patient's doctor, or hospital, or even home visits.

If your registry uses this approach, then you should use code "3" for patients whose vital status (alive or dead) could not be ascertained at the last vital status check: these patients are lost to follow-up. The last *date at which they were known to be alive* should be given in variables 16-18.

Code "3" should be used for patients known to have emigrated, since they are also lost to follow-up: the *date of emigration* should be given in variables 16-18.

'Passive' follow-up

Passive follow-up refers to the situation in which the registry routinely receives information from one or more reliable sources on the vital status of *all registered patients*.

These sources vary widely between registries, but may include social security or health insurance files, or a regional or national index of persons who have died. The information may be derived in various ways, such as by computer linkage with the registry database, manual scanning of the death index, or supply of details about all deaths in the registry's territory.

The key features of passive follow-up for international survival comparisons are that:

- the registry uses this approach for updating its own data for local analyses of survival, and
- the registry's procedures reliably identify ***all deaths* of registered cancer patients, *not just* the deaths for which cancer is mentioned on the death certificate***, and
- the registry can reliably assume that registered cancer patients are alive, unless information about a patient's death has been received from one or more of these sources.

If your registry uses passive follow-up, patients who are *not known to be dead* would normally be assumed to be alive on the date of the most recent linkage between the registry and a death index or other vital status records. The vital status of those patients would be coded as "1" (alive).

However, if some patients cannot be traced by any passive follow-up procedure, their vital status may remain undetermined: it would then be coded as "9" (unknown).

When you submit your data, *we will ask you to tell us* the last date when you performed linkage or other follow-up to determine the vital status of your patients.

Variables 16-18 Date of the patient's last known vital status

This is the most recent date for which the patient's **last known vital status** (variable 15) was available.

If the patient is dead, the **date of last known vital status** should be the date of death.

If the patient is *known* to be dead (variable 15 is coded as "2"), but the date of death is *not known*, the **date of last known vital status** should be coded to 99,99,9999 (see page 32).

If the patient has emigrated, the **date of last known vital status** should be the date of emigration.

If the patient has been lost to follow-up, the **date of last known vital status** should be the date of loss to follow-up.

If the patient is considered to be alive, but ***not*** emigrated or lost to follow-up, the **date of last known vital status** should be one of the following:

- 31 December of the last year for which follow-up of all patients is believed to be complete
- the date on which the registry last checked that patient's vital status, e.g. contact with the patient's doctor or a home visit (for registries that perform active follow-up), or linkage with a death index (for registries that perform passive follow-up) (see page 14)
- the date when the registry extracted the data file for this study from its database

Variable 16 Day of last known vital status

Numeric variable, one or two digits.

1-31 = the day of the date of last known vital status

99 = the day of this date is not known

Note: please tell us if the day of last known vital status cannot be provided for ***any*** of your patients.

Note: please see comments above (variables 12-14) about the imputation of dates.

Variable 17 Month of last known vital status

Numeric variable, one or two digits.

1-12 = the month of the date of last known vital status

99 = the month of this date is not known

Note: please tell us if the month *of last known vital status cannot be provided for* ***any*** *of your patients.*

Note: please see comments above *(variables 12-14) about the imputation of dates.*

Variable 18 Year of last known vital status

Numeric variable, four digits.

YYYY = the year of the date of last known vital status, from 1995 onwards

9999 = the year of this date is not known

Variable 19 Basis of diagnosis

Numeric variable, one digit.

This variable indicates the degree of certainty with which a diagnosis of cancer has been established, in the specific context of survival analysis:

Code Meaning

Not microscopically verified

1 = Clinical diagnosis ***only***

2 = Clinical investigation without a tissue diagnosis (e.g. endoscopy without biopsy, or imaging such as X-ray, ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI])

3 = Clinical diagnosis, not otherwise specified [i.e. it is not known if code “1” or “2” applies]

Microscopically verified

4 = Cytologically confirmed (includes blood film examination for leukaemia)

5 = Histologically confirmed (includes bone marrow biopsy for leukaemia)

6 = Microscopically verified, not otherwise specified [i.e. not known if code “4” or “5” applies]

Evidence of cancer does not include the date of diagnosis

7 = Death-certificate-only registration (DCO) ***[see note]***

8 = Autopsy only - malignancy detected only at autopsy ***[see note]***

No information

9 = Unknown

Note:

Cancers registered ***solely*** on the basis of a death certificate (code 7) or autopsy (code 8) are usually included in cancer *incidence* statistics for the year in which they are registered.

For DCO and autopsy-detected cases, however, the true date of diagnosis and the duration of survival are unknown. Therefore, they cannot normally be included in *survival* analyses. A few cancer registries do not even record DCOs or autopsy-detected cancers.

If your cancer registry ***did*** register such cases during the calendar period covered by your data submission, however, ***you must include DCO and autopsy-detected cancers in the data you submit for this study***, to enable comparative quality control.

Variable 20 ICD-O-3 Topography

Alphanumeric variable, four characters.

Tumour site (topography) should be coded to the third edition of the International Classification of Diseases (ICD-O-3)[1].

Please provide the full 4-character ICD-O-3 code, but ***without the decimal point (".")*.** Thus, liver cancer will be C220 or C221 and prostate cancer will be C619. With this minor modification, the anatomic site of the **index cancers** will be coded as:

Stomach cancer: C160-C166; C168-C169

Colon cancer: C180-C189; C199

Rectal cancer: C209; C210-C212, C218

Note: includes anus and anal canal, C210-C218.

Liver cancer: C220-C221

Note: includes intrahepatic bile ducts, C221.

Lung cancer: C340-C343; C348-C349

Note: trachea (ICD-O-3 C339) will not be included in this study.

Breast cancer: C500-C506; C508-C509

Cervical cancer: C530-C531; C538-C539

Ovarian cancer: C480-C482; C569; C570-C574; C577-C579

Note: includes peritoneum and retroperitoneum, C480-C482, where cancers of high-grade serous morphology often originate in the fallopian tube, C570

Note: includes other and unspecified female genital organs, C577-C579.

Prostate cancer: C619

Leukaemia: You should select **leukaemias** for your data file **on the basis of their morphology code (variable 21), and *not*** on the basis of their topography code. You can use ***any*** valid ICD-O-3 topography code, but without the decimal point (“.”), as specified above.

Variable 21 ICD-O-3 Morphology

Numeric variable, four digits.

Tumour morphology should be coded to the third edition of the International Classification of Diseases for Oncology (ICD-O-3)[1].

For microscopically confirmed tumours, the ICD-O-3 range of morphology codes is:

8000-9989

For haematological malignancies, the ICD-O-3 range of morphology codes is:

9590-9989

This range of morphology codes should be used to select all leukaemias and other haematological malignancies, including the lymphomas. This range of codes is the same for children and adults.

Leukaemia is the **only index cancer** for which you should use the ICD-O-3 morphology code to select cases for your data submission: all tumour records with an ICD-O-3 morphology code in the range 9590-9989 should be included. The **other nine index cancers** should be selected on the basis of the ICD-O-3 *topography* code (variable 20).

Selection and grouping of the adult leukaemias for survival analyses will be based on the categories established by a consensus of haematologists, pathologists and epidemiologists in the HAEMACARE Working Group[6-8]. The HAEMACARE manual for coding and reporting haematological malignancies exists in English[9] and Spanish (available on request).

Childhood leukaemias will be grouped differently from the adult leukaemias, on the basis of the third revision of the International Classification of Childhood Cancers[10] (ICCC-3). The ICCC-3 groupings are based on ICD-O-3 morphology codes.

For solid tumours *without* microscopic verification, you should use:

9999 This means the absence of data in the CONCORD study; it is not an ICD-O-3 code.

Note: this code is only valid for solid tumours, not leukaemias. Leukaemias are ***defined by their morphology***, so they must have a morphology code in the range 9590-9989.

Variable 22 Behaviour

Numeric variable, one digit.

Survival analyses will only include invasive, primary, malignant neoplasms. However, we will also report the *distribution of tumour behaviour* for each cancer. This will enable comparison of the intensity of diagnostic activity between contributing areas, e.g. the proportion of women with cervical cancer who were registered with *in situ* carcinoma.

Therefore, if your registry collects data on tumours that are benign (behaviour code 0), of uncertain behaviour (1) or *in situ* (2), such as *in situ* carcinoma of the cervix, ***please include records for all neoplasms*** (behaviour codes 0-3) diagnosed at an **index site** when submitting your data.

Please do *not* select tumours for inclusion in your data files on the basis of tumour behaviour.

Tumour behaviour should be coded to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). The coding of tumour behaviour has been the same in all revisions of ICD-O.

Code		Meaning
0	=	Benign
1	=	Uncertain whether benign or malignant
2	=	Carcinoma *in situ*
3	=	Malignant, primary site

The behaviour codes below are included in ICD-O-3, but they are not usually used by cancer registries. We show them for completeness.

If your data ***do*** include behaviour codes 6 and 9, however, ***please do not recode them*** before data submission. Instead, ***please provide us with a description*** of how the codes have been used in your data:

Code		Meaning
6	=	Malignant, metastatic site
9	=	Malignant, uncertain whether primary or metastatic site

STAGE OF DISEASE AT DIAGNOSIS **Optional**

Provision of data on stage at diagnosis (variables 23-37) is *optional*.

"Tumour stage" describes how far the cancer has spread at the time of diagnosis. It is a key determinant of survival (prognostic factor). Knowledge of the stage at diagnosis of cancer patients is increasingly important for the interpretation of international survival comparisons[11-15]. Where possible, we will perform analyses of survival in relation to stage at diagnosis.

Among the registries that collect data on stage, information of satisfactory quality is often available for most of the 10 **index cancers**, at least for more recent years.

If your registry ***does not collect any data on tumour stage***, you should assign the codes 9, 99 or 999 (etc.) to ***all*** stage variables (variables 23-37) in every tumour record (see list on page 32). However, ***you must ensure that your data files meet the overall specification***, as summarised on page 32 of this Annex!

If your registry ***does collect data on stage***, but you choose ***not*** to submit data for one or more stage variables, please assign the codes 9, 99 or 999 (etc.) to those variables in every tumour record, depending on how many digits are specified for those variables (see list on page 32).

If you ***do*** submit data on stage, please supply stage data ***only for patients diagnosed from 1 January 2001 onwards***. For patients diagnosed before 2001, please assign the codes 9, 99 or 999 (etc.) to ***all*** stage variables (variables 23-37) in every tumour record, depending on how many digits are specified for those variables (see list on page 32). Data on stage at diagnosis for patients diagnosed before 2001 will *not be included* in quality control or survival analyses.

Many different coding schemes are being used to categorise tumour stage in registries around the world[16].

We will try to obtain data on **at least one widely used categorisation of stage** at diagnosis for each tumour (details in pages 21-31), to enable analysis of survival by stage at diagnosis:

SEER Summary Stage 2000 **TNM (both pathological and clinical)**

Condensed TNM

Dukes' stage (colon and rectum)

FIGO stage (cervix and ovary)

Tumour size

No. of lymph nodes examined

No. of lymph nodes positive for tumour

If you wish to supply data on stage at diagnosis, but your data on stage are not coded ***either*** to TNM 7th edition ***or*** to any of the other specific classifications in this list, ***please contact us before submitting your data.***

Variable 23 SEER Summary Stage 2000 Optional

Numeric variable, one digit.

SEER Summary Stage 2000 is a simple categorisation of stage, developed by the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programme. The North American Association of Central Cancer Registries uses SEER Summary Stage 2000[17] (http://seer.cancer.gov/tools/ssm/). We borrow text from the introduction here. It has been in use in the US and Canada since 1 January 2001.

"Summary stage" is the most basic way of categorising how far a cancer has spread from its point of origin. Summary staging uses all the information available in the medical record; it is a **combination of the most precise clinical and pathological evidence for the extent of disease**. Many population-based cancer registries report summary stage for their registered cases, because the staging categories are sufficiently broad to enable measurement of progress in cancer control.

We expect that North American registries will supply SEER Summary Stage 2000 coded directly for cases diagnosed 2001-2003, but derived from Collaborative Stage for cases diagnosed in 2004 and later (http://seer.cancer.gov/tools/collabstaging). If your registry plans to supply SEER Summary Stage 2000 coded in any other way, ***we request that you inform us*** of the procedures you have used. The comparability of these staging schemes over time is addressed on the following SEER web-page:

http://seer.cancer.gov/seerstat/variables/seer/yr1973_2009/lrd_stage/index.html

Regional spread of disease is divided into several categories, according to the method of spread of the cancer:

Code		Meaning
0	=	*In situ*
1	=	Localised only
2	=	Regional spread by direct extension ***only***
3	=	Regional lymph nodes involved ***only***
4	=	Regional spread by ***both*** direct extension ***and*** lymph node involvement
5	=	Regional, NOS (not otherwise specified) – use this code if there is regional spread of the cancer, but ***the route of spread is not known***
7	=	Distant site(s) or lymph node(s) are involved

9 = Unknown if there is extension or metastasis (unstaged, unknown or unspecified), ***or***

this is a ***death-certificate-only*** case, ***or***

this is an ***autopsy-only*** case

TNM stage (variables 24-29) **Optional**

The Tumour-Nodes-Metastasis (TNM) classification of stage at diagnosis uses a combination of clinical and pathological evidence, like SEER Summary Stage 2000.

The TNM classification is published by the Union for International Cancer Control (UICC). We will use the 7th edition of the TNM manual[18]. This is identical to the classification published by the American Joint Committee on Cancer (AJCC) in 2009[19]. If you have stage data that are coded to earlier editions of TNM, ***please contact us before submitting your data.***

The three components of TNM are tumour size (T); the status of regional lymph nodes, i.e. the extent of lymph node invasion by tumour (N), and whether there is metastasis (spread of disease to an organ or organs distant from the organ of origin) (M).

TNM stage data may be based on pathological evidence ("p") or clinical evidence ("c").

Variable 24 Pathological T **Optional**

Numeric variable, one digit.

This variable encodes information on the physical size of the tumour.

For the nine solid **index cancers** (i.e. excluding leukaemia), up to 4 sub-categories (a, b, c, d) exist for each of the stage categories pT1, pT2, pT3 and pT4. These sub-categories should be coded in the same way as the parent category: for example, pT1a should be coded to "1", in the same way as pT1.

For **cervical cancer only**, additional sub-categories exist: pT1a1, pT1a2, pT1b1 and pT1b2 should be coded to "1", in the same way as pT1. Similarly, sub-categories pT2a1 and pT2a2 should be coded to "2", in the same way as pT2.

The following codes will be used:

Code Meaning

0 = pT0 – no histological evidence of primary tumour

1 = pT1 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories pT1a, pT1b and pT1c, as well as for sub-categories pT1a1, pT1a2, pT1b1 and pT1b2 (cervix only)

2 = pT2 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories pT2a, pT2b and pT2c, as well as for sub-categories pT2a1, pT2a2 (cervix only)

3 = pT3 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories pT3a and pT3b

4 = pT4 – tumour of any size, with direct extension to adjacent organs

This code should also be used for sub-categories pT4a, pT4b, pT4c and pT4d

8 = is – *in situ* carcinoma

9 = pTX – unknown: primary tumour cannot be assessed histologically

Variable 25 Pathological N Optional

Numeric variable, one digit.

This variable encodes the extent of involvement of regional lymph nodes with tumour.

For cancers of the stomach, colon, rectum and breast, several subcategories of pN1, pN2 and pN3 exist (a, b and c). These should be coded in the same way as the parent category: for example, pN2b should be coded to “2”, in the same way as pN2.

The following codes will be used:

Code Meaning

0 = pN0 – no regional lymph nodes involved with tumour, histologically

1 = pN1 – the content of this category varies with the cancer (see TNM manual[18])

For colon, rectum and breast, this code should also be used for sub-categories pN1a, pN1b and pN1c

2 = pN2 – the content of this category varies with the cancer (see TNM manual[18])

For colon, rectum and breast, this code should also be used for sub-categories pN2a, pN2b and pN2c

3 = pN3 – the content of this category varies with the cancer (see TNM manual[18])

For stomach, this code should also be used for sub-categories pN3a and pN3b

For breast, this code should also be used for sub-categories pN3a, pN3b and pN3c

9 = pNX – unknown: regional lymph nodes cannot be assessed histologically

Variable 26 Pathological M Optional

Numeric variable, one digit.

This variable encodes information on the presence or absence of distant metastases.

For cancers of the colon, rectum and prostate, several subcategories of pM1 exist (a, b and c). These should be coded to “1”, in the same way as for pM1.

The following codes will be used:

Code		Meaning
1	=	pM1 – Distant metastases have been microscopically confirmed *This code should also be used for sub-categories pM1a, pM1b and pM1c*
9	=	Unknown – this is not a TNM code (see below). It should be used when no data are available on pathological M status

Note:

The codes pM0 and pMX are ***not valid*** in TNM 7th edition[18]: see note on variable 29 below.

Variable 27-29 Clinical TNM stage Optional

Clinical data on tumour stage may be available from clinical examination, or from imaging of the tumour (X-ray, computed tomography [CT], magnetic resonance imaging [MRI], etc.).

Clinical data may be the only available data on tumour stage, if no surgical or invasive diagnostic procedure has been performed.

These variables are optional. If you choose not to supply them, please assign the code 9 to these variables in every tumour record.

Variable 27 Clinical T Optional

Numeric variable, one digit.

This variable encodes information on the physical size of the tumour.

Clinical data on the T component of stage should ***only*** be submitted if pathological data (variable 24) are ***not*** available.

For the nine solid **index cancers** (i.e. excluding leukaemia), up to 4 sub-categories (a, b, c, d) exist for each of the stage categories cT1, cT2, cT3 and cT4. These sub-categories should be coded in the same way as the parent category: for example, cT1a should be coded to "1", in the same way as cT1.

For **cervical cancer only**, additional sub-categories exist: cT1a1, cT1a2, cT1b1 and cT1b2 should all be coded to "1", in the same way as cT1. Similarly, sub-categories cT2a1 and cT2a2 should both be coded to "2", in the same way as cT2.

The following codes will be used:

Code	Meaning
0	= cT0 – no evidence of primary tumour
1	= cT1 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories cT1a, cT1b and cT1c, as well as for sub-categories cT1a1, cT1a2, cT1b1 and cT1b2 (cervix only)

2 = cT2 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories cT2a, cT2b and cT2c, as well as for sub-categories cT2a1, cT2a2 (cervix only)

3 = cT3 – the content of this category varies with the cancer (see TNM manual[18])

This code should also be used for sub-categories cT3a and cT3b

4 = cT4 – tumour of any size, with direct extension to adjacent organs

This code should also be used for sub-categories cT4a, cT4b, cT4c and cT4d

8 = is – *in situ* carcinoma

9 = cTX – unknown: primary tumour cannot be assessed

Variable 28 Clinical N Optional

Numeric variable, one digit.

This variable encodes information on the involvement of regional lymph nodes with tumour.

Clinical data on the N component of stage should ***only*** be submitted if pathological data (variable 25) are ***not*** available.

For cancers of the stomach, colon, rectum and breast, several subcategories of cN1, cN2 and cN3 exist (a, b and c). These should be coded in the same way as the parent category: for example, cN2b should be coded to “2”, in the same way as cN2.

The following codes will be used:

Code		Meaning
0	=	cN0 – no regional lymph nodes involved with tumour
1	=	cN1 – the content of this category varies with the cancer (see TNM manual[18])
		For colon, rectum and breast, this code should also be used for sub-categories cN1a, cN1b and cN1c
2	=	cN2 – the content of this category varies with the cancer (see TNM manual[18])
		For colon, rectum and breast, this code should also be used for sub-categories cN2a, cN2b and cN2c
3	=	cN3 – the content of this category varies with the cancer (see TNM manual[18])
		For stomach, this code should also be used for sub-categories cN3a and cN3b
		For breast, this code should also be used for sub-categories cN3a, cN3b and cN3c
9	=	cNX – unknown: regional lymph nodes cannot be assessed

Variable 29 Clinical M Optional

Numeric variable, one digit.

This variable encodes information on the presence or absence of distant metastases.

For cancers of the colon, rectum and prostate, several subcategories of cM1 exist (a, b and c). These sub-categories should be coded to “1”, in the same way as for cM1.

The following codes will be used:

Code		Meaning
0	=	cM0 – No metastases
1	=	cM1 – Metastases

Note:

If the clinician does not record the presence of metastases, ***it is assumed*** under the TNM 7th edition that no metastases are present (cM0): such cases should be coded to “0”.

The code “MX” was used in earlier editions of TNM to indicate that the metastatic status of the tumour was unknown. However, clinical assessment of metastasis can be based on physical examination alone, so cMX is no longer considered an appropriate code.

The code cMX is ***not valid*** in TNM 7th edition.

Variables 30-32 Condensed TNM Optional

The condensed TNM scheme for recording tumour stage was developed by the European Network of Cancer Registries[20] for tumour records in which the individual values of T and/or N and/or M are not explicitly recorded. Condensed TNM is based on the TNM 6th edition[21].

Condensed TNM data are only requested if ***neither*** pathological TNM data (variables 24-26) ***nor*** clinical TNM data (variables 27-29) are available.

There is a direct correspondence with the simplified stage classification that is often recorded by cancer registries, in which the extent of disease is classified as localised, regional or distant.

Variable 30 Condensed T Optional

Numeric variable, one digit.

Code	Meaning
1 =	L - Localised disease

Localised disease means:

T1 and T2 tumours for cancers of the stomach, colon, rectum, liver, lung, cervix, prostate

T1, T2 and T3 for breast cancer

T1 for cancer of the ovary (note: T2 tumours of the ovary are considered as ***advanced***)

2 = A - Advanced disease

Advanced disease means:

T3 and T4 tumours for cancers of the stomach, colon, rectum, liver, lung, cervix, prostate

T4 for breast (note: T3 tumours of the breast are considered as ***localised***)

T2 and T3 for ovary

9 = X – Cannot be assessed: no information on tumour size category

Variable 31 Condensed N Optional

Numeric variable, one digit.

Code	Meaning
1	= N0 – No regional lymph node invasion by tumour
2	= N+ – Regional lymph nodes invaded by tumour
9	= NX – Cannot be assessed: no information on nodal status

Variable 32 Condensed M Optional

Numeric variable, one digit.

This code is based on the best available information - clinical, instrumental or pathological. Clinical signs and findings are sufficient to justify classifying a tumour as having metastasised (M+), even without *pathological* confirmation of metastatic deposits.

Code	Meaning
1	= M0 – No distant metastasis
2	= M+ – Distant metastases present
9	= MX – Cannot be assessed: no information on whether metastases are present

Variable 33 Dukes' stage Optional

Numeric variable, one digit.

This variable is optional. If you choose not to supply it, please assign the code 9 to this variable in every tumour record.

Dukes' stage[22] is a specialised classification of tumour stage for cancers of the ***colon and rectum only***. For **all other index cancers**, please assign the code 9 to every tumour record.

The TNM classification is preferable, because it is more detailed.

Dukes' stage should ***only*** be reported if TNM stage data (variables 24-29) are not available.

Dukes' stage was later modified[23] to include a category for metastasis (group D), and sub-categories for direct extension in groups B and C. Modified Dukes' stage is no longer recommended for clinical use, but it is still widely used.

Code	Meaning
1	= Dukes' stage A (this is equivalent to T1N0M0 or T2N0M0)
2	= Dukes' stage B (this is equivalent to T3N0M0 or T4N0M0)
3	= Dukes' stage C (this is equivalent to T(any)N1M0 or T(any)N2M0)
4	= Dukes' stage D (this is equivalent to T(any)N(any)M1)
9	= Dukes' stage missing: no information on Dukes' stage

Variable 34 FIGO stage Optional

Numeric variable, one digit.

This variable is optional. If you choose not to supply it, please assign the code 9 to this variable in every tumour record.

FIGO stage[24] is a specialised classification of tumour stage for **cervical, ovarian** and other gynaecological cancers. For **all other index cancers**, please assign the code 9 to this variable in every tumour record.

The TNM classification is preferable, because it is more detailed.

FIGO stage should ***only*** be reported if TNM stage data (variables 24-29) are not available.

FIGO stage provides five broad categories:

Stage 0	carcinoma *in situ* (common in cervical cancer)
Stage I	confined to the organ of origin
Stage II	invasion of surrounding organs or tissue
Stage III	spread to distant nodes or tissue within the pelvis
Stage IV	distant metastasis(es)

Cancer of the cervix (C530, C531, C538, C539)

Code	Meaning
0 =	FIGO Stage 0 – carcinoma *in situ*
1 =	FIGO Stage I – Tumour confined to cervix (extension to corpus uteri should be disregarded) *This code should also be used for sub-categories IA, IA1, IA2, IB, IB1 and IB2*
2 =	FIGO Stage II – Tumour invades beyond uterus but not to pelvic wall or lower third of vagina *This code should also be used for sub-categories IIA, IIA1, IIA2 and IIB*
3 =	FIGO Stage III – Tumour extends to pelvic wall or lower third of vagina, or causes hydronephrosis *This code should also be used for sub-categories IIIA and IIIB*

4 = FIGO Stage IVA – Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis

5 = FIGO Stage IVB – Distant metastasis

9 = FIGO Stage unknown

Cancer of the ovary (C569) or Fallopian tube (C570)

Code Meaning

1 = FIGO Stage I – Tumour limited to one or both ovaries*

This code should also be used for sub-categories IA, IB and IC

2 = FIGO Stage II – Tumour involves one or both ovaries* with pelvic extension

This code should also be used for sub-categories IIA, IIB and IIC

3 = FIGO Stage III – Tumour involves one or both ovaries* with microscopically confirmed peritoneal metastasis outside the pelvis, and/or regional lymph node metastasis

This code should also be used for sub-categories IIIA, IIIB and IIIC

4 = FIGO Stage IV – Distant metastasis outside the peritoneal cavity

9 = FIGO Stage unknown

*** For malignancies of the Fallopian tubes (C570), replace "ovaries" with "Fallopian tubes".**

Variable 35 Tumour size Optional

Numeric variable, from one to three digits.

Tumour size (maximum tumour diameter) must be reported in **millimetres**, as an integer.

For **breast cancer**, tumour size should be based on histological examination, if available.

For **lung cancer**, tumour size may be available by imaging.

It is difficult to be prescriptive about the maximum physical dimensions of a tumour. We will accept values in the range 1 - 300mm (1mm – 30cm). For example, a tumour with a maximum diameter of 35mm (3.5cm) would be coded as “35”.

Code		Meaning
1-300	=	maximum tumour diameter, **in millimetres**
999	=	maximum tumour diameter is not known, ***or***
		maximum tumour diameter is not applicable (**leukaemia**), ***or***
		this variable will not be supplied

Zero is not a valid tumour dimension. If no data are available for a solid tumour, please code this variable as 999.

Variable 36 Number of lymph nodes examined Optional

Numeric variable, one or two digits.

Report the exact ***number of lymph nodes examined***, as recorded in the pathological record: valid range 0-98.

This variable should be coded to 99 in ***all records*** if:

- you choose not to supply this variable, ***or***
- the data file is for **leukaemia**

For the nine **solid tumours**, this variable should be coded to 99 if:

- no information is available on the number of lymph nodes examined, ***or***
- no pathological examination was done

Variable 37 Number of lymph nodes involved Optional

Numeric variable, one or two digits.

Report the exact ***number of involved lymph nodes (lymph nodes containing tumour cells)***, as recorded in the pathological report: valid range 0-98.

This variable should be coded to 99 in ***all records*** if:

- you choose not to supply this variable, ***or***
- the data file is for **leukaemia**

For the nine **solid tumours**, this variable should be coded to 99 if:

- no information is available on the number of involved lymph nodes, ***or***
- lymph nodes *were* involved, but the *number* of involved lymph nodes is unknown, ***or***
- no pathological examination was done

Appendix B: Ethical approvals

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Michel Coleman
Professor of Epidemiology and Vital Statistics
NCDE/EPH
LSHTM

5 April 2013

Dear Professor Coleman,

Study Title: **CONCORD – global surveillance of cancer survival**
LSHTM ethics ref: **6396**

Thank you for your application of 26 March 2013 for the above research, which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

The application is approved until 31 December 2016.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document	Version	Date
LSHTM ethics application	n/a	
Protocol		22 June 2012

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. At the end of the study, please notify the committee via form E5.

Yours sincerely,

Professor John DH Porter
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

31 August 2016

Statutory approval from Health Research Authority (HRA)

Downloaded and extracted from http://www.hra.nhs.uk/documents/2016/08/ecc-register.xls

Application Number	0543	
Reference	ECC 3-04(i)/2011	
Other Refs		
Application Title	Cancer survival in five continents: a worldwide population based study (CONCORD2)	
Application Summary	This application from the London School of Hygiene and Tropical Medicine set out details of the UK arm of a global surveillance of cancer survival systematic comparison of international differences and trends in cancer survival.	
Applicant Organisation Name	London School of Hygiene and Tropical Medicine	
Contact Name	Professor Michel Coleman	
Address	London School of Hygiene and Tropical Medicine	
	Keppel Street	
	London	
Postcode	WC1E 7HT	
Telephone	02076127849	
Email	michel.coleman@lshtm.ac.uk	
Medical Purposes	Y	preventative medicine
	□	medical diagnosis
	□	medical research, approved by a research ethics committee
	□	the provision of care and treatment
	Y	the management of health and social care services
	□	informing individuals about their physical or mental health or condition, the diagnosis of their condition or their care and treatment
Cohort/Population	All adults (15-99 years) who were normally resident in the territory covered by the contributing cancer registry when diagnosed with cancer of the breast (women), colon, rectum, lung, ovary, prostate, stomach, liver or cervix; or with leukaemia during the period 1995-2007. These malignancies will be referred to as "index cancers". In this context, "cancer" means a tumour that is malignant (i.e. not benign), invasive (i.e. not in situ or preinvasive) and primary i.e. it originates in the organ in question and is not a result of spread (metastasis) from cancer in another organ.	
Description of confidential patient information used	date of birth, diagnosis, date of death, gender	
S251 Class(es)	Y	Support for cancer registry purposes
	□	Class I - making the person less readily identifiable
	□	Class II - present or past geographical locations of patients
	□	Class III - to identify and contact patients to obtain consent
	□	Class IV - linking multiple sources;validating quality and completeness; avoiding error
	□	Class V - audit, monitoring, & analysis of healthcare provision
	□	Class VI - granting of access to data for purposes I-V
Sponsor	London School of Hygiene and Tropical Medicine	
Status	Approved	
Next Review Date	09/05/2017	
Notes		

Appendix C: Sensitivity analysis

	Type I epithelial including endometrioid (original analysis)			Type I excluding endometrioid			Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)			Type II epithelial including endometrioid			Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI		NS (%)	95% CI				NS (%)	95% CI		NS (%)	95% CI			
AFRICA																
Algerian registries																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			.		.	.		.		
2005-2009	***41.6***	*16.1*	*67.2*	***41.6***	*16.1*	*67.2*	0.0	0.0	***37.1***	*24.6*	*49.5*	***37.1***	*24.6*	*49.5*	0.0	0.0
Libya (Benghazi)																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			.		.	.		.		
2005-2009	.		.	.		.			***5.6***	0.0	13.5	***5.2***	*0.0*	*12.7*	0.4	7.1
Mauritius*																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			.		.	.		.		
2005-2009	.		.	.		.			***73.9***	52.9	94.8	***74.5***	*55.6*	*93.5*	-0.6	-0.8
South Africa (Eastern Cape)																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			.		.	.		.		
2005-2009	.		.	.		.			***100.0***	86.1	100.0	***100.0***	*86.1*	*100.0*	0.0	0.0
Tunisia (Central)																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			.		.	.		.		
2005-2009	.		.	.		.			***47.3***	25.0	69.6	***52.2***	*31.0*	*73.4*	-4.9	-10.4
AMERICA (CENTRAL AND SOUTH)																
Argentinian registries																
1995-1999	.		.	.		.			.		.	.		.		
2000-2004	.		.	.		.			**19.6**	11.4	27.8	**22.0**	13.3	30.7	-2.4	-12.2
2005-2009	**30.8**	16.3	45.2	**32.6**	18.7	46.5	-1.8	-5.8	**30.5**	21.9	39.2	**29.9**	21.5	38.3	0.6	2.0

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Brazilian registries																				
1995-1999	.			.	.			.			**29.1**	15.7	-	42.5	**32.3**	20.3	-	44.3	-3.2	-11.0
2000-2004	**46.7**	35.5	-	58.0	.			.			**38.3**	29.6	-	47.0	**41.5**	33.4	-	49.7	-3.2	-8.4
2005-2009	***40.9***	*24.2*	-	*57.5*	**39.7**	27.4	-	52.0	1.2	2.9	**29.2**	17.7	-	40.7	**29.3**	17.8	-	40.9	-0.1	-0.3
Chile (Los Rios)																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	**55.2**	39.8	-	70.7	***49.4***	*29.1*	-	*69.6*	5.8	10.5	**18.1**	6.3	-	29.9	**30.3**	16.4	-	44.2	-12.2	-67.4
Colombia (Cali)																				
1995-1999	**44.8**	29.3	-	60.2	.			.			**29.1**	18.2	-	40.0	**33.1**	22.3	-	43.9	-4.0	-13.7
2000-2004	**55.4**	38.0	-	72.9	**41.0**	25.5	-	56.5	14.4	26.0	**27.1**	21.8	-	32.5	**30.2**	25.3	-	35.2	-3.1	-11.4
2005-2009	**77.1**	64.7	-	89.6	***62.1***	*44.5*	-	*79.6*	15.0	19.5	**32.0**	20.5	-	43.4	**38.0**	26.5	-	49.5	-6.0	-18.8
Cuba*																				
1995-1999	***70.6***	*58.3*	-	*82.9*	.			.			**53.4**	45.1	-	61.7	**55.5**	47.5	-	63.4	-2.1	-3.9
2000-2004	**61.8**	50.1	-	73.5	.			.			**44.7**	39.9	-	49.5	**44.8**	40.1	-	49.6	-0.1	-0.2
2005-2009	**74.6**	64.7	-	84.6	**68.9**	58.5	-	79.3	5.7	7.6	**39.2**	29.3	-	49.1	**46.9**	38.9	-	54.9	-7.7	-19.6
Ecuador (Quito)																				
1995-1999	.			.	.			.			**35.3**	21.0	-	49.6	**37.0**	22.6	-	51.5	-1.7	-4.8
2000-2004	.			.	.			.			**35.1**	21.6	-	48.7	**37.8**	25.2	-	50.3	-2.7	-7.7
2005-2009	**60.2**	40.9	-	79.5	***59.2***	*40.2*	-	*78.2*	1.0	1.7	**55.0**	44.6	-	65.5	**54.7**	44.4	-	64.9	0.3	0.5
Puerto Rico*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	**47.2**	33.7	-	60.8	**41.6**	25.3	-	57.8	5.6	11.9	**29.5**	23.3	-	35.7	**32.0**	25.9	-	38.2	-2.5	-8.5
2005-2009	**62.2**	43.7	-	80.8	**40.5**	18.5	-	62.4	21.7	34.9	**36.2**	26.9	-	45.5	**39.4**	30.2	-	48.6	-3.2	-8.8
AMERICA (NORTH)																				
Canada*																				
1995-1999	**58.6**	55.8	-	61.4	**53.9**	50.0	-	57.9	4.7	8.0	**28.0**	26.6	-	29.3	**33.2**	31.9	-	34.5	-5.2	-18.6
2000-2004	**62.9**	60.0	-	65.8	**56.4**	52.5	-	60.3	6.5	10.3	**29.8**	28.5	-	31.1	**34.8**	33.5	-	36.1	-5.0	-16.8
2005-2009	**69.4**	64.7	-	74.0	**60.4**	51.9	-	68.9	9.0	13.0	**33.7**	30.9	-	36.6	**38.6**	35.9	-	41.3	-4.9	-14.5

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
US registries																				
1995-1999	**58.3**	57.1	-	59.5	**52.5**	51.0	-	54.1	5.8	9.9	**33.4**	32.9	-	33.9	**37.2**	36.7	-	37.7	-3.8	-11.4
2000-2004	**61.7**	60.6	-	62.8	**54.0**	52.5	-	55.6	7.7	12.5	**34.4**	33.9	-	34.8	**38.3**	37.8	-	38.7	-3.9	-11.3
2005-2009	**65.9**	63.9	-	67.9	**57.0**	54.6	-	59.4	8.9	13.5	**36.1**	34.5	-	37.6	**39.9**	38.4	-	41.4	-3.8	-10.5
ASIA																				
Chinese registries																				
1995-1999	.			.	.			.			**40.5**	27.8	-	53.2	**40.9**	28.1	-	53.7	-0.4	-1.0
2000-2004	**66.3**	58.4	-	74.3	**58.7**	49.3	-	68.1	7.6	11.5	**41.9**	34.1	-	49.6	**44.9**	37.2	-	52.6	-3.0	-7.2
2005-2009	**59.3**	46.1	-	72.5	**56.2**	40.1	-	72.2	3.1	5.2	**45.0**	38.4	-	51.6	**46.4**	40.2	-	52.7	-1.4	-3.1
Cyprus*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	***57.5***	*38.5*	-	*76.5*	***60.6***	*39.3*	-	*81.9*	-3.1	-5.4	**42.0**	26.9	-	57.2	**41.6**	26.6	-	56.6	0.4	1.0
Hong Kong*																				
1995-1999	**64.0**	52.9	-	75.1	**66.1**	53.2	-	79.0	-2.1	-3.3	**26.0**	16.8	-	35.3	**31.7**	23.3	-	40.2	-5.7	-21.9
2000-2004	**71.3**	62.5	-	80.1	**66.3**	55.4	-	77.3	5.0	7.0	**33.0**	26.9	-	39.0	**40.2**	34.2	-	46.1	-7.2	-21.8
2005-2009	**82.9**	72.4	-	93.4	***76.6***	*69.5*	-	*83.7*	6.3	7.6	**61.5**	54.8	-	68.2	**66.6**	60.5	-	72.7	-5.1	-8.3
Indian registries																				
1995-1999	.			.	.			.			**22.4**	13.0	-	31.9	**20.7**	11.7	-	29.6	1.7	7.6
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	***31.7***	*15.7*	-	*47.8*	***37.1***	*19.0*	-	*55.2*	-5.4	-17.0	***21.6***	*7.4*	-	*35.8*	***20.8***	*7.1*	-	*34.5*	0.8	3.7
Indonesia (Jakarta)																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	***54.2***	*32.4*	-	*76.0*	***72.2***	*50.6*	-	*93.7*	-18.0	-33.2	.			.	**22.3**	0.4	-	44.2		
Israel*																				
1995-1999	**54.6**	45.7	-	63.4	**51.0**	38.7	-	63.3	3.6	6.6	**35.6**	31.4	-	39.8	**38.4**	34.3	-	42.5	-2.8	-7.9
2000-2004	**57.5**	48.8	-	66.2	**43.8**	30.0	-	57.5	13.7	23.8	**36.1**	32.0	-	40.1	**39.1**	35.3	-	42.9	-3.0	-8.3
2005-2009	**53.9**	31.0	-	76.8	**48.3**	27.2	-	69.3	5.6	10.4	**28.4**	11.3	-	45.4	**29.2**	11.6	-	46.8	-0.8	-2.8

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Japanese registries																				
1995-1999	**48.7**	40.5	-	56.8	**53.1**	44.4	-	61.9	-4.4	-9.0	**26.2**	21.1	-	31.2	**27.5**	22.3	-	32.7	-1.3	-5.0
2000-2004	**53.4**	48.2	-	58.5	**55.9**	50.0	-	61.8	-2.5	-4.7	**30.5**	26.9	-	34.1	**33.1**	29.6	-	36.6	-2.6	-8.5
2005-2009	**48.9**	27.2	-	70.5	**47.0**	26.0	-	68.0	1.9	3.9	**37.0**	32.0	-	41.9	**40.6**	35.5	-	45.7	-3.6	-9.7
Jordan*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	***22.2***	*3.1*	-	*41.4*	.			.			**18.3**	6.4	-	30.3	**21.4**	8.4	-	34.3	-3.1	-16.9
2005-2009	***0.0***	*0.0*	-	*0.0*	***7.4***	*0.0*	-	*18.1*	-7.4	0.0	***0.0***	*0.0*	-	*0.0*	***0.0***	*0.0*	-	*0.0*	0.0	0.0
Korea*																				
1995-1999	**65.5**	59.0	-	72.1	**67.3**	60.1	-	74.5	-1.8	-2.7	**37.9**	33.3	-	42.4	**40.4**	35.9	-	44.9	-2.5	-6.6
2000-2004	**64.9**	59.6	-	70.3	**64.0**	58.1	-	70.0	0.9	1.4	**37.7**	33.5	-	42.0	**40.9**	36.9	-	45.0	-3.2	-8.5
2005-2009	**60.8**	50.7	-	70.8	**64.1**	56.3	-	71.9	-3.3	-5.4	**39.5**	33.8	-	45.1	**41.2**	35.2	-	47.1	-1.7	-4.3
Malaysia (Penang)																				
1995-1999	***49.3***	*35.6*	-	*63.1*	.			.			**52.4**	38.0	-	66.7	**54.8**	41.0	-	68.6	-2.4	-4.6
2000-2004	***70.5***	*60.6*	-	*80.4*	***60.6***	*51.0*	-	*70.3*	9.9	14.0	**27.5**	14.3	-	40.7	**31.3**	18.8	-	43.9	-3.8	-13.8
2005-2009	**72.9**	59.7	-	86.0	***62.8***	*45.4*	-	*80.3*	10.1	13.9	**47.3**	31.6	-	63.1	**47.8**	31.6	-	63.9	-0.5	-1.1
Mongolia*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	.			.	.			.			***68.3***	*51.2*	-	*85.3*	***69.3***	*52.7*	-	*85.8*	-1.0	-1.5
Qatar*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	.			.	.			.			***31.9***	*6.7*	-	*57.1*	***35.2***	*8.8*	-	*61.5*	-3.3	-10.3
Saudi Arabia*																				
1995-1999	**70.1**	51.6	-	88.6	***53.7***	*34.5*	-	*72.8*	16.4	23.4	**42.9**	23.2	-	62.5	**46.5**	26.1	-	67.0	-3.6	-8.4
2000-2004	**49.7**	25.3	-	74.1	***53.6***	*37.5*	-	*69.8*	-3.9	-7.8	**31.9**	16.9	-	46.9	**33.5**	17.9	-	49.2	-1.6	-5.0
2005-2009	.			.	.			.			.			.	.			.		

		Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
		NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Taiwan*																					
	1995-1999	**59.5**	52.4	-	66.6	**59.4**	51.3	-	67.4	0.1	0.2	**35.0**	29.2	-	40.7	**38.8**	33.3	-	44.3	-3.8	-10.9
	2000-2004	**61.8**	56.3	-	67.3	**60.7**	54.1	-	67.2	1.1	1.8	**35.8**	31.3	-	40.3	**39.8**	35.7	-	43.9	-4.0	-11.2
	2005-2009	**61.3**	53.8	-	68.7	**61.5**	53.1	-	69.9	-0.2	-0.3	***35.3***	*12.3*	-	*58.3*	***37.4***	*13.1*	-	*61.7*	-2.1	-5.9
Thai registries																					
	1995-1999	***70.3***	*57.8*	-	*82.8*	***66.9***	*53.5*	-	*80.3*	3.4	4.8	***45.1***	*31.3*	-	*59.0*	***50.5***	*37.2*	-	*63.8*	-5.4	-12.0
	2000-2004	**62.9**	52.3	-	73.4	***57.8***	*49.2*	-	*66.4*	5.1	8.1	**32.1**	18.0	-	46.1	**32.1**	17.7	-	46.4	0.0	0.0
	2005-2009	**71.9**	60.8	-	83.0	***66.7***	*52.5*	-	*80.9*	5.2	7.2	**44.4**	35.2	-	53.6	***48.8***	*40.5*	-	*57.0*	-4.4	-9.9
Turkey (Izmir)																					
	1995-1999	**60.3**	49.8	-	70.7	**59.7**	46.6	-	72.7	0.6	1.0	**40.5**	31.8	-	49.2	**44.5**	36.7	-	52.4	-4.0	-9.9
	2000-2004	**58.4**	48.0	-	68.9	**51.4**	38.4	-	64.4	7.0	12.0	**39.3**	27.8	-	50.8	**42.5**	30.6	-	54.3	-3.2	-8.1
	2005-2009	**56.9**	42.6	-	71.3	***64.6***	*51.9*	-	*77.3*	-7.7	-13.5	**31.2**	11.2	-	51.3	**37.8**	22.4	-	53.3	-6.6	-21.2
EUROPE																					
Austria*																					
	1995-1999	**56.4**	50.4	-	62.4	**56.8**	48.9	-	64.7	-0.4	-0.7	**39.6**	37.1	-	42.0	**40.7**	38.3	-	43.1	-1.1	-2.8
	2000-2004	**61.3**	55.6	-	67.1	**59.8**	51.6	-	67.9	1.5	2.4	**36.7**	34.5	-	39.0	**38.8**	36.6	-	41.0	-2.1	-5.7
	2005-2009	**59.9**	48.9	-	70.8	**42.9**	21.3	-	64.5	17.0	28.4	**40.0**	36.0	-	44.1	**42.6**	38.7	-	46.5	-2.6	-6.5
Belgium*																					
	1995-1999	.			.	.			.			.			.	.			.		
	2000-2004	**65.2**	56.3	-	74.1	**59.8**	48.3	-	71.4	5.4	8.3	**35.8**	31.1	-	40.6	**39.7**	35.1	-	44.3	-3.9	-10.9
	2005-2009	**62.9**	52.9	-	73.0	**53.8**	37.4	-	70.2	9.1	14.5	**35.4**	31.3	-	39.4	**39.1**	35.2	-	42.9	-3.7	-10.5
Bulgaria*																					
	1995-1999	**42.2**	32.8	-	51.6	**39.0**	28.2	-	49.8	3.2	7.6	**30.2**	25.6	-	34.9	**31.7**	27.2	-	36.1	-1.5	-5.0
	2000-2004	**49.1**	42.7	-	55.4	**47.7**	40.3	-	55.1	1.4	2.9	**33.9**	30.2	-	37.7	**35.3**	31.8	-	38.8	-1.4	-4.1
	2005-2009	**43.8**	33.4	-	54.2	**49.2**	40.9	-	57.6	-5.4	-12.3	**32.6**	23.8	-	41.3	**32.5**	23.1	-	41.9	0.1	0.3
Croatia*																					
	1995-1999	**53.7**	45.3	-	62.1	**43.0**	32.1	-	53.9	10.7	19.9	**35.7**	28.9	-	42.5	**38.3**	31.6	-	45.1	-2.6	-7.3
	2000-2004	**55.5**	47.6	-	63.4	**47.6**	37.1	-	58.1	7.9	14.2	**33.4**	29.3	-	37.5	**36.9**	32.9	-	40.8	-3.5	-10.5
	2005-2009	**54.0**	42.0	-	65.9	**61.9**	48.3	-	75.5	-7.9	-14.6	**28.1**	20.2	-	35.9	**30.0**	22.1	-	38.0	-1.9	-6.8

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Czech Republic*																				
1995-1999	**44.3**	39.1	-	49.6	**46.6**	39.5	-	53.7	-2.3	-5.2	**30.8**	28.0	-	33.5	**32.1**	29.5	-	34.7	-1.3	-4.2
2000-2004	**46.9**	42.8	-	50.9	**46.1**	40.7	-	51.4	0.8	1.7	**32.9**	30.4	-	35.5	**35.0**	32.6	-	37.3	-2.1	-6.4
2005-2009	**53.2**	45.9	-	60.5	**51.8**	43.2	-	60.4	1.4	2.6	**40.4**	36.7	-	44.1	**41.9**	38.2	-	45.7	-1.5	-3.7
Denmark*																				
1995-1999	**50.8**	45.8	-	55.9	**49.0**	42.5	-	55.5	1.8	3.5	**23.9**	21.3	-	26.5	**27.7**	25.2	-	30.2	-3.8	-15.9
2000-2004	**47.4**	41.9	-	52.8	**44.5**	37.4	-	51.6	2.9	6.1	**28.4**	25.6	-	31.3	**31.4**	28.6	-	34.1	-3.0	-10.6
2005-2009	**69.6**	62.9	-	76.3	**67.0**	58.1	-	75.9	2.6	3.7	**30.1**	23.2	-	37.0	**34.7**	28.7	-	40.6	-4.6	-15.3
Estonia*																				
1995-1999	**43.0**	27.5	-	58.4	**39.9**	21.9	-	58.0	3.1	7.2	**26.0**	18.6	-	33.4	**27.4**	20.4	-	34.5	-1.4	-5.4
2000-2004	**46.2**	33.9	-	58.4	**44.2**	31.1	-	57.2	2.0	4.3	**32.9**	26.2	-	39.5	**33.5**	27.0	-	39.9	-0.6	-1.8
2005-2009	**75.3**	61.5	-	89.0	**69.6**	56.7	-	82.5	5.7	7.6	**31.2**	22.5	-	39.8	**33.0**	24.2	-	41.9	-1.8	-5.8
Finland*																				
1995-1999	**45.3**	39.3	-	51.3	**58.9**	49.4	-	68.4	-13.6	-30.0	**38.7**	34.9	-	42.5	**38.2**	34.7	-	41.6	0.5	1.3
2000-2004	**48.2**	43.2	-	53.1	**58.2**	50.3	-	66.1	-10.0	-20.7	**40.1**	36.2	-	44.0	**40.2**	36.9	-	43.5	-0.1	-0.2
2005-2009	**66.4**	59.3	-	73.6	**67.3**	55.9	-	78.7	-0.9	-1.4	**46.3**	40.9	-	51.7	**49.4**	44.6	-	54.3	-3.1	-6.7
French registries																				
1995-1999	**47.0**	40.7	-	53.2	**46.7**	39.6	-	53.8	0.3	0.6	**28.9**	25.7	-	32.1	**30.9**	27.7	-	34.2	-2.0	-6.9
2000-2004	**53.2**	46.8	-	59.6	.			.		0.0	**35.8**	33.2	-	38.4	**38.5**	35.9	-	41.0	-2.7	-7.5
2005-2009	***56.7***	*36.5*	-	*76.9*	**46.9**	41.4	-	52.4	9.8	17.3	**24.8**	9.0	-	40.7	**27.8**	10.0	-	45.6	-3.0	-12.1
German registries																				
1995-1999	**52.7**	48.2	-	57.1	**50.6**	45.1	-	56.0	2.1	4.0	**34.0**	31.9	-	36.0	**35.7**	33.7	-	37.7	-1.7	-5.0
2000-2004	**57.6**	54.3	-	60.9	**55.0**	50.8	-	59.2	2.6	4.5	**36.6**	35.1	-	38.1	**38.6**	37.2	-	40.1	-2.0	-5.5
2005-2009	**46.3**	32.7	-	59.8	**48.0**	41.2	-	54.9	-1.7	-3.7	**35.4**	32.3	-	38.5	**36.5**	32.8	-	40.2	-1.1	-3.1
Iceland*																				
1995-1999	.			.	.			.			**21.1**	9.8	-	32.4	**24.2**	11.9	-	36.5	-3.1	-14.7
2000-2004	.			.	.			.			**30.6**	15.5	-	45.7	**32.2**	16.2	-	48.3	-1.6	-5.2
2005-2009	**56.4**	32.3	-	80.4	***57.4***	*39.5*	-	*75.3*	-1.0	-1.8	***41.5***	*26.9*	-	*56.1*	***40.5***	*22.6*	-	*58.5*	1.0	2.4

		Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
		NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Ireland*																					
	1995-1999	**55.9**	46.0	-	65.8	**55.0**	42.8	-	67.1	0.9	1.6	**21.9**	17.9	-	25.9	**24.8**	20.7	-	28.8	-2.9	-13.2
	2000-2004	**53.4**	44.9	-	61.9	**47.7**	37.0	-	58.3	5.7	10.7	**24.7**	20.8	-	28.6	**28.2**	24.3	-	32.1	-3.5	-14.2
	2005-2009	**73.0**	63.5	-	82.5	**75.3**	64.6	-	86.0	-2.3	-3.2	**25.7**	13.0	-	38.3	**29.0**	14.9	-	43.1	-3.3	-12.8
Italian registries																					
	1995-1999	**58.0**	54.0	-	61.9	**56.2**	51.3	-	61.1	1.8	3.1	**33.2**	31.3	-	35.1	**35.9**	34.0	-	37.7	-2.7	-8.1
	2000-2004	**56.6**	53.2	-	60.1	**53.4**	49.1	-	57.7	3.2	5.7	**36.1**	34.3	-	37.9	**38.7**	36.9	-	40.4	-2.6	-7.2
	2005-2009	**62.9**	57.6	-	68.3	**57.1**	50.1	-	64.1	5.8	9.2	**38.4**	32.5	-	44.2	**41.7**	35.5	-	47.9	-3.3	-8.6
Latvia*																					
	1995-1999	***57.4***	*44.5*	-	*70.4*	***57.1***	*42.8*	-	*71.4*	0.3	0.5	**34.8**	28.9	-	40.7	**35.0**	29.0	-	40.9	-0.2	-0.6
	2000-2004	**50.2**	39.0	-	61.3	**48.9**	37.0	-	60.8	1.3	2.6	**37.5**	32.4	-	42.5	**37.8**	32.8	-	42.9	-0.3	-0.8
	2005-2009	**51.2**	32.8	-	69.6	**51.9**	32.9	-	70.9	-0.7	-1.4	**34.8**	26.6	-	43.0	**35.1**	26.9	-	43.3	-0.3	-0.9
Lithuania*																					
	1995-1999	**43.5**	31.2	-	55.7	**40.9**	28.2	-	53.7	2.6	6.0	**31.7**	27.6	-	35.8	**32.1**	28.0	-	36.2	-0.4	-1.3
	2000-2004	**48.2**	37.6	-	58.8	**42.6**	30.9	-	54.3	5.6	11.6	**29.2**	25.5	-	33.0	**30.4**	26.7	-	34.2	-1.2	-4.1
	2005-2009	**52.4**	40.3	-	64.5	**38.4**	25.3	-	51.4	14.0	26.7	**25.3**	14.5	-	36.1	**29.3**	19.8	-	38.7	-4.0	-15.8
Malta*																					
	1995-1999	**63.1**	48.5	-	77.8	.			.		0.0	***26.0***	*16.4*	-	*35.6*	***29.1***	*19.7*	-	*38.6*	-3.1	-11.9
	2000-2004	.			.	.			.			**32.2**	22.4	-	42.0	**37.0**	26.1	-	48.0	-4.8	-14.9
	2005-2009	**58.0**	48.1	-	68.0	**52.3**	40.6	-	64.0	5.7	9.8	***29.7***	*18.7*	-	*40.7*	***37.0***	*25.9*	-	*48.1*	-7.3	-24.6
Netherlands*																					
	1995-1999	**49.7**	45.8	-	53.6	**46.8**	41.8	-	51.8	2.9	5.8	**27.7**	25.8	-	29.5	**30.8**	28.9	-	32.6	-3.1	-11.2
	2000-2004	**57.1**	53.2	-	61.0	**53.0**	48.0	-	58.0	4.1	7.2	**29.1**	27.4	-	30.9	**33.0**	31.2	-	34.7	-3.9	-13.4
	2005-2009	**56.4**	47.4	-	65.5	**53.5**	45.9	-	61.1	2.9	5.1	**28.1**	19.0	-	37.1	**31.3**	21.3	-	41.2	-3.2	-11.4
Norway*																					
	1995-1999	**57.2**	50.4	-	64.0	**53.6**	45.1	-	62.1	3.6	6.3	**29.2**	26.2	-	32.3	**33.2**	30.2	-	36.3	-4.0	-13.7
	2000-2004	**65.8**	60.0	-	71.7	**62.4**	54.9	-	69.8	3.4	5.2	**33.8**	30.9	-	36.7	**37.7**	34.8	-	40.5	-3.9	-11.5
	2005-2009	**61.9**	52.0	-	71.9	**56.1**	43.7	-	68.5	5.8	9.4	**34.2**	28.4	-	40.0	**36.9**	31.1	-	42.7	-2.7	-7.9

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Poland*																				
1995-1999	**45.4**	36.6	-	54.1	**45.0**	34.5	-	55.5	0.4	0.9	**30.9**	27.1	-	34.7	**32.4**	28.6	-	36.1	-1.5	-4.9
2000-2004	**44.4**	40.8	-	48.0	**44.8**	39.8	-	49.8	-0.4	-0.9	**31.3**	29.4	-	33.1	**33.0**	31.2	-	34.7	-1.7	-5.4
2005-2009	**52.5**	48.0	-	57.1	**49.6**	43.5	-	55.7	2.9	5.5	**31.3**	28.1	-	34.5	**34.4**	31.5	-	37.3	-3.1	-9.9
Portugal*																				
1995-1999	**50.8**	38.9	-	62.8	**50.4**	36.0	-	64.8	0.4	0.8	**30.0**	23.7	-	36.4	**31.9**	25.9	-	37.9	-1.9	-6.3
2000-2004	**55.8**	48.6	-	63.0	**57.0**	48.8	-	65.2	-1.2	-2.2	**35.5**	31.9	-	39.1	**36.9**	33.3	-	40.5	-1.4	-3.9
2005-2009	**68.4**	60.8	-	76.1	**61.8**	52.0	-	71.7	6.6	9.6	**36.3**	29.0	-	43.6	**39.4**	31.8	-	46.9	-3.1	-8.5
Romania (Cluj)																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	.			.	.			.			.			.	.			.		
2005-2009	***68.0***	*52.3*	-	*83.7*	***58.5***	*37.4*	-	*79.6*	9.5	14.0	**49.7**	33.8	-	65.7	**53.5**	38.3	-	68.7	-3.8	-7.6
Russia (Arkhangelsk)																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	**45.2**	31.8	-	58.6	***48.4***	*35.4*	-	*61.4*	-3.2	-7.1	**23.7**	12.4	-	34.9	**24.7**	13.1	-	36.3	-1.0	-4.2
2005-2009	**56.5**	37.8	-	75.2	***60.5***	*43.1*	-	*77.9*	-4.0	-7.1	**32.3**	17.0	-	47.7	**33.5**	18.3	-	48.7	-1.2	-3.7
Slovakia*																				
1995-1999	.			.	.			.			.			.	.			.		
2000-2004	**44.5**	37.5	-	51.5	**45.1**	36.4	-	53.7	-0.6	-1.3	**30.8**	26.6	-	35.1	**32.5**	28.4	-	36.5	-1.7	-5.5
2005-2009	**47.6**	35.1	-	60.1	**47.2**	34.1	-	60.3	0.4	0.8	**29.5**	23.8	-	35.1	**32.0**	26.3	-	37.7	-2.5	-8.5
Slovenia*																				
1995-1999	**50.9**	37.4	-	64.3	**44.6**	23.9	-	65.3	6.3	12.4	**27.8**	22.6	-	33.0	**32.3**	27.1	-	37.4	-4.5	-16.2
2000-2004	**59.8**	50.4	-	69.3	**57.5**	44.6	-	70.4	2.3	3.8	**30.4**	25.0	-	35.9	**35.5**	30.3	-	40.8	-5.1	-16.8
2005-2009	**53.2**	36.4	-	70.0	**53.4**	35.7	-	71.2	-0.2	-0.4	**30.3**	21.8	-	38.8	**33.1**	24.2	-	41.9	-2.8	-9.2
Spanish registries																				
1995-1999	**55.0**	50.1	-	59.9	**50.6**	43.8	-	57.4	4.4	8.0	**28.5**	25.1	-	31.9	**34.1**	31.0	-	37.1	-5.6	-19.6
2000-2004	**59.6**	54.4	-	64.8	**52.5**	45.6	-	59.3	7.1	11.9	**31.9**	28.8	-	35.1	**37.4**	34.5	-	40.4	-5.5	-17.2
2005-2009	**49.7**	39.7	-	59.6	**47.3**	36.4	-	58.3	2.4	4.8	**35.7**	31.2	-	40.3	**37.9**	33.2	-	42.5	-2.2	-6.2

	Type I epithelial including endometrioid (original analysis)				Type I excluding endometrioid				Absolute difference in NS	Relative difference in NS	Type II epithelial excluding endometrioid (original analysis)				Type II epithelial including endometrioid				Absolute difference in NS	Relative difference in NS
	NS (%)	95% CI			NS (%)	95% CI					NS (%)	95% CI			NS (%)	95% CI				
Sweden*																				
1995-1999	.			.	.			.			**40.3**	38.3	-	42.3	**40.3**	38.3	-	42.3	0.0	0.0
2000-2004	.			.	.			.			**41.1**	39.0	-	43.2	**41.1**	39.0	-	43.2	0.0	0.0
2005-2009	.			.	.			.			**35.0**	26.7	-	43.3	**35.0**	26.7	-	43.3	0.0	0.0
Swiss registries																				
1995-1999	**52.7**	43.5	-	61.8	**48.6**	38.1	-	59.0	4.1	7.8	**28.9**	24.7	-	33.0	**31.9**	27.7	-	36.1	-3.0	-10.4
2000-2004	**57.4**	49.8	-	65.1	**48.4**	37.2	-	59.5	9.0	15.7	**31.7**	28.0	-	35.4	**35.1**	31.5	-	38.6	-3.4	-10.7
2005-2009	**63.0**	51.4	-	74.5	**56.8**	33.2	-	80.3	6.2	9.8	**38.0**	32.3	-	43.7	**41.1**	35.7	-	46.5	-3.1	-8.2
United Kingdom*																				
1995-1999	**48.6**	46.8	-	50.4	**46.7**	44.4	-	49.0	1.9	3.9	**21.6**	20.8	-	22.3	**24.8**	24.0	-	25.5	-3.2	-14.8
2000-2004	**54.3**	52.5	-	56.1	**50.5**	48.2	-	52.7	3.8	7.0	**22.7**	22.0	-	23.4	**26.4**	25.7	-	27.1	-3.7	-16.3
2005-2009	**59.5**	55.3	-	63.8	**56.9**	51.2	-	62.5	2.6	4.4	**25.0**	23.6	-	26.5	**28.3**	26.8	-	29.8	-3.3	-13.2
OCEANIA																				
Australian registries																				
1995-1999	**58.3**	53.7	-	62.8	**54.0**	48.5	-	59.6	4.3	7.4	**29.3**	27.3	-	31.2	**32.7**	30.7	-	34.6	-3.4	-11.6
2000-2004	**62.5**	58.0	-	66.9	**55.7**	50.3	-	61.2	6.8	10.9	**30.2**	28.4	-	32.0	**33.9**	32.1	-	35.7	-3.7	-12.3
2005-2009	**64.2**	57.2	-	71.2	**56.2**	46.7	-	65.7	8.0	12.5	**31.2**	25.5	-	36.8	**35.2**	30.0	-	40.3	-4.0	-12.8
New Zealand*																				
1995-1999	**51.1**	42.6	-	59.6	**52.2**	41.7	-	62.7	-1.1	-2.2	**23.8**	19.8	-	27.8	**27.2**	23.2	-	31.3	-3.4	-14.3
2000-2004	**69.1**	60.1	-	78.1	**68.2**	55.7	-	80.6	0.9	1.3	**23.9**	20.3	-	27.6	**29.7**	26.0	-	33.4	-5.8	-24.3
2005-2009	**40.5**	19.4	-	61.6	**35.1**	14.8	-	55.4	5.4	13.3	**23.4**	14.3	-	32.6	**24.2**	15.0	-	33.3	-0.8	-3.4

*Data with 100% coverage of the national population. NS = net survival. Italics denote net survival estimates that are not age-standardised. Where data for two or more calendar periods of diagnosis were merged, the net survival estimates are underlined. Registries with fewer than 10 women for any stage (all calendar periods combined) were not included in the analysis.