Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership

Camille Maringe[a], Sarah Walters[a], John Butler[b], Michel P Coleman[a], Neville Hacker[c], Louise Hanna[d], Berit J Mosgaard[e], Andy Nordin[f], Barry Rosen[g], Gerda Engholm[h], Marianne L Gjerstorff[i], Juanita Hatcher[j], Tom B Johannesen[k], Colleen E McGahan[l], David Meechan[m], Richard Middleton[n], Elizabeth Tracey[o], Donna Turner[p], Michael A Richards[q], Bernard Rachet[a] and the ICBP Module 1 Working Group*

[a] Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine

[b] Gynaecological Oncology Fellow, St Bartholomew's and Royal Marsden Hospitals, London, UK

[c] School of Women's and Children's Health, University of New South Wales, and Gynaecological Cancer Centre, Royal Hospital for Women, Sydney, New South Wales, Australia

[d] Velindre NHS Trust, Cardiff, UK

[e] Herlev University Hospital, Copenhagen, Denmark

[f] East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK

[g] University of Toronto, Toronto, Ontorio, Canada

[h] Department of Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark

[i] Danish Cancer Registry, Statens Serum Institut - National Institute for Health Data and Disease Control, Copenhagen, Denmark

[j] Alberta Health Services, Edmonton, Alberta, Canada

[k] Norwegian Cancer Registry, Oslo, Norway

[l] Cancer Surveillance & Outcomes, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

[m] Trent Cancer Registry, Sheffield, UK

[n] Northern Ireland Cancer Registry, Belfast, UK

[o] Cancer Institute New South Wales, Sydney, New South Wales, Australia

[p] CancerCare Manitoba, Winnipeg, Manitoba, Canada

[q] National Cancer Action Team, Department of Health, London, UK

Correspondence to:

Camille Maringe, Msc

Cancer Research UK Cancer Survival Group

Department of Non Communicable Disease Epidemiology

London School of Hygiene and Tropical Medicine

Keppel Street

London WC1E 7HT

UK

Email: Camille.Maringe@lshtm.ac.uk

Tel: +44 (0) 20 7297 2856

Fax: +44 (0) 20 7580 6897

* ICBP Module 1 Working Group

Programme Board: Søren Brostrøm (Danish National Board of Health, Hospital Services and Emergency Management, Copenhagen, Denmark); Heather Bryant (Canadian Partnership Against Cancer, Toronto, Ontario, Canada); David Currow (Cancer Institute New South Wales, Sydney, New South Wales, Australia); Anna Gavin (Northern Ireland Cancer Registry, Belfast, UK); Gunilla Gunnarsson (Swedish Association of Local Authorities and Regions, Stockholm, Sweden); Jane

Hanson (Welsh Cancer National Specialist Advisory Group, Cardiff, UK); Todd Harper (Cancer Council Victoria, Carlton, Victoria, Australia); Stein Kaasa (University Hospital of Trondheim, Trondheim, Norway); Michael A Richards (National Cancer Action Team, Department of Health, London, UK); Michael Sherar (Cancer Care Ontario, Toronto, Ontario, Canada); Bob Thomas (Department of Health, Melbourne, Victoria, Australia)

Module 1 collaborators and cancer registries: Jan Adolfsson (Regional Cancer Centre, Stockholm County Council and the CLINTEC Department Karolinska Institutet, Stockholm, Sweden); Ole Andersen (National Board of Health, Health Planning Division, Copenhagen, Denmark); Heather Bryant (Canadian Partnership Against Cancer, Toronto, Ontario, Canada); Andy Coldman (Cancer Surveillance & Outcomes, British Columbia Cancer Agency, Vancouver, British Columbia, Canada); Dhali Dhaliwal (CancerCare Manitoba, Winnipeg, Manitoba, Canada); Rebecca Elleray (Trent Cancer Registry, Sheffield, UK); Gerda Engholm (Department of Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark); David Forman (Section of Cancer Information, International Agency for Research on Cancer, Lyon, France); Colin Fox (Northern Ireland Cancer Registry, Belfast, UK); Marianne L Gjerstorff (Danish Cancer Registry, Statens Serum Institut - National Institute for Health Data and Disease Control, Copenhagen, Denmark); Juanita Hatcher (Alberta Health Services, Edmonton, Alberta, Canada); Charlotte Hosbond (National Board of Health, Copenhagen, Denmark); Tom B Johannesen (Norwegian Cancer Registry, Oslo, Norway); Loraine Marrett (Cancer Care Ontario, Toronto, Ontario, Canada); Colleen E McGahan (Cancer Surveillance & Outcomes, British Columbia Cancer Agency, Vancouver, British Columbia, Canada); David Meechan (Trent Cancer Registry, Sheffield, UK); John McLaughlin (Cancer Care Ontario, Toronto, Ontario, Canada); Richard Middleton (Northern Ireland Cancer Registry, Belfast, UK); Diane Nishri (Cancer Care Ontario, Toronto, Ontario, Canada); Nicola Quin (Cancer Council Victoria, Carlton, Victoria, Australia); Linda Rabeneck (Cancer Care Ontario, Toronto, Ontario, Canada); Carol Russell (Alberta Health Services, Edmonton, Alberta, Canada); Janey Shin (Canadian Partnership Against Cancer, Toronto, Ontario, Canada); Andy Smith (Trent Cancer Registry, Sheffield, UK); Elizabeth

Tracey (Cancer Institute New South Wales, Sydney, New South Wales, Australia); Donna Turner (CancerCare Manitoba, Winnipeg, Manitoba, Canada)

Clinical Committee: John Butler (St Bartholomew's and Royal Marsden Hospitals, London, UK); Neville Hacker (School of Women's and Children's Health, University of New South Wales, and Gynaecological Cancer Centre, Royal Hospital for Women, Sydney, Australia); Louise Hanna (Velindre NHS Trust, Cardiff, UK); Thomas Högberg (Skåne University Hospital, Lund, Sweden); Berit Jul Mosgaard (Herlev University Hospital, Copenhagen, Denmark); Gunnar Kristensen (The Norwegian Radium Hospital, Oslo, Norway); Andy Nordin (East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK); Johnny Price (Belfast City Hospital, Belfast, Northern Ireland); Barry Rosen (University of Toronto, Toronto, Ontario, Canada)

Central Analytic Team: Camille Maringe, Sarah Walters, Michel P Coleman, Bernard Rachet, (Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine, London, UK)

Acknowledgements

We thank the cancer registry staff in all jurisdictions, whose sustained efforts in data collection and quality control over many years have made possible this study of ovarian cancer survival and stage at diagnosis. The authors would like to thank Martine Bomb, Catherine Foot and Donia Sadik at Cancer Research UK for their logistical support.

Disclaimers

This study was funded by the Department of Health, England (London, UK), and Cancer Research UK (London, UK). The Northern Ireland Cancer Registry is funded by the Northern Ireland Public Health Agency. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of any government agency.

Stage at diagnosis and ovarian cancer survival: evidence from the International Cancer Benchmarking Partnership

Abstract

Objective: We investigate what role stage at diagnosis bears in international differences in ovarian cancer survival.

Methods: Data from population-based cancer registries in Australia, Canada, Denmark, Norway, and the UK were analysed for 20,073 women diagnosed with ovarian cancer during 2004-7. We compare the stage distribution between countries and estimate stage-specific one-year net survival and the excess hazard up to 18 months after diagnosis, using flexible parametric models on the log cumulative excess hazard scale.

Results: One-year survival was 69% in the UK, 72% in Denmark and 74-75% elsewhere. In Denmark, 74% of patients were diagnosed with FIGO stage III-IV disease, compared to 60-70% elsewhere. International differences in survival were evident at each stage of disease; women in the UK had lower survival than in the other four countries for patients with FIGO stage III-IV disease (61.4% *vs.* 65.8-74.4%). International differences were widest for older women and for those with advanced stage or with no stage data.

Conclusion: Differences in stage at diagnosis partly explain international variation in ovarian cancer survival, and a more adverse stage distribution contributes to comparatively low survival in Denmark. This could arise because of differences in tumour biology, staging procedures or diagnostic delay. Differences in survival also exist within each stage, as illustrated by lower survival for advanced disease in the UK, suggesting unequal access to optimal treatment. Population-based data on cancer survival by stage are vital for cancer

surveillance, and global consensus is needed to make stage data in cancer registries more consistent.

Introduction

International differences in ovarian cancer survival are wide, persistent and largely unexplained, even between high-income countries with similar health systems [1]. We investigate whether these differences in overall survival may be explained by variation in stage at diagnosis or in stage-specific survival.

The International Cancer Benchmarking Partnership (ICBP) is a consortium of cancer registries, clinicians and epidemiologists using population-based data to examine international survival differences. We aim to provide benchmarks against which progress in outcomes can be evaluated, and which will help to refine policy for cancer control. Five countries (Australia, Canada, Denmark, Norway and the UK) contributed to this study of ovarian cancer.

Material and methods

Data

The ICBP collected population-based cancer registration data from Australia (New South Wales, Victoria), Canada (Alberta, British Columbia, Manitoba, Ontario), Denmark, Norway and the UK (eight regional registries covering all of England; Northern Ireland, Wales) for 137,199 women diagnosed with a cancer of the ovary (including Fallopian tubes and adnexa: ICD-10 C56; C57.0-C57.9) during 1995-2007. Women diagnosed with a benign, uncertain or

borderline malignancy, in situ or metastatic tumour were ineligible (webappendix para 1). Extensive quality control has been documented [1].

To conduct survival analyses by stage at diagnosis, we used data from the most recent 4 years of the period 1995-2007, for which stage data were more complete, and from the 11 (of 18) cancer registries in which at least half of all women diagnosed in 2004-07 had a valid stage. The excluded registries (Victoria, Australia; Ontario, Canada; four English regional registries and Wales, UK) represented 54% of the original population base. Finally, 20,073 women were included in the analyses, of whom 14,948 (74.5%) had complete stage information on their registry record.

The classification and coding of stage at diagnosis varies, both clinically and between cancer registries. We developed guidelines for harmonising data on stage from disparate classification systems into a final, comparable variable for survival analysis (Walters *et al*, Comparability of stage data in cancer registries in six countries: lessons from the International Cancer Benchmarking Partnership, *in review*). We requested data coded to the TNM classification of stage, including separate information on the extent of the tumour (T), nodal involvement (N) and metastases (M) [2]. We prioritised pathological stage data (pT, pN) except for metastases, where we preferred clinical stage (cM). For some patients, only the grouped TNM stage was available. For many patients, registries submitted data coded to the International Federation of Gynaecology and Obstetrics (FIGO) staging system, which maps to the grouped TNM stages. For patients with TNM and/or FIGO data, we defined a final FIGO stage.

In New South Wales (and for some Norwegian patients with no TNM or FIGO stage) stage was categorised as ‘localised’, ‘regional’, or ‘distant’. We also mapped TNM and FIGO to a

145 'localised, regional, distant' structure, based on the US Surveillance, Epidemiology and End
146 Results Summary Stage 2000 (SEER SS2000) (Walters *et al, in review*). SEER SS2000 is
147 closely equivalent to the Australian and Norwegian systems, but better documented and more
148 widely known [3]. We present results using both SEER SS2000 (all countries) and FIGO
149 (without Australia). There is general equivalence between FIGO stages I-II and SEER
150 SS2000 'localised' and 'regional', and between FIGO stages III-IV and SEER SS2000
151 'distant'. For simplicity here, stages I-IV will refer to FIGO, and 'localised', 'regional' or
152 'distant' to SEER SS2000.

153 *Statistical analyses*

154 We used flexible parametric models with the *stpm2* command [4] implemented in Stata
155 version 12 (StataCorp LP, College Station, TX; webappendix para 2) to model net survival
156 [5]. We censored patients at three years and estimated net survival and excess mortality up to
157 18 months after diagnosis, to ensure greater stability in the modelled estimates. Background
158 mortality was derived from life tables of all-cause mortality rates for women in each
159 jurisdiction by single year of age and calendar year at death [1]. Excess mortality is the
160 excess (cancer-related) hazard of death at specific time points since diagnosis, and can be
161 thought of as the mortality rate from the cancer alone.

162 Models were stratified by stage at diagnosis, including patients with missing data on stage as
163 a distinct category. We allowed for variation with time since diagnosis in the effect of age at
164 diagnosis and country; interactions were included to model non-proportionality between
165 countries (webappendix para 3). All-ages estimates were age-standardised using stage-
166 specific weights (webappendix table 1) derived from the age distribution of patients in all

jurisdictions combined, in the age categories 15-44, 45-54, 55-64, 65-74, 75-84 and 85-99 years.

We conducted multiple imputation by chained equations to ascertain the probable stage distribution for tumours with missing stage, using the *ice* command in Stata [6-8] (webappendix para 4). We ran the imputation model 15 times, obtaining 15 imputed datasets. We report the overall stage distribution combined under Rubin's rules [8]. The same modelling strategy for stage-specific survival was then repeated on each of the 15 imputed datasets, and the range of estimates compared to the estimate based on the observed stage data.

Findings

Distributions by stage and age

Mean age at diagnosis varied from 63.8 to 65.2 years. Women with more advanced stage were older in all jurisdictions (Table 1, Figure 1), but the age distribution of unstaged women varied: compared to women with metastatic disease (stage IV; 'distant'), unstaged women were on average 4-12 years older in Norway and Canada, 1-2 years older in Denmark and the UK, and slightly younger in Australia.

Insert Table 1

The proportion of unstaged tumours ranged from 4% (Norway) to 32% (UK). The proportion increased with age, reaching 40% of 70-99 year-old women in Canada and the UK (Figure 1).

Insert Figure 1

Among women with a recorded stage, Canada and Norway had similar stage distributions, with nearly half of all women diagnosed in stage III. The UK and Australia also had similar distributions, with a higher proportion of 'localised' tumours (23% *vs.* less than 15% elsewhere).

Denmark had a very high proportion of women with stage IV tumours (43% *vs.* 23% or less elsewhere) and the lowest proportion in stage III (31% *vs.* 38% or more). The proportion with stage I tumours was similar in Canada, Denmark and Norway (20-23%) and higher in the UK (33%) (Table 1).

Imputing stage where it was missing did not substantially alter the distribution of stage in any country. The range of proportions of women diagnosed in stage III-IV changed from 61-74% to 64-75% (Table 1).

Net survival

Age-standardised one-year net survival was lowest for women in the UK (68.8%), intermediate in Denmark (72.5%) and highest in Canada (74.2%), Norway (74.3%) and Australia (74.9%). In each age group, overall net survival (all stages combined) was lowest in the UK (Table 2).

Insert Table 2

In all countries, one-year net survival was about 40% lower for women aged 70-99 years than for women aged 15-49 years, and for women diagnosed at stage IV than at stage I. The international differences in survival by age were larger for women with more advanced disease or missing stage (Table 2).

Among women with early disease (stage I; 'localised'), women in Denmark and Australia had lower age-standardised survival (94-95%) than elsewhere (over 97%). Survival for women with stage I cancers in Denmark was lower than for women with stage II disease. Among women with 'regional' cancers, survival was 85.6% in Australia compared to 93-96% elsewhere.

Among women with stage III-IV or 'distant' cancer, women in the UK had the lowest net survival at one year. Survival from 'distant' disease ranged from 61.4% in the UK to 65.8-66.6% in Australia, Denmark and Norway, and 74.4% in Canada.

Excess mortality

The excess hazard was highest one month after diagnosis and became relatively constant after the sixth month. International variation in the excess hazard was greatest for women with early-stage disease (Figure 2).

For stage I disease, women in Denmark had the highest excess mortality up to 18 months after diagnosis. Women with 'localised' or 'regional' disease in Australia had consistently high excess mortality up to 18 months. Women in the UK with stage II-III or 'distant' disease had relatively high excess mortality at all time points between 1 and 18 months (Figure 2).

Insert Figure 2

Impact of missing data on net survival

When we imputed stage for women with missing data and included them in the survival analyses, stage-specific survival was lower in all countries. This effect was largest in Canada at all stages, and for UK women with stage IV (or 'distant') disease. In Canada, stage-specific

survival was up to 11% lower when imputed data were included, and the apparent survival advantage for most stage categories diminished or disappeared (Figure 3).

Insert Figure 3

Discussion

This is the first attempt to produce a rigorous international comparison of survival from ovarian cancer by stage at diagnosis using routinely-collected data from population-based cancer registries. The design is important, both because of the size of the dataset, and because it includes all women in a given region or country, regardless of their age, social status, co-morbidity or prognosis, not just the small and highly selected sub-sets of patients usually recruited into clinical trials. Such studies are invaluable for international cancer surveillance, but quality assurance is particularly important [9].

Age-standardised one-year net survival from ovarian cancer was 68.8% in the UK, and from 72.5% to 74.9% in the other four countries. The international range in survival (6.1%) is narrower than in a previous analysis (10.2%) [1], because seven of the eighteen registries were excluded for incomplete stage data, and there were differences in methodology and period of incidence. One-year survival was lower in the UK, despite a relatively favourable stage distribution. International differences in survival were evident within each stage category: the differences were larger for older women and those with tumours of advanced stage or unrecorded stage.

For most cancers, earlier stage is associated with earlier diagnosis, and low stage-specific survival may indicate sub-optimal treatment. Epithelial ovarian cancer represents over 90% of ovarian cancers, and there are two distinct sub-types rather than a stepwise progression

from one stage to the next. ‘Type I’ tumours are typically mucinous, clear-cell, low-grade serous or endometrioid carcinomas that present relatively early (stage I-II; ‘localised’ or ‘regional’). ‘Type II’ tumours are usually more aggressive and diagnosed at advanced stage with high-grade serous, carcinosarcomatous or undifferentiated morphology [10].

International differences in the distribution of stage at diagnosis may therefore reflect differences in both tumour biology and timing of diagnosis in addition to completeness, consistency and quality of staging. Differences in stage-specific survival may arise because of these factors, but also from differences in treatment. We consider these potential explanations below, together with their policy implications.

Countries where survival is low could have a higher prevalence of the more aggressive ‘type II’ tumours. The proportion of patients with stage III-IV or ‘distant’ tumours varied from 60.0% in Australia to 63.9% in the UK, 65.8% in Canada, 69.8% in Norway and 74.5% in Denmark. The proportion of serous tumours, most of which (90%) would have been high-grade [11], was also highest in Denmark and Norway supporting an apparently higher proportion of ‘type II’ tumours. Specific morphology codes were available for 66-79% of women and were imputed where missing or non-specific (analysis not shown).

Given the different clinical behaviour of type I and type II ovarian cancers, international differences in stage distribution may not all be attributable to differences in time to diagnosis [12;13]. There may be some diagnostic delay among women with type II cancers in the UK and Denmark, where the proportion with advanced disease was 26.1% and 43.6%, respectively, compared to 18-20% in Canada and Norway. Overall, however, the stage distribution in the UK is relatively favourable, and it is unlikely that delayed diagnosis explains lower survival in that country.

The proportion of tumours with missing stage data varied from 3.8% (Norway) to 31.7% (UK), although analyses were restricted to registries where at least 50% of tumours were staged. We used imputation to deal with any potential bias from missing stage data. Even without data on treatment and co-morbidity, imputation remains the most robust method of dealing with missing data [7]. We do not consider that the international differences in stage distribution or stage-specific survival arise because of differences in the completeness of stage data.

We prioritised stage data in the same way for each patient and each country with a single protocol and a pre-defined algorithm to obtain a final stage variable. However, we had no control over the availability of the raw data or the quality of the original staging procedures.

It was not possible to obtain FIGO and TNM stage data on ovarian cancer from all countries. This necessitated mapping the FIGO system to the SEER SS2000 system. Mapping was relatively straightforward: we estimated potential misclassification of just 0.2% of node-positive tumours with no extra-pelvic extension and for which individual T, N and M data were unavailable (Walters *et al*, *in review*). Such minor misclassification is unlikely to explain why women in Australia had the highest overall net survival (75.2%) but those with 'regional' disease had lower survival than elsewhere (85.6% *vs.* 93.0%-95.5%). This difference was reduced when women with imputed stage were included, suggesting that the low survival for 'regional' disease in Australia was partly driven by low survival among the large number of elderly women with a known stage.

The quality of staging may contribute to international differences in both stage distribution and stage-specific survival. For example, sub-optimal staging in which nodal involvement and extra-pelvic metastases are missed, meaning that stage III disease would be coded as

297 stage I [14;15], could explain the surprising finding that survival among elderly women in
298 Denmark with stage I cancer was lower than for stage II. The low proportion of stage III
299 cancers in Denmark (30.8% *vs.* 37.8%-49.6% elsewhere) and the high proportion of stage IV
300 (43.6% *vs.* 17.9%-26.1%) could also arise because some stage III tumours were misclassified
301 as stage IV: this is suggested by rather high survival in both stage categories compared to
302 other countries. Misclassification could arise if women were categorised as stage IV in
303 Denmark solely on the presence of pleural effusion, whereas other jurisdictions also required
304 malignant cytology of pleural fluid.

305 Evaluating the impact of staging investigations on stage distributions and stage-specific
306 survival would require data on the determinants of stage [16], for example full staging
307 laparotomy or cross-sectional imaging, and whether extent of disease was confirmed by
308 histology or cytology.

309 All five countries have long-established, complete and reliable cancer registration.
310 Nonetheless, there may be differences in the extent to which primary peritoneal cancers
311 (ICD-10 C48) are mistakenly recorded as ovarian cancer (C56), given the similarities with
312 the presentation of ovarian cancer. The extent to which cancers registered as primary ovarian
313 cancer may in fact be metastatic (e.g. from colorectal cancer) may also vary, and a higher
314 proportion of such cancers, which have poor prognosis, may be expected in countries such as
315 the UK with high recorded incidence of ovarian cancer and a higher proportion of non-
316 specific morphology (33% *vs.* less than 26% elsewhere).

317 Population-based international comparisons of stage and stage-specific survival for ovarian
318 cancer thus remain difficult. Resolving the difficulties will require a new global consensus on
319 staging (Walters *et al, in review*). Nonetheless, this dataset of 20,000 women with ovarian

cancer broadens our understanding of international differences in survival. Stage-specific survival and the relationships between stage and age, and stage and morphology (data not shown) are consistent with clinical expectation. The stage distributions also largely reflect previously published figures [17-20], despite differences in categorisation.

This study raises several policy issues. Women in the UK had the lowest overall survival despite a relatively favourable stage distribution. Survival for women diagnosed at an early stage (I-II; 'localised' or 'regional') was average, but for women with advanced disease (stage III-IV; 'distant') survival was significantly lower than in other countries. The UK should consider whether the treatment of women with stage III-IV cancer conforms to that in the other four countries. The proportion of patients with missing data on stage was higher in the UK than elsewhere. It should be investigated whether this is because fewer women are in fact staged, or because transmission of stage data to the cancer registries is less complete than elsewhere.

Women in Australia, Norway and Canada had very similar levels of overall survival. Survival in Canada with known stage was relatively high for women with stages I, III and IV, but when imputed stage data were included, this apparent advantage disappeared. One-quarter of women in Canada were missing data on stage, and these women were generally older, with lower survival. This was in contrast with Australia, where older women were almost as likely to be staged as younger women. Canada should investigate whether staging of elderly women with ovarian cancer needs to be improved. Norway had relatively complete staging and high age-standardised survival for women with early-stage disease. This survival advantage was not apparent for women with more advanced disease, however, and the management of these patients should perhaps be reviewed.

Denmark had the least favourable stage distribution and the second lowest overall survival. This could arise because of differences in tumour biology or because of delayed diagnosis for type I or type II disease.

Conclusion

One-year net survival is significantly lower in the UK than in Australia, Canada, Norway and Denmark. Lower overall survival in the UK arises because of particularly low survival among women with advanced disease: the management of these women should be investigated. In Denmark, the more advanced stage distribution may arise because of a higher prevalence of aggressive type II cancers, or because of delays in diagnosis.

Population-based survival comparisons are powerful because they include all patients, and are up-to-date and affordable. To facilitate such research, global agreement is needed on the classification system for stage at diagnosis. International protocols should be issued or updated to standardise both clinical practice on staging and the routine transmission of these data to population-based cancer registries. Information on the determinants of stage should be captured, to facilitate quality assurance and robust international comparisons of stage and stage-specific survival.

Conflict of interest statement

M.A Richards is the National Cancer Director (England, funded by the Department of Health). All remaining authors have no conflict of interest.

Reference List

[1] 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;377:127-38.

[2] Sobin LH, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. 7 ed. Oxford: Union for International Cancer Control (UICC), Wiley-Blackwell; 2009.

[3] Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA. SEER Summary Staging Manual - 2000: Codes and Coding Instructions. Bethesda: National Cancer Institute; 2001.

[4] Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. The Stata Journal 2009;9(2):265-90.

[5] Pohar-Perme M, Stare J, Estève J. On estimation in relative survival. Biometrics 2012;68(1):113-20.

[6] Royston P. Multiple Imputation of Missing Values: Update of ice. The Stata Journal 2005;5:527-36.

[7] Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. Int J Epidemiol 2010;39:118-28.

[8] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30(4):377-99.

[9] Erridge SC, Moller H, Price A, Brewster D. International comparisons of survival from lung cancer: pitfalls and warnings. Nat Clin Pract Oncol 2007;4(10):570-7.

[10] Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. American Journal of Surgical Pathology 2010;34(3):433-43.

[11] Schmeler KM, Gershenson DM. Low-grade serous ovarian cancer: a unique disease. Curr Oncol Rep 2008;10(6):519-23.

[12] Lataifeh I, Marsden DE, Robertson G, Gebski V, Hacker NF. Presenting symptoms of epithelial ovarian cancer. Aust N Z J Obstet Gynaecol 2005;45(3):211-4.

[13] Nagle CM, Francis JE, Nelson AE, Zorbas H, Luxford K, de FA, et al. Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2011;29(16):2253-8.

[14] Zanetta G, Rota S, Chiari S, Bonazzi C, Bratina G, Torri V, et al. The accuracy of staging: An important prognostic determinator in stage I ovarian carcinoma. Annals of Oncology 1998;9(10):1097-101.

[15] Marx C, Bendixen A, Hogdall C, Ottosen C, Kehlet H, Ottesen B. Organisation and quality of primary surgical intervention for ovarian cancer in Denmark. Acta Obstetricia et Gynecologica Scandinavica 2007;86(12):1496-502.

[16] Sant M, Allemani C, Capocaccia R, Hakulinen T, Aareleid T, Coebergh JWW, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer 2003;106:416-22.

[17] Engel J, Eckel R, Schubert-Fritschle G, Kerr J, Kuhn W, Diebold J, et al. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. European Journal of Cancer 2002;38(18):2435-45.

[18] Kosary CL. Chapter 16, Cancer of the ovary. In: Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, editors. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program; 2007. p. 133-44.

[19] Australian Institute of Health and Welfare and National Breast and Ovarian Cancer Centre. Ovarian cancer in Australia, and overview 2010. Canberra: AIHW: Cat. no. CAN 48; 2010 Feb.

[20] Hannibal CG, Cortes R, Engholm G, Kjaer SK. Survival of ovarian cancer patients in Denmark: excess mortality risk analysis of five-year relative survival in the period 1978-2002. Acta Obstet Gynecol Scand 2008;87(12):1353-60.

Table and figure legends

Table 1. Number and mean age of ovarian cancer patients diagnosed during 2004-2007, country and stage at diagnosis (FIGO and SEER Summary Stage 2000), before and after imputation

Legend:

[1] Australia: New South Wales

[2] Canada: Alberta, British Columbia and Manitoba

[3] United Kingdom: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

[4] Number of patients before imputation

Figure 1. Proportions of ovarian cancer patients with missing data on stage and observed cumulative stage distribution by age at diagnosis and country, FIGO and SEER Summary Stage 2000

Notes:

Australia: New South Wales; Canada: Alberta, British Columbia and Manitoba; UK: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

Table 2. One-year net survival (%) overall, age-standardised and age-specific, by stage at diagnosis and country for ovarian cancer patients diagnosed during 2004-2007

Legend:

[1] Australia: New South Wales

[2] Canada: Alberta, British Columbia and Manitoba

[3] United Kingdom: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

[4] The all-ages estimates vary slightly between the FIGO and SEER SS2000 analyses because Australian patients are included in net survival models in the SEER SS2000 analyses

Figure 2. Age-standardised excess hazard (per 1,000 person-years, log scale) from ovarian cancer patients with known stage, by stage, country and time since diagnosis: FIGO stage and SEER Summary Stage 2000

Notes:

Australia: New South Wales; Canada: Alberta, British Columbia and Manitoba; UK: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

Figure 3. Age-standardised one year net survival from ovarian cancer by stage at diagnosis and country using known stage and imputed stage, FIGO and SEER Summary Stage 2000

Legend:

X survival estimate derived from women with known stage

I range of survival estimates derived for all women after imputation of stage where it was missing (see text)

Notes:

Australia: New South Wales; Canada: Alberta, British Columbia and Manitoba; UK: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

Webappendix

Study population and details of methodoloy

Supplementary table 1. Stage-specific sets of weights used for age standardisation of ovarian cancer estimates

Table 1. Number and mean age of ovarian cancer patients diagnosed during 2004-2007, country and stage at diagnosis (FIGO and SEER Summary Stage 2000), before and after imputation

	FIGO stage			%		SEER Summary Stage 2000			%	
Country	Stage	Number[4]	Mean age	Observed	After imputation	Stage	Number[4]	Mean age	Observed	After imputation
New South Wales (Australia[1])						All patients	1,714	63.8		
						Missing stage	166	65.4	9.7	
						Localised	358	56.5	23.1	23.3
						Regional	257	62.5	16.6	16.7
						Distant	933	66.8	60.3	60.0
Canadian provinces[2]	All patients	2,311	63.9			All patients	2,311	63.9		
	Missing stage	584	71.6	25.3		Missing stage	584	71.6	25.3	
	I	392	55.0	22.7	22.1	Localised	245	53.2	14.2	14.1
	II	224	60.0	13.0	12.2	Regional	379	59.1	21.9	20.1
	III	829	62.8	48.0	47.8	Distant	1,103	63.9	63.9	65.8
	IV	282	67.1	16.3	17.9					
Denmark	All patients	2,296	65.2			All patients	2,296	65.2		
	Missing stage	524	67.6	22.8		Missing stage	524	67.6	22.8	
	I	359	60.8	20.3	20.0	Localised	219	61.2	12.4	12.2
	II	99	61.7	5.6	5.6	Regional	251	61.1	14.2	13.8
	III	554	63.6	31.3	30.8	Distant	1,302	65.7	73.5	74.0
	IV	760	67.2	42.9	43.6					

Norway	**All patients**	1,843	65.2			**All patients**	1,843	65.2		
	Missing stage	171	76.5	9.3		**Missing stage**	70	78.7	3.8	
	I	391	58.7	23.4	22.1	**Localised**	217	58.7	12.2	12.1
	II	140	63.8	8.4	8.1	**Regional**	326	61.9	18.4	18.2
	III	829	65.4	49.6	49.6	**Distant**	1,230	66.5	69.4	69.8
	IV	312	67.5	18.7	20.2					
UK registries[3]	**All patients**	11,909	64.7			**All patients**	11,909	64.7		
	Missing stage	3,781	67.8	31.7		**Missing stage**	3,781	67.8	31.7	
	I	2,681	57.1	33.0	30.5	**Localised**	1,886	56.1	23.2	21.5
	II	478	63.2	5.9	5.6	**Regional**	1,275	60.9	15.7	14.4
	III	3,127	65.5	38.5	37.8	**Distant**	4,967	66.7	61.1	64.1
	IV	1,842	68.7	22.7	26.1					

[1] Australia: New South Wales

[2] Canada: Alberta, British Columbia and Manitoba

[3] United Kingdom: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

[4] Number of patients before imputation

Table 2. One-year net survival (%) overall, age-standardised and age-specific, by stage at diagnosis and country for ovarian cancer patients diagnosed during 2004-2007

		New South Wales (Australia[1])			Canadian provinces[2]			Denmark			Norway			UK registries[3]		
		NS (%)	95% CI		NS (%)	95% CI		NS (%)	95% CI		NS (%)	95% CI		NS (%)	95% CI	
FIGO stage																
All patients	All ages				**74.7**	73.3	76.1	**72.6**	71.1	74.2	**73.9**	72.3	75.6	**68.6**	67.9	69.3
	Age-standardised				**74.1**	73.4	74.8	**72.4**	71.6	73.1	**74.3**	73.5	75.1	**68.7**	68.3	69.1
	15-49				**93.9**	93.4	94.5	**93.1**	92.5	93.7	**93.9**	93.3	94.5	**92.8**	92.3	93.2
	50-69				**83.2**	82.1	84.4	**80.9**	79.6	82.2	**83.2**	81.9	84.5	**78.0**	77.3	78.7
	70-99				**55.0**	52.7	57.4	**54.6**	52.2	56.9	**56.0**	53.4	58.6	**48.3**	47.1	49.5
Stage I	All ages				**97.7**	96.2	99.1	**93.3**	91.0	95.7	**98.5**	97.2	99.7	**97.3**	96.6	97.9
	Age-standardised				**97.3**	96.3	98.3	**94.7**	93.6	95.8	**98.5**	97.9	99.2	**97.2**	96.9	97.6
	15-49				**99.3**	98.7	100.0	**99.4**	98.9	100.0	**99.0**	98.0	100.0	**98.9**	98.4	99.3
	50-69				**98.1**	97.0	99.3	**97.0**	95.4	98.7	**98.5**	97.4	99.7	**97.4**	96.8	98.0
	70-99				**93.1**	86.9	99.3	**81.0**	73.7	88.4	**97.8**	95.0	100.0	**94.6**	92.9	96.4
Stage II	All ages				**92.3**	89.0	95.6	**96.0**	92.0	100.0	**93.2**	89.1	97.3	**89.7**	87.0	92.4
	Age-standardised				**91.7**	89.9	93.5	**95.9**	94.0	97.8	**93.6**	91.8	95.5	**89.9**	88.5	91.3
	15-49				**96.5**	94.6	98.4	**98.4**	96.7	100.0	**97.4**	95.5	99.3	**95.9**	94.0	97.8
	50-69				**93.4**	90.4	96.3	**96.6**	93.2	100.0	**95.0**	91.9	98.2	**91.5**	89.1	93.9
	70-99				**86.3**	79.9	92.7	**93.1**	86.2	100.0	**88.9**	82.0	95.7	**83.7**	78.8	88.6
Stage III	All ages				**83.5**	81.3	85.6	**81.0**	78.2	83.8	**76.2**	74.0	78.5	**69.8**	68.3	71.3
	Age-standardised				**82.3**	80.6	83.9	**79.9**	77.7	82.1	**77.5**	75.9	79.1	**70.3**	69.2	71.4
	15-49				**90.0**	86.7	93.2	**88.4**	83.5	93.4	**90.9**	87.3	94.4	**84.1**	81.1	87.0
	50-69				**87.0**	84.8	89.2	**85.7**	82.9	88.5	**87.4**	85.2	89.6	**76.4**	74.6	78.2
	70-99				**74.0**	69.7	78.3	**68.8**	62.8	74.9	**55.8**	51.3	60.2	**57.1**	54.5	59.6

Stage IV	All ages				**57.0**	51.9	62.1	**59.8**	56.6	63.0	**55.0**	50.2	59.8	**51.7**	49.6	53.8
	Age-standardised				**57.0**	53.4	60.7	**57.9**	55.6	60.2	**54.5**	51.2	57.8	**52.6**	51.1	54.1
	15-49				**62.0**	50.1	73.9	**82.5**	75.2	89.9	**72.7**	61.9	83.5	**71.5**	65.9	77.1
	50-69				**68.0**	61.8	74.3	**72.4**	68.5	76.2	**72.5**	66.5	78.4	**66.3**	63.6	69.1
	70-99				**45.4**	38.0	52.7	**40.5**	35.7	45.2	**35.8**	29.2	42.4	**35.7**	32.8	38.6
Missing stage	All ages				**46.5**	43.2	49.7	**62.7**	59.0	66.5	**29.3**	22.7	35.8	**52.6**	51.3	53.9
	Age-standardised				**51.3**	48.9	53.7	**60.7**	57.9	63.5	**38.1**	31.9	44.4	**51.0**	50.0	52.0
	15-49				**84.9**	78.3	91.4	**91.6**	86.7	96.5	**73.2**	40.5	100.0	**88.2**	86.0	90.4
	50-69				**68.2**	62.8	73.6	**73.4**	68.4	78.3	**47.6**	32.2	63.1	**67.9**	65.9	70.0
	70-99				**28.9**	24.6	33.1	**46.5**	40.8	52.3	**22.5**	15.5	29.4	**31.2**	29.3	33.1
SEER Summary Stage 2000																
All patients[4]	All ages	**75.2**	73.6	76.8	**74.8**	73.4	76.2	**72.7**	71.2	74.2	**73.9**	72.3	75.6	**68.7**	68.0	69.4
	Age-standardised	**74.9**	73.9	75.9	**74.2**	73.3	75.0	**72.5**	71.6	73.4	**74.3**	73.4	75.3	**68.8**	68.4	69.2
	15-49	**95.8**	94.9	96.7	**94.2**	93.3	95.2	**93.2**	92.0	94.4	**94.9**	93.8	95.9	**92.6**	92.1	93.2
	50-69	**85.3**	83.8	86.8	**83.6**	82.2	84.9	**81.0**	79.5	82.5	**84.2**	82.6	85.8	**77.9**	77.1	78.7
	70-99	**54.4**	51.3	57.4	**54.7**	51.9	57.4	**54.6**	51.8	57.5	**54.5**	51.5	57.6	**48.7**	47.4	49.9
Localised	All ages	**94.0**	92.0	96.0	**98.1**	96.4	99.9	**91.5**	88.2	94.9	**97.3**	94.6	99.9	**98.0**	97.3	98.7
	Age-standardised	**94.2**	93.0	95.5	**97.7**	96.5	98.9	**94.2**	92.8	95.6	**97.8**	96.5	99.1	**98.0**	97.6	98.3
	15-49	**99.8**	99.6	100.0	**99.4**	98.6	100.0	**99.3**	98.6	100.0	**99.8**	99.3	100.0	**99.0**	98.5	99.5
	50-69	**98.0**	96.8	99.3	**98.3**	96.7	99.9	**96.4**	94.1	98.7	**98.8**	97.3	100.0	**98.0**	97.3	98.7
	70-99	**78.2**	70.7	85.7	**94.3**	87.1	100.0	**76.8**	67.0	86.6	**92.1**	82.7	100.0	**96.3**	94.4	98.1
Regional	All ages	**84.3**	80.5	88.1	**94.0**	91.9	96.2	**95.6**	93.2	98.1	**94.6**	92.3	97.0	**93.0**	91.7	94.4
	Age-standardised	**85.6**	83.7	87.4	**93.5**	92.4	94.7	**95.5**	94.2	96.7	**95.0**	94.0	96.1	**93.0**	92.3	93.7
	15-49	**96.2**	94.6	97.8	**98.4**	97.6	99.2	**98.9**	98.1	99.6	**98.8**	98.2	99.5	**98.4**	97.8	99.0
	50-69	**90.0**	87.0	92.9	**95.6**	94.0	97.3	**96.8**	95.0	98.7	**96.6**	95.0	98.2	**94.9**	93.8	96.1
	70-99	**69.8**	62.4	77.2	**86.2**	81.1	91.3	**90.6**	85.3	96.0	**89.0**	84.2	93.8	**85.7**	82.7	88.8

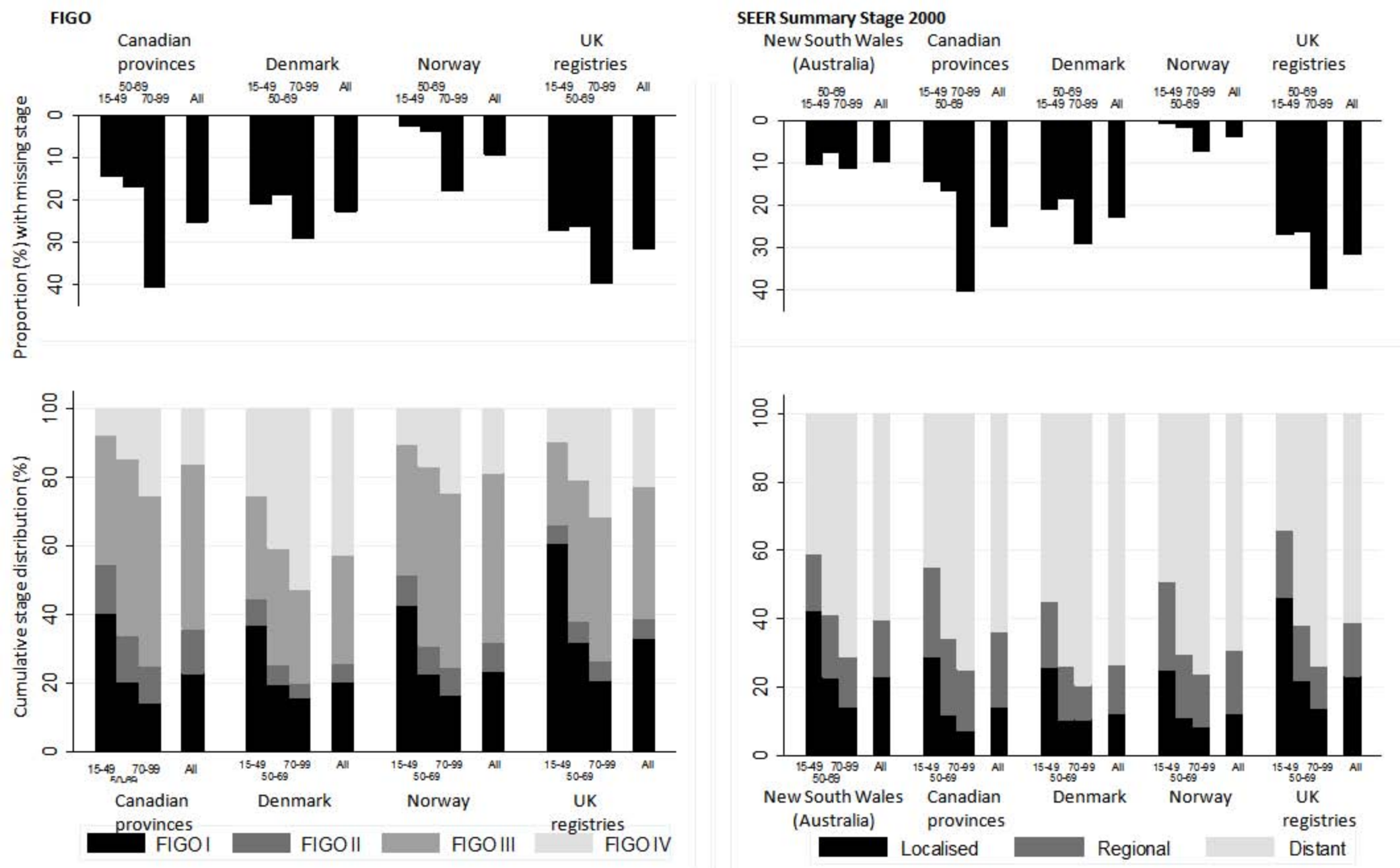
Distant	All ages	**65.0**	62.6	67.5	**76.3**	74.2	78.5	**66.8**	64.6	68.9	**65.6**	63.5	67.7	**60.9**	59.7	62.1
	Age-standardised	**66.6**	65.2	68.1	**74.4**	73.1	75.8	**65.8**	64.4	67.2	**66.1**	64.8	67.4	**61.4**	60.7	62.1
	15-49	**92.1**	90.2	94.0	**90.3**	88.2	92.3	**90.4**	88.4	92.4	**92.6**	91.0	94.2	**86.2**	84.8	87.6
	50-69	**77.5**	75.0	80.1	**80.8**	78.8	82.9	**75.2**	73.0	77.4	**78.6**	76.4	80.8	**69.8**	68.5	71.1
	70-99	**45.7**	41.8	49.7	**63.9**	59.8	67.9	**48.4**	44.6	52.2	**44.1**	40.5	47.7	**45.0**	43.2	46.8
Missing stage	All ages	**66.2**	60.1	72.2	**48.4**	45.2	51.7	**62.7**	59.0	66.4	**28.6**	20.0	37.2	**52.7**	51.3	54.0
	Age-standardised	**64.5**	61.2	67.8	**53.6**	51.9	55.3	**60.9**	59.0	62.9	**36.9**	32.8	41.0	**51.3**	50.4	52.3
	15-49	**93.2**	91.0	95.4	**88.9**	86.7	91.1	**90.2**	88.2	92.1	**82.1**	76.6	87.5	**87.9**	85.8	89.9
	50-69	**79.6**	74.8	84.4	**69.9**	66.7	73.1	**75.9**	72.7	79.0	**64.1**	55.3	73.0	**67.8**	65.9	69.7
	70-99	**44.2**	35.2	53.3	**30.5**	26.6	34.5	**44.6**	39.6	49.6	**18.3**	9.5	27.0	**31.4**	29.6	33.3

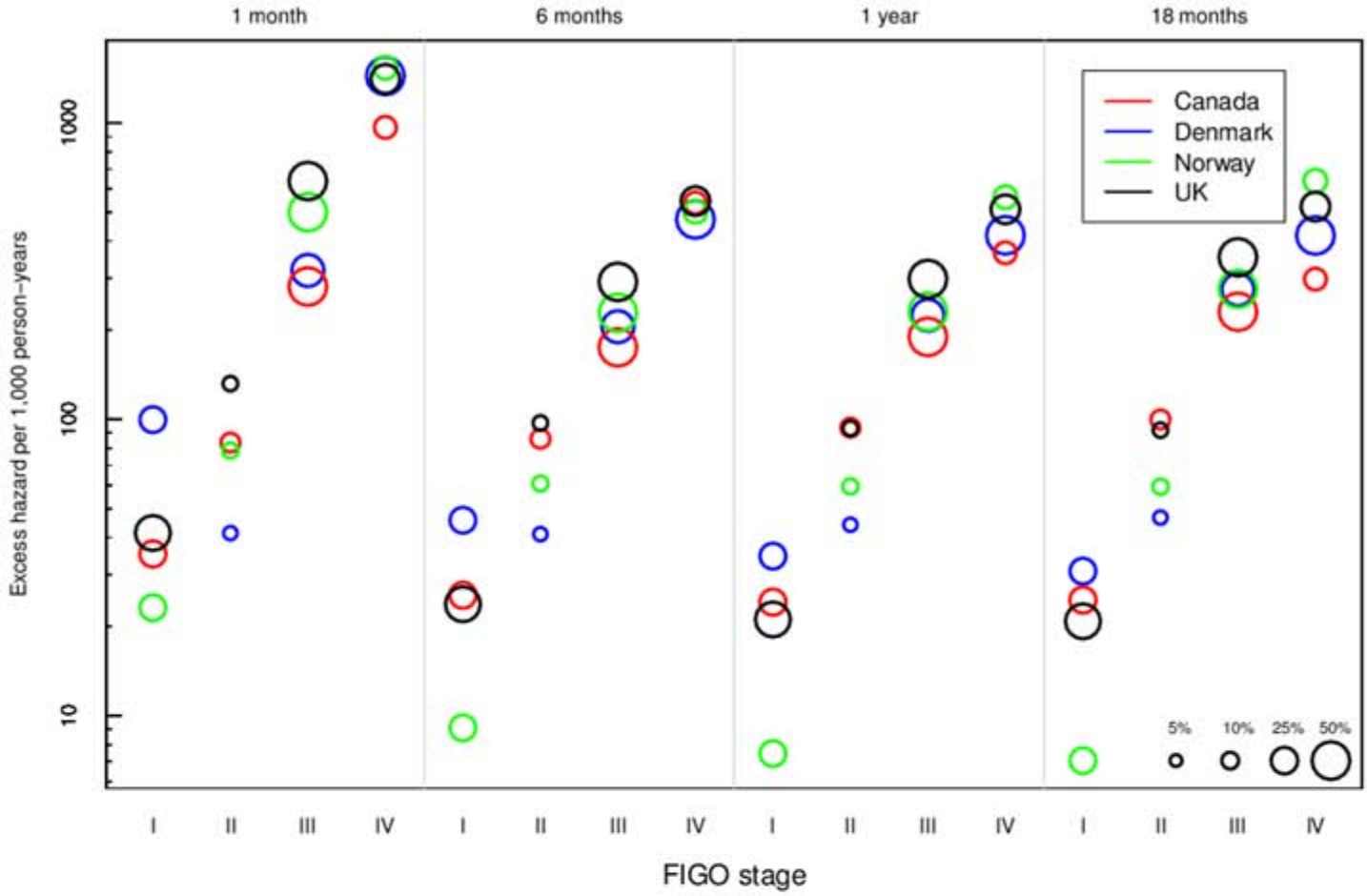
[1] Australia: New South Wales

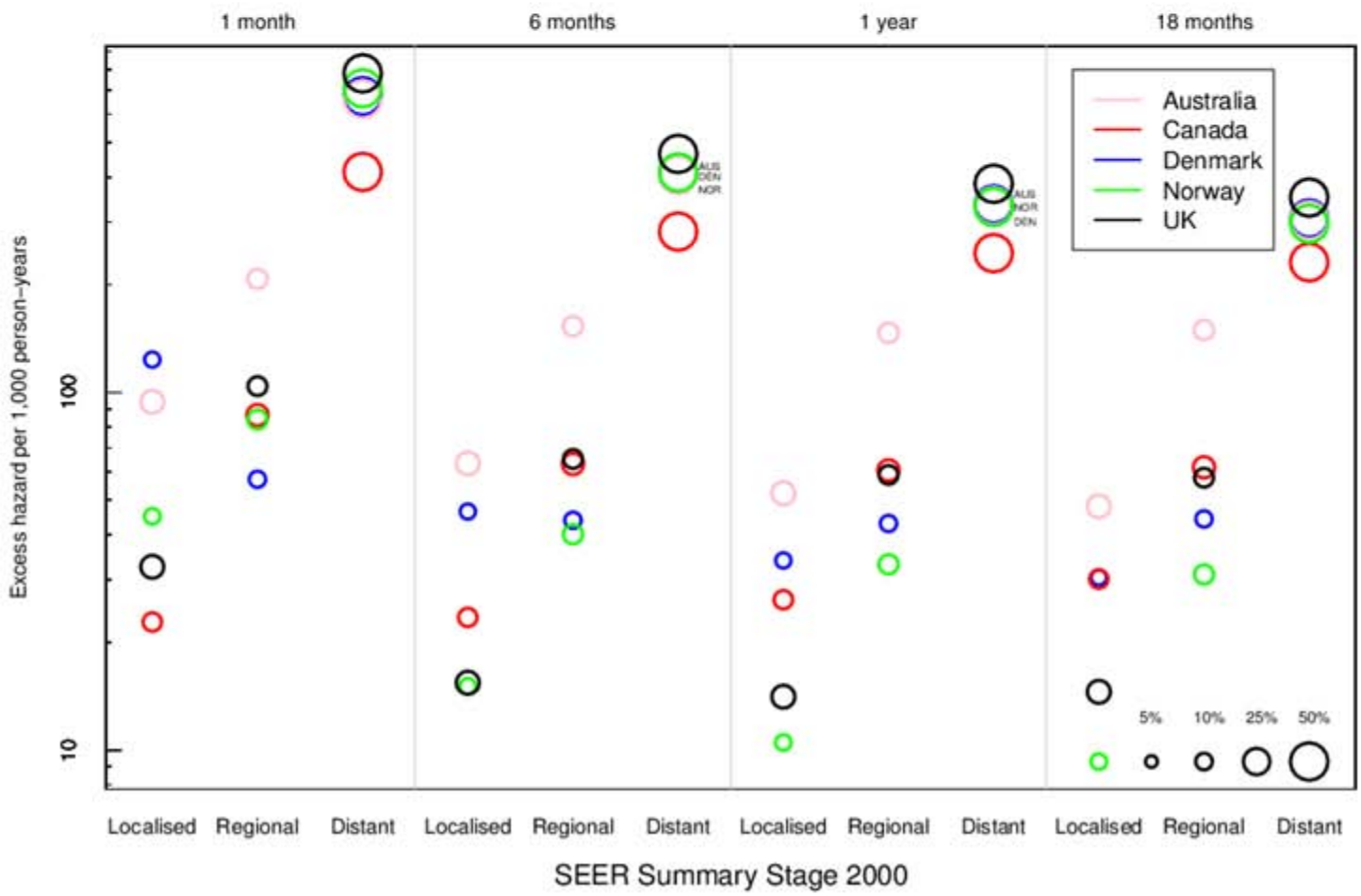
[2] Canada: Alberta, British Columbia and Manitoba

[3] United Kingdom: Northern and Yorkshire Cancer Registry and Information Service (NYCRIS), Eastern Cancer Registration and Information Centre (ECRIC), South West Cancer Intelligence Service (SWCIS) and West Midlands Cancer Intelligence Unit (WMCIU) in England; Northern Ireland

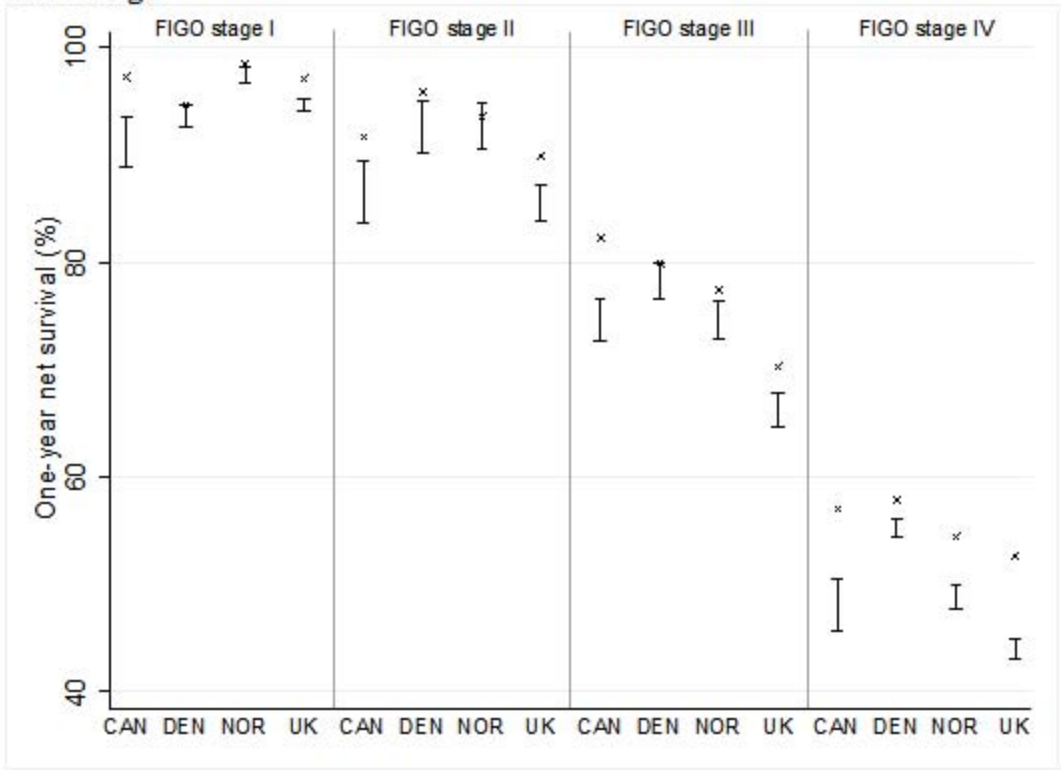
[4] The all-ages estimates vary slightly between the FIGO and SEER SS2000 analyses because Australian patients are included in net survival models in the SEER SS2000 analyses


FIGO
SEER Summary Stage 2000
Canadian provinces
Denmark
Norway
UK registries
New South Wales (Australia)
50-69
15-49 70-99 All
Proportion (%) with missing stage
0 10 20 30 40
Cumulative stage distribution (%)
0 20 40 60 80 100
FIGO I
FIGO II
FIGO III
FIGO IV
Localised
Regional
Distant


1 month
6 months
1 year
18 months
Canada
Denmark
Norway
UK
Excess hazard per 1,000 person−years
1000
100
10
5%
10%
25%
50%
I
II
III
IV
FIGO stage


1 month
6 months
1 year
18 months
Australia
Canada
Denmark
Norway
UK
Excess hazard per 1,000 person−years
100
10
5%
10%
25%
50%
Localised
Regional
Distant
SEER Summary Stage 2000

FIGO stage



SEER Summary Stage 2000