What explains global variation in population-based survival from malignant melanoma of the skin?

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Thesis submitted in accordance with the requirements for the degree of
Doctor of Philosophy of the
University of London

July 2024

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No *ad hoc* funding received
This research is part of the CONCORD programme for the global surveillance of cancer survival, on which I have been working since 2015

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Declaration

I, Veronica Di Carlo, 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.

This is a research paper style thesis. Two papers have been published and one paper is to be submitted for publication soon. I am the lead author of all three papers. As the lead author, I conducted the literature review, planned and produced the analysis and drafted the manuscripts. The co-authors provided feedback and contributed to the interpretation of results and the final drafts of the papers.

Name:

London, 27 November 2023

A Mimi e Cocò, che sempre saranno.

Acknowledgement

I would like to thank my supervisors, Prof Claudia Allemani and Prof Michel Coleman for always being by my side. What you thought me during these past few years goes way beyond science. I will always be grateful for the time we spent together.

Thank you to the late Professor Jacques Estève, for being part of my advisory panel. It was my honour. I will always remember our last chat on a warm July evening.

A special thanks to my colleagues in the Cancer Survival Group, Missy, Pamela, Naomi, and Fatima: you are family.

I would like to thank Francesco, for always believing in me and supporting me physically and morally during the ups and downs of these past few years. Thank you, mummy and daddy, Manu, Rosaria and Calliope; without you I would not be who I am.

My last and special thanks to Eva and Olivia; life with you is magic. You made me a better person.

Abbreviations

AJCC: American Joint Committee on Cancer

BRAF: B-Raf Proto-Oncogene, Serine/Threonine Kinase

CTLA-4: Cytotoxic T-lymphocyte Associated Protein 4

EMA: European Medical Agency

Erβ: Oestrogen Receptor β

FDA : Food and Drug Administration

ICDO: International Classification of Disease for Oncology

ICSS: International Cancer Survival Standard

IL2: Cytokine Interleukin-2

KIT: Receptor tyrosine kinase

NICE: National Institute for Health and Care Evaluation

SEER: Surveillance, Epidemiology, and End Results

TNM: Tumour Node Metastasis

UICC: Union for International Cancer Control

Abstract

This thesis provides a comprehensive examination of the reasons for world-wide differences in survival from cutaneous melanoma. It comprises five chapters, of which three are research papers.

Population-based cancer survival estimates are key to assess the overall effectiveness of a health system in managing cancer. The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3) included data for more than 37.5 million cancer patients diagnosed during 2000-2014 with one of 18 cancers, including melanoma. It highlighted substantial world-wide disparities in survival for most solid tumours. Age-standardised five-year net survival for adults (15-99 years) diagnosed with melanoma of the skin during 2010-2014 was 90% or higher in the USA, Australia, New Zealand and most Nordic countries, but 60% or lower in Ecuador, China, Korea, Singapore and Taiwan. This PhD thesis examines the impact of some of the main established prognostic factors on survival disparities world-wide, as well as some of the more controversial prognostic factors.

Following an introduction to the background, aims and methods of the research in Chapter 1, the second chapter (*Research paper 1*) is focused on stage at diagnosis and trends in one-year net survival for patients diagnosed with distant-stage disease in the US during 2001-2013. *Research paper 1* is the largest population-based study to date to show an improvement in one-year survival for distant-stage melanoma in the US, particularly among younger patients, from 2010. This improvement is likely to be a consequence of the introduction of immune-checkpoint-inhibitors and other targeted treatments for metastatic and unresectable disease. Persistent survival inequalities between Blacks and Whites were also shown, suggesting differential access to treatment.

Chapter 3 (*Research Paper 2*) is focused on the most controversial prognostic factor for melanoma: morphology. This chapter provides, for the first time, world-wide comparisons of population-based survival after five years since diagnosis for the main morphological subtypes of melanoma, for over 1.5 million adults diagnosed during 2000–2014. Chapter 3 highlights the less favourable distribution of morphological subtypes in Asia and Central and South America, and the poorer prognosis for nodular and acral lentiginous melanomas. The results from the multivariable analysis on data provided by four registries with complete information on stage and treatment shows that later stage at diagnosis does not fully explain the higher excess risk of death for nodular and acral lentiginous melanoma than for superficial spreading melanoma. I hope that Chapter 3 may serve as the basis to persuade clinicians, dermatologists, pathologists and other experts of the importance of morphology as a relevant

prognostic factor for melanoma of the skin, and that national and international clinical guidelines may in due course be updated to include morphology as a core item in the pathology report.

In Chapter 4 (*Research Paper 3*) I have aimed to explain the reasons for the generally higher survival in women than in men with cutaneous melanoma. These differences were particularly pronounced in Brazil, Bulgaria, Ecuador, Lithuania, Poland, Romania, Russia and Türkiye. Men with melanoma were generally older than women. Men were also more frequently diagnosed with melanomas with a poor prognosis, especially melanomas located on the scalp and neck, or with metastatic disease. These reasons may help to explain the survival disadvantage for men with melanoma.

To our knowledge, this is the largest international study of population-based survival trends from cutaneous melanoma. Its world-wide coverage, the robust and rigorous methodology deployed for centralised data collection, data quality assessment and statistical analysis analyses, and the relevance of the research findings on the role of each prognostic factor, will provide a baseline against which countries can monitor the progress of their efforts to improve the control of melanoma, and will set a benchmark for future global comparisons.

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2. **Di Carlo V,** Coleman MP, Allemani C, on behalf of the US CONCORD Working Group. *Survival trends from melanoma of the skin in the USA, by sex and stage at diagnosis: Results for 578, 430 adult patients diagnosed during 2001-2014 (CONCORD-3),* North American Association of Central Cancer Registries / International Association of Cancer Registry combined annual conference, **Vancouver BC, Canada,** 9-13 June 2019, p40.
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4. **Di Carlo V**, Coleman MP, Allemani C, on behalf of the CONCORD Working Group. *Variation in morphology and survival from malignant melanoma of the skin in the GRELL countries. XLIV*[e] réunion du GRoupe pour l'Enregistrement du cancer dans les pays de Langue Latine (GRELL), **Lisbon, Portugal,** 29-31 May 2019.

Media coverage

1. [**Di Carlo V** cited in] Jesitus J. Morphology drives melanoma risk: specifying histologic subtypes can drive better outcomes for patients and improve research. Dermatology Times, 8 May 2022. https://www.dermatologytimes.com/view/morphology-drives-melanoma-risk

1. Background, aims and methods overview

1.1 Melanoma of the skin: epidemiology and incidence

Malignant melanoma develops from the melanocytes, neural crest-derived cells responsible for the production of melanin. Melanin is a vital pigment that gives colour to skin, hair and eye and which protects them from the sun's ultraviolet (UV) rays. Melanocytes are located in the deepest layer of the epidermis, but also in mucosal surfaces and the uveal tract. Malignant melanoma can arise in any of those areas. The following thesis will focus only on cutaneous melanoma.

Cutaneous malignant melanoma is the most common type of melanoma, but the rarest malignancy of the skin. Basal cell and squamous cell carcinoma, also known as non-melanoma skin tumours, are the most common types of cancers of the skin. Those malignancies originate from keratinocytes, which are responsible for the production of keratins, proteins that form the structural framework of epithelial cells and allow skin to resist damage. The incidence of non-melanoma skin cancer in fair-skinned populations approaches the total incidence of all other cancers combined,[1] and 5-year survival approximates 100%.[2] However, international studies on population-based incidence and survival for keratinocytes tumours are scarce. Cancer registries rarely record non-melanoma skin cancers. The high frequency of keratinocytes tumours and the complexity of registering multiple tumours for each patient translates in a very high workload that the cancer registries, often with limited resources or understaffed, can not support.[3]

Ultraviolet radiation (UV) is the main risk factor for cutaneous melanoma. The UV spectrum is conventionally divided into three wavebands: UVA, UVB and UVC. UVA is longer wavelength (315-399 nanometres) accounting for more than 90% of solar radiation reaching the Earth and present all year round. It is not absorbed by the ozone layer and it can penetrate deeper layers of the skin. UVB is medium wavelength UV (280-314 nm): it is mostly absorbed by the ozone layer, however some waves do reach the Earth's surface. Its intensity increases during summer. UVC, the shortest wavelength UV (less than 290 nm), does not reach the Earth because it is completely filtered by the ozone layer. Both UVA and UVB are classified as Group 1 carcinogen with sufficient evidence for carcinogenesis in humans by the International Association for Research on Cancer.[4] People with fair skin, blonde or red hair and blue eyes, and who sunburn easily, are at particularly high risk.

Epidemiological studies[5-7] also showed that the total number of melanocytic naevi is a strong independent risk factor for cutaneous melanoma, particularly on the trunk and limbs.[8] The

presence of dysplastic or atypical nevi also increases the risk of melanoma,[9,10] and it is estimated that 29-49% of non-familial melanoma cases occur in the setting of a pre-existing dysplastic nevus.[11] People with multiple atypical mole (atypical mole syndrome) have 7 to 10-fold the risk of developing melanoma than the general population.[12] The risk is increased further if one or more first or second degree relatives have been diagnosed with malignant melanoma (familial atypical mole syndrome).[13]

Over the past 50 years, the incidence of cutaneous melanoma has been rising in most Caucasian populations.[14-21] In 2020, the age-standardised incidence rates reached their highest level for men and women in Australia (42.9 per 100,000 person-year) and Denmark (33.6), respectively.[22] In Oceania, North America and most European countries, cutaneous melanoma ranks among the 10 most common cancers.[23] By contrast, it is a rare disease in people of Asian or African origin, where incidence rates are as much as ten-fold lower, in the range 0.4-3.0 per 100,000 person-years.[22]

Although incidence is much lower than in fair skinned population, melanoma of the skin in Asians and in populations with predominately dark skin has distinct histopathologic features, with higher proportions of the more aggressive acral lentiginous and nodular subtypes.[24,25] The reasons for the disparity in incidence rates are still unclear, although part of the explanation may lie in genetically defined ethno-geographic variation in susceptibility to UV radiation.[26]

1.2 Prevention, diagnosis, stage and treatment

From the end of last century, traditional public health efforts in most countries in Europe, Oceania and North America have focused on prevention to reduce hazardous sun exposure and raising awareness on the importance of the recognition of the early symptoms of melanoma.[27-29]

The first campaign aimed at raising awareness on the importance of skin cancer prevention was launched by Cancer Council Victoria in 1981. The famous “Slip-Slop-Slap” campaign invited avoiding unhealthy sun exposure by slipping on a shirt, slopping on sunblock, and slapping on a sun hat.[30] The campaign soon achieved national coverage and contributed to a significant and sustained improvement in sun protection behaviour, particularly among younger people.[31] Soon after, the “Slip-Slop-Slap-Wrap” campaign was also launched used in New Zealand, with the last word being an encouragement to wear sunglasses to protect against UV radiation. Several other countries followed Australia’s and New Zealand’s

examples and started similar awareness and prevention campaigns, aimed at the general public or at specific groups at higher risk of developing skin cancer within the population.

In 2016, the “Cover-up Mate” campaign in England targeted all men subject to occupational sun exposure, such as agricultural and construction workers, gardeners and sports-players and encouraged them to wear sunscreen when working outdoor. In 2017, through a funny video in French, Greek, Italian, Spanish and Thai language the “Help a Dane” appeal went viral on social networks. It invited locals of these favourite Danish holiday destination to help protecting Danes in the sun and share their knowledge about prevention of sunburns.[32]

Together with prevention, public health effort has also largely focused on early detection of cutaneous lesions. The so-called “ABCDE” rule[33] identifies Asymmetry, Border irregularity, Colour variation, Diameter larger than 6 mm and Evolution of a mole or nevus as warning signs for melanoma and, more broadly, skin cancer. If experiencing any of those symptoms, a person is encouraged to seek medical advice. Because of the warning signs are clear and well-defined, most cutaneous melanomas are brought to doctors’ attention directly by the patients at an early stage of the disease.[34,35] During physical examination, the doctor should note the size, shape, colour and texture of any moles and whether they are bleeding, or crusting.

If the mole is suspicious, a skin biopsy is needed to establish diagnosis of a cutaneous melanoma. If the pathologist will confirm the diagnosis, prognostic factors such as tumour thickness, ulceration or mitotic rate will also be investigated to help determine the stage of disease. If the tumour size is greater than 1mm, or is ulcerated, a sentinel lymph node biopsy can be performed to check for spread to the sentinel lymph node, the lymph nodes most likely to receive lymphatic drainage from the primary tumour.

Further, to improve the outcome, treatment based on accurate staging is fundamental. The American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) defined the Tumour Node Metastasis (TNM) classification system for melanoma in its 7th edition[36] as follows:

Table 1 - Summary of the classification of malignant melanoma of the skin in TNM (8th edition)

T	Thickness of infiltration [mm]	Ulceration
T1	≤1 mm	T1a: no ulceration, T1b: ulceration
T2	>1 to 2 mm	T2a: no ulceration, T2b: ulceration
T3	>2 to 4 mm	T3a: no ulceration, T3b: ulceration
T4	>4 mm	T4a: no ulceration, T4b: ulceration
N	**No. metastatic nodes**	
N1	1	N1a: clinically occult*, N1b: clinically detected, N1c: in transit, satellite without regional nodal metastasis
N2	2-3	N2a: clinically occult*, N2b: clinically detected, N2c: in transit, satellite without regional nodal metastasis
N3	≥4	
M	**Metastasis**	
M0	No distant metastasis	
M1	Distant metastasis	M1a: skin, soft tissue including muscle, and/or non-regional lymph node M1b: lung with or without M1a sites of disease M1c: non-CNS† visceral sites with or without M1a or M1b sites of disease M1d: CNS† with or without M1a, M1b or M1c sites of disease

*Clinically occult (i.e., detected by sentinel lymph node biopsy); †Central nervous system

Table 2 – American Joint Committee on Cancer (AJCC) clinical stage (8th edition)

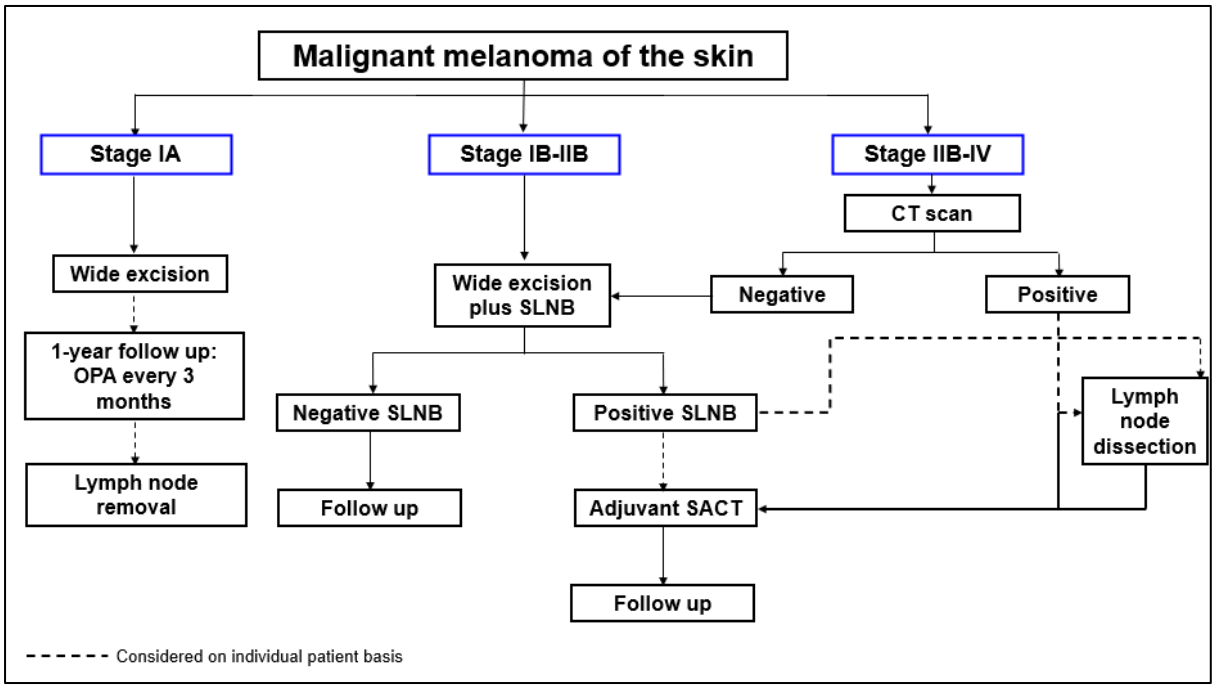
Clinical stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0
III	T1-4	N1-3	M0
IV	T1-4	N0-3	M1

Tis: melanoma in situ

The 8th edition of TNM classification was subsequently published in 2018,[37] after the data collection for this study was completed.

Various treatments are available depending on the stage of the tumour. In Figure 1, the main treatment strategies as recommended by the National Institute for Health and Care Evaluation are reported.[38]

Figure 1 – Current treatment options for malignant melanoma of the skin based on stage at diagnosis



SACT: Systemic anti-cancer therapy

Wide local excision is the primary treatment for the vast majority of melanomas, with recommended excision margins varying depending on the location and tumour thickness. For *in situ* melanoma, margins of at least 0.5 cm are recommended. For invasive melanomas, the margin width should be 1 cm for tumours with a Breslow thickness up to 1.0 mm, and 2 cm for tumours with Breslow thickness equal or higher than 1.0 mm.[39] If the nearby lymph nodes are abnormally hard or sentinel lymph node biopsy confirms the presence of tumour cells, then a lymph node dissection is usually advised. Adjuvant systemic anti-cancer therapy is then performed, if a sentinel lymph nodes involvement is confirmed. A therapeutic lymph node dissection is offered to people with palpable stage IIIB to IIID melanoma, or cytologically or histologically confirmed nodal disease detected by imaging.

The treatment of metastatic or unresectable melanoma has mainly had a palliative intent until a few years ago, when only two drugs, the chemotherapeutic agent dacarbazine and the cytokine interleukin-2 (IL2) were used to treat advanced disease. In the last 10 years, however, significant improvements in treatment have been reported, involving the use of targeted treatments and immunotherapy.

Immunotherapy uses the patient's immune system to fight the cancer. The surface of T cells (immune cells) host checkpoint proteins, such as CTLA-4 and PD-1, responsible for keeping the immune system in check. When those proteins link to other proteins on the cancer cells, B7 and PDL-1 respectively, they stop the T cell from fighting the cancer. Immune checkpoint inhibitor therapies, CTLA-4 and PD-1 inhibitors, block the CTLA-4 and PD-1 and allow T cells to kill the cancer cells.

Ipilimumab, approved by the Food and Drug Administration (FDA) in the United States and by the European Medicine Agency (EMA) in 2011, is a type of CTLA-4 inhibitor. A phase III randomised clinical trial[40] on patients treated with ipilimumab showed a 1-year overall survival as high as 45.6% compared with less than 30.0% for those treated with the standard therapy alone. The PD-1 inhibitors pembrolizumab and nivolumab, approved in the USA in 2014 and the following year in Europe, showed larger survival improvements in phase III clinical trials (1-year observed survival higher than 70.0%).[41,42]

Currently, in the UK, pembrolizumab is recommended as an option for the adjuvant treatment of completely resected stage IIB, IIC or stage III melanoma with lymph node involvement in adults. Until recently, standard care for people with completely resected melanoma was routine surveillance. Clinical evidence shows that adjuvant pembrolizumab increases how long people live without the cancer coming back compared with placebo.[42] Nivolumab is

recommended as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease.[41]

Innovations in the treatment of metastatic melanoma also involve targeted therapy, which commonly interferes with the function of molecular targets that are involved in the progression and spread of cancer. Genetic mutations in the BRAF, NRAS, KIT and MEK genes are frequent in people diagnosed with melanoma. Approximately half of the patients present with a mutation in the BRAF gene,[43] and the BRAF V600E mutation is the most common.

Vemurafenib was proved to increase short-term survival for patients with metastatic disease and the BRAF V600E mutation. The phase III randomised clinical trial comparing vemurafenib with dacarbazine in 675 patients diagnosed with metastatic cutaneous melanoma estimated an overall 6-month survival of 84% [78-89%] in the vemurafenib group compared to 64% [56-73%] in the dacarbenize.[44] Following this evidence, FDA and EMA approved the drug in 2011 and 2012 respectively. Other targeted treatments as dabrafenib (FDA, EMA 2013), trametinib (FDA 2013, EMA 2014) and cobimetinib (FDA, EMA 2015) showed similar or much higher improvement in overall survival compared to old lines of treatment.

In the UK, dabrafenib with trametinib is recommended as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults. There are currently no adjuvant treatments available for stage III BRAF V600 mutation-positive melanoma and there is a substantial risk of the cancer returning and becoming incurable. Dabrafenib with trametinib is a new adjuvant treatment aimed at curing the cancer by reducing the likelihood that it will spread. It is therefore an important development in managing stage III melanoma. Clinical trial evidence shows that dabrafenib with trametinib extends the length of time people have before their melanoma recurs compared with routine surveillance. Evidence from the trial and from clinical experts strongly suggests that it also increases the overall length of time people live by reducing how many people develop metastatic disease. [45]

1.3 The prognostic role of morphology

Cutaneous melanomas can be grouped in four main morphological subtypes following the ICD-O-3[46] morphology classification, characterised by specific clinical features: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma.[47]

Superficial spreading melanoma (ICD-O-3 morphology code 8743) is the most common morphological subtype in fairer-skinned population and is associated with intermittent sun

exposure in younger ages.[48,49] It tends to grow in size[50] and it is most frequent on the back and shoulders in men and on the legs in women. It is generally associated with a very good prognosis.[51]

Nodular melanoma (8721) is the second most common subtype among fairer-skinned population. It is most likely to penetrate into the deeper layers of the skin if not removed and is more common on the back, head and neck.[50-53] It is characterised by a much poorer prognosis than superficial spreading melanoma.[54]

Lentigo maligna melanoma (8742) tends to develop in older adults, mostly on the face, which is chronically exposed to the sun.[55] It is characterised by slower progression and is rarely lethal.[51,56]

Acral lentiginous melanoma (8744) is very rare in fairer-skinned populations, but much more common in Asians and Blacks. It is not associated with sun exposure, because it usually develops on sun-protected areas of the body, such as the palms, the sole of the foot and underneath the nails.[57] The aetiology for acral lentiginous melanoma is not yet totally understood. A history of trauma or higher mechanical stress have been frequently proposed as a trigger for acral lentiginous melanoma, since tumours develop on weight-bearing areas of the body or sites that are highly susceptible to mechanical injury.[58-60] It has a poor prognosis, and its diagnosis is often delayed. Due to the rarity of the disease, there is a lack of epidemiological studies on survival and it is not clear whether, after controlling for stage, the prognosis for acral lentiginous melanoma would be different from that of other subtypes.

Despite the aforementioned differences in behaviour and progression, the prognostic role of morphology in melanoma survival is controversial. National and international clinical guidelines indicate stage at diagnosis as the most relevant prognostic factor. The prevalent idea is that melanomas of different morphological subtypes converge in their biologic behaviour once they metastasise.[61] Recommended treatment options do not differ between morphological subtypes of disease at the same stage of diagnosis, and clinical guidelines indicate morphology as an optional item to be included in pathology reports.

1.4 Aim and objectives

My research project, embedded in the CONCORD programme for the global surveillance of cancer survival, aims to produce the first detailed analysis on world-wide international differences in survival from cutaneous melanoma.

The CONCORD programme started in 2000, and its first cycle analysed survival for about 2 million patients diagnosed during 1990-94 with breast, colon, rectal or prostate cancer, and followed up to 1999.[62] Data were contributed by 101 cancer registries in 31 countries world-wide. In 2015, the second cycle of the CONCORD programme (CONCORD-2) established the global surveillance of cancer survival trends by analysing data on 25.7 million patients diagnosed with one of 10 most common cancers during 1995-2009, and followed up to 31 December 2009.Data were contributed by 279 cancer registries in 67 countries world-wide.[63] In 2018, the third cycle of the programme (CONCORD-3) updated survival trends to 2014.[64] CONCORD-3 obtained anonymised, individual tumour records for over 37 million patients diagnosed with one of 18 most common cancers, including melanoma, during 2000-2014 and followed-up to 31 December 2014. Data were provided by 322 population-based cancer registries in 71 countries world-wide.

CONCORD-3 highlighted a high and stable trends in age-standardised 5-year net survival for most solid tumours in North America, Oceania and several European countries. Survival for most solid tumours in adults increased also in Eastern Europe over the 15 years to 2014, but it remained lower than in the rest of Europe.

CONCORD-3 also showed persistent inequalities in survival from cutaneous melanoma at global level, with lower age-standardised 5-year net survival in countries in Asia, especially in South-East Asia, and in Latin America, than in North America, Oceania and Europe.

The current project aims to explore the reasons for the persistent gap in survival from melanoma of the skin between world regions. Specific objectives of the project are:

1. **Objective 1 – Research Paper 1**: to examine trends in population-based short-term survival for metastatic (“distant”) melanoma, before and after the introduction of novel therapies to treat metastatic and unresectable disease.
2. **Objective 2 – Research Paper 2**: to evaluate the impact that morphological distribution and survival by morphological subtypes have on the international differences in prognosis when all melanomas are combined.
3. **Objective 3 – Research Paper 2:** to evaluate whether the different distributions of the main prognostic factors, i.e., sex, age and stage at diagnosis, may contribute to explain the survival differences between morphological subtypes.
4. **Objective 4 – Research Paper 3**: factors that contribute explaining the higher survival for women in all countries.

5. **Objective 5 – Research Paper 3**: to estimate survival for melanomas arising in specific anatomic locations known to have poor prognosis at the clinical level, i.e., melanomas located on the scalp and neck or melanomas of the genital tract in women.

1.5 Data and methods

I performed a secondary analysis of anonymised data collected for patients diagnosed with cutaneous melanoma during 2000-2014 as part of the third cycle of the CONCORD programme (CONCORD-3).

Overall, 284 cancer registries in 59 countries submitted data on 2,303,095 anonymised individual records for adults diagnosed with melanoma, defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision (ICD-O-3).[46] Data were collected using the same data specification, and were centrally validated for adherence to the protocol and consistency through a rigorous 3-phase data quality control procedure.

CONCORD-3 restricted survival analysis to malignant melanoma (ICD-O-3 behaviour code 3) arising in the skin (ICD-O-3 topography codes C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9), and scrotum (C63.2). Overall, 716,554 records (31%) for tumours that were benign, in situ, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or on patients with age outside the range 15-99 years, or with incomplete data were considered ineligible for analysis.

A further 8,069 records (0.3%) registered only from a death certificate or discovered at autopsy were excluded from analysis because their duration of survival was unknown, as well as records for which the vital status or sex was unknown and those with an invalid date or sequence of dates. Overall, 1,578,482 patients diagnosed with a primary, invasive, malignant cutaneous melanoma during 2000-2014 were included in survival analysis.

For each cancer registry, the proportion of histologically verified tumours, the proportion of melanomas with an unspecified histology (malignant melanoma, NOS ICD-O-3 morphology code 8720) and the proportion of patients lost to follow-up or censored within 5 years of diagnosis were calculated to evaluate and compare data quality between countries and world region.

Cancer registries use different techniques to assess the vital status of cancer patients. Passive follow-up requires records to be linked to regional or national vital statistics systems, using

key variables that varies by country, state or region, i.e., national insurance number, ID number, names and date of birth or a combination of them. Tumour records that match to a death record are updated with the date of death. Active follow-up is also widely adopted: registries routinely contact treating physicians, family doctors or hospitals to record the vital status for each cancer patient. Some registries determine the vital status by contact with the patient's family, by telephone or home visit, or with the village administration. The proportion of patients lost to follow-up is relevant to countries using active follow-up; alternatively, the proportion of patients censored alive before five years from diagnosis pertains to countries where passive follow-up techniques are in place.

The CONCORD-3 protocol requested data on core variables, such as demographics data (sex, full date of birth, region of residence and race/ethnicity where available), follow up for vital status (full date of death or date on which the patient was last known or believed to be alive) and tumour details (full date of diagnosis, topography and morphology). Complete and accurate dates (day, month, year) of birth, diagnosis and vital status are needed for comparison of cancer survival estimates.[65]

Cancer registries were also invited to provide data on the initial course of treatment as optional variables. Many population-based cancer registries do not routinely collect data on the treatments received by each cancer patient. Others only record the information on whether a specific treatment was given or not and the date it was given, without full details of each treatment for all patients. For this reason, all the treatment variables were collected as binary (yes/no) variables, together with the date of the treatment when it was offered to the patient. The treatment variables included the first cancer-directed surgery (excluding procedures performed for diagnostic purposes only), radiotherapy and systemic therapy, with no distinction between chemotherapy, immunotherapy or targeted treatment.

Net survival was estimated for patients diagnosed with cutaneous melanoma for each registry and country contributing data to CONCORD-3. Net survival is the probability that cancer patients survive their cancer up to a given time since diagnosis (e.g., 5 years), after controlling for competing causes of death (background mortality).

Net survival can be estimated in two general frameworks: cause-specific or relative survival. In the cause-specific survival framework, the exact cause of death is available for each cancer patient known to be dead by the end of the established follow-up. Only deaths that have been attributed to the cancer in analysis as the underlying cause of death are considered as events; patients whose death was attributed to other causes are censored at the time of their death. Therefore, net survival estimated in a cause-specific setting is highly dependent on the

accuracy of the death certification and the selection of the underlying cause of death. This makes comparisons between countries or regions within the same country, or over time very difficult, because geographical and temporal differences in selection and coding of the underlying cause of death are well known.[66-71]

Relative survival is thus preferred, particularly when we aim to compare survival between regions, countries or over time. Estimating cancer survival within a relative survival framework avoids the problems related to the inaccuracies in the cause of death because the information is not required in the estimation.

Cancer patients can die because of their cancer or because of other causes. The aim of relative survival is to isolate the excess hazard of death due to the specific cancer in analysis.

The observed hazard for a cancer patient can be described as follow:

$$h_o(t) = h_P(t) + h_E(t)$$

where $h_o(t)$ is the observed (all-cause) hazard, when the event of interest is death from any cause; $h_P(t)$ is the hazard due to other causes and $h_E(t)$ is the excess hazard due to cancer. The cancer hazard can be therefore estimated as the difference between the observed hazard and the population hazard:

$$h_E(t) = h_O(t) - h_P(t)$$

$h_P(t)$ is the mortality for a comparable group of individuals from the general population, with the same characteristics as the patients with respect to the main factors impacting survival, such as sex, age, race/ethnicity and socio-economic status, and assumed to be practically free of the cancer of interest. The population mortality is obtained from the life tables of background mortality (described below).

The net survival function can be estimated from the hazard function as:

$$S_E(t) = \exp\left(-\int_0^t h_E(u)du\right)$$

In the relative survival framework, net survival is defined as survival for cancer patients in the hypothetical situation where the disease under study would be the only possible cause of death.

Net survival can be estimated with parametric, semi-parametric and non-parametric methods. In my research project, I used non-parametric methods and, for a subset of analyses, I used semi-parametric methods.

The cumulative net probability of survival up to time *t* is defined as:

$$S_C(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{S_{o_i}(t)}{S_{p_i}(t)} = exp[-H_c(t)]$$

where $S_{Oi}(t)$ is the observed survival of the individual cancer patient (events are all deaths), $S_{Pi}(t)$ is the expected (population) survival and $H_c(t)$ is the cumulative cancer hazard at time t. Non-parametric methods make no assumptions on the distribution of the cancer hazard.

In all three research papers, I estimated net survival with the non-parametric Pohar Perme estimator.[72] This is the only unbiased estimator of net survival because it takes into account that informative censoring is more frequent in older patients. It estimates net survival for each individual, after each event or censoring, by giving individual weights equal to the inverse probability of survival up to a given time *t* in the general population. In this way, older patients, who are progressively more under-represented among survivors as follow-up progresses, will receive more weight because their corresponding survival probability in the general population is lower.

In parametric and semi-parametric methods, the cancer hazard for a single patient *i* can be expressed as:

$$h_c(t|X_i) = h_0(t) \times exp(X_i\beta)$$

where X is a set of covariables for the individual *i,* for example age, sex, socio-economic status etc; $h_0(t)$ is the baseline hazard function and describes how the hazard rate changes over the follow-up time; $X_i\beta$ is a linear predictor, function of X_i covariables. In parametric and semi-parametric, a functional form of the baseline hazard $h_0(t)$ is assumed.

For a few sub-analyses in *Research Papers 1* and *2*, I estimated net survival using semi-parametric methods. These methods are preferred to the non-parametric when the interest is focused on estimating the impact that a given covariables has on the cancer hazard. In a model, it is also possible to control for potential confounders, include time-varying effect and potential interactions.

I fitted a flexible parametric survival model on the log hazard scale to estimate the effect of relevant covariables on the hazard of death for cutaneous melanoma in *Research Papers 1*

and *2*. In *Research Paper 1*, I estimated the excess hazard of death for blacks compared to whites diagnosed with distant-stage melanoma in the United States after controlling for sex and age at diagnosis. In *Research Paper 2*, I estimated the excess hazard of death for each morphologic subtypes, after controlling for major confounders, i.e., sex, age and stage at diagnosis in countries where data on stage and morphology were complete (Norway, Spain and Germany). Modelling, unlike non-parametric methods, allows to control for potential confounders when estimating the excess hazard of death for a given exposure. Caution needs to be used when using models, because they are based on assumptions on the parametric or semi-parametric distribution of the baseline hazard and other prognostic factors; a same hazard model can not be deployed for different countries in analysis. This is the main reason why, for international comparison involving hundreds of registries world-wide, non-parametric methods are preferred.

Data on mortality in the general population among which cancer patients reside is key to estimate net survival. Expected survival and the related population mortality are extracted from the population life tables. A complete life table is a set of all-cause mortality rates by single year of age, sex and calendar year for a given region, country or territory. It represents the force of mortality in the general population, when all the causes of death are considered. Mortality rates by race/ethnicity, urban/rural residence or socio-economic status can be also estimated, providing that data on death counts and populations are available by sub-group. The use of accurate life tables is crucial because they represent the background mortality of the population under study, among which the cancer patients reside.

I constructed all the life tables by single year of age, sex and calendar year used in CONCORD-3, using the raw data provided by each cancer registry. I used three different approaches, based on the type of mortality data available from each registry. When death and population counts by single year of age or age group were available, I adopted a flexible multivariable Poisson modelling approach using a restrictive cubic spline function on age[73] to derive sex- and age-specific mortality rates. This approach allowed to model mortality rates by race/ethnicity when this information was available on the death counts and population. Registries could also submit unsmoothed mortality rates for their registry, i.e., simple ratio between death counts and population by sex, single year of age (or age group) and year (or calendar period). To derive smoothed mortality rates for the given population, I used the Ewbank relational method.[74] Where no data were available from the registry or a national statistical office, I used the abridged UN Population Division life tables and interpolated these using the Elandt-Johnson method.[75] I produced statistical reports for each life table, plotting the life expectancies at birth and the probabilities of death at given age intervals for the first

and last year of available data. The reports also included graphics of the raw and smoothed mortality curves on both logarithmic and arithmetic scales, together with the plots of the deviance residuals at each age to evaluate the performance of the flexible Poisson model, when this method was used. Cancer registries in Israel, Malaysia, New Zealand, Singapore and the United States provided raw data by race/ethnicity, therefore mortality rates were further stratified by race/ethnicity. All life tables are freely accessible on the Cancer Survival Group website;[76] they are a relevant tool for any cancer registry aiming at producing net survival estimates.

All survival estimates were age-standardised to allow for fair and robust comparisons between countries and over time. The age distribution of cancer patients varies between countries and over time, and cancer survival varies with age. Therefore, valid international comparison of survival estimates for all ages combined requires age-standardisation to take into account for these differences. The age-standardised estimate is a weighted average of the age-specific estimates. The International Cancer Survival Standard (ICSS) weights have been widely adopted for international comparisons.[77] Age is grouped in five categories: 15-44, 45-54, 55-64, 65-74 and 75-99 years. The weights are attributed to each age-group within three clusters of cancers defined by their pattern of age-incidence: increasing incidence by age (cluster 1, most cancers); broadly stable incidence by age (cluster 2), and decreasing incidence by age (cluster 3). The weights are shown in Table 2.

Table 1.2 – International Cancer Survival Standard weights

Age group (years)	ICSS 1	ICSS 2	ICSS 3
15-44	0.07	0.28	0.60
45-54	0.12	0.17	0.10
55-64	0.23	0.21	0.10
65-74	0.29	0.20	0.10
75-99	0.29	0.14	0.10

Melanoma of the skin belongs to the second cluster, because its incidence is rather constant with increasing age.

The cohort approach was used to estimate net survival for patients diagnosed during 2000-2004 and 2005-2009, while the period approach was adopted for those diagnosed during 2010-2014. To estimate five-year net survival, the cohort approach requires that all the patients included in the analysis had the potential to be followed up for at least 5 years. The period approach allows estimation of five-year survival when five years of follow-up are not available for all cancer patients. For example, if we need to estimate five-year net survival for patients diagnosed during 2010-2014 and follow-up is only available to 31 December 2014,

the period approach will combine the partial probabilities of survival up to five full years for those diagnosed in 2010 or later, and the conditional survival probabilities up to five years for those diagnosed between 2005 and 2009 who were still alive at 1 January 2010. The key assumption is that the conditional probabilities of survival observed during the previous years of follow-up would remain constant over the next few years, until all patients diagnosed during 2010-2014 have been followed up for a full five years, by the end of 2019. Such an assumption may not hold if survival has been improving over time. In this situation, “period estimates” are conservative, and will be slightly lower than the corresponding cohort estimates when complete follow-up is available for all patients. Nevertheless, empirical evidence shows that they are a good approximation to the cohort estimates.[78]

In *Research Paper 3* I used the complete approach to estimate 5-year net survival for patients diagnosed during 2009-2014 and followed up to the end of 2014. The complete approach is an extension of the traditional cohort approach, and it is used when not all cancer patients have a potential full follow up time. For example, in the cohort of patients diagnosed during 2009-2014, only the patients diagnosed in 2009 had full five years of follow-up by 31 December 2014. The use of the complete approach allows to estimate survival of patients diagnosed in the period of interest, i.e. 2009-2014, as for the cohort approach, even if not all the patients have full potential follow-up.

Preface to Chapter 2

Stage at diagnosis is the most important prognostic factor for survival from cutaneous melanoma. If detected at an early stage, melanoma can be surgically removed with margins that are clear of tumour, leading to a very high survival. Metastatic melanoma was a deadly disease until a decade ago. Up to 2011, the prognosis for metastatic melanoma was generally very poor, with survival as low as 16% at five years after diagnosis in the US.[79,80] The two therapies available until then, the chemotherapeutic agent dacarbazine and the cytokine interleukin-2 (IL2), were used with solely palliative intent.[81-83]

In recent years, significant improvements in treatment, involving the use of targeted therapies and immunotherapy, have led to unprecedented clinical benefit. The CTLA-4 inhibitor ipilimumab was the first immunotherapy approved for melanoma by the US Food and Drug Administration (FDA) and by the European Medicine Agency (EMA), in 2011, followed by the PD-1 inhibitors pembrolizumab and nivolumab in the US (2014) and in Europe (2015).

Randomised clinical trials of immunotherapies for metastatic and unresectable melanoma of the skin showed a dramatic improvement in short-term survival. A phase III randomised clinical trial[40] showed that one-year overall survival was as high as 46% for patients treated with ipilimumab compared to less than 30% for those treated with the standard therapy alone. Phase III clinical trials on patients treated with pembrolizumab and nivolumab showed even larger survival improvements (one-year observed survival higher than 70%).[41,42]

Innovations in the treatment of metastatic and unresectable melanoma also involved targeted therapies, most of which are designed to interfere with the function of molecular targets involved in the progression and spread of cancer. Genetic mutations in the BRAF, NRAS, KIT and MEK genes are frequent in people diagnosed with melanoma. Approximately half of all melanoma patients present with a mutation in the BRAF gene,[43] and the BRAF V600E mutation is the most common. Vemurafenib, the first targeted treatment for patients with metastatic melanoma who have a mutation in the BRAF V600E gene, was approved in 2011 in the US and in 2012 in Europe, after the evidence of a phase III randomised clinical trial showing a substantial improvement in six-month survival (84% *vs.* 64%) compared with patients treated with dacarbanize.[44] Other targeted treatments, such as dabrafenib (FDA, EMA 2013), trametinib (FDA 2013, EMA 2014) and cobimetinib (FDA, EMA 2015) showed similar or much higher improvement in overall survival than previous lines of treatment.

Nine large randomized controlled trials of immune checkpoint inhibitor therapies and targeted therapies in the adjuvant setting have been completed and continue to mature. All have shown improvements for recurrence-free survival compared with placebo or an active control arm, but not consistently for distant metastases–free survival or overall survival.

Over a short period of time, the treatment landscape for melanoma in adjuvant setting has shifted dramatically. Now multiple treatment options are available, as a result of the latest trials with immunotherapy and molecular targeted therapy.[84,85] The approval or licencing of adjuvant therapies came after 2014, the latest year of incidence for which CONCORD-3 collected data and the latest year of follow up. However, it is important to report some of the key dates and approvals, that may serve as a reference for future studies. In 2015, the FDA approved ipilimumab as an adjuvant therapy for patients with stage III melanoma. In December 2021, pembrolizumab was approved for the adjuvant treatment of adult and paediatric patients (aged 12 years or older) with stage IIB or IIC melanoma following complete resection. In June 2022 the FDA granted accelerated approval to dabrafenib in combination with trametinib for the treatment of adult and paediatric patients (aged 6 years or older) with unresectable or metastatic solid tumours with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Last, in October 2023 nivolumab was approved for the adjuvant treatment of completely resected Stage IIB and IIC melanoma in patients aged 12 years and older.

Patients included in clinical trials are highly selected, generally young and with few or no comorbidities, so they do not represent the entire cohort of patients who could benefit from a new line of treatment.[86-89] Therefore, the promising results of a clinical trial require validation at a population level, when all patients can be included in the analyses, regardless of their age, socio-economic status, comorbidities, etc.

This chapter addresses the question of whether population-based short-term net survival from distant-stage cutaneous melanoma, at one year since diagnosis, improved in the US during 2001-2013, when new treatments for metastatic and unresectable disease were approved. The US registries were selected for this analysis because the availability and completeness of information on stage was excellent for all participating registries. Given the huge population and number of cases, it was also possible to estimate net survival for each calendar year of diagnosis during that period.

The results in this chapter show a dramatic improvement in one-year net survival from 2010, particularly for younger patients. The increasing trend starts one year before FDA approval of the new lines of treatment in 2011. This may be because some patients may have been

recruited to clinical trials, which started well before 2010. This may be particularly the case for younger patients, who experienced the larger improvement. Additionally, patients may have received the newer treatments through the FDA's expanded access programs, which provide access to investigational drugs, before their official approval, to patients with life-threatening conditions who cannot be enrolled in clinical trials.

Chapter 2 also documents persistent survival inequalities between Blacks and Whites, suggesting differential access, even to these new treatments. Black patients were more likely to be diagnosed with distant melanoma, but survival inequalities by race persisted even when stratifying the analyses by stage at diagnosis.[90,91]

Recent studies on survival from mucosal melanoma after the introduction of new lines of treatments showed conflicting results.[92-95] Mucosal melanoma is genetically distinct from cutaneous melanoma (Furney 2013) with higher incidences in KIT and NRAS mutations but a lower rate of BRAF V600 alterations.[96,97] In general, mucosal melanoma has a lower tumour mutational burden than cutaneous melanoma, and DNA mutations caused by chronic ultraviolet sun exposure are not its major disease mechanism.[98] Such distinctions at the molecular level may lead to different responses to immunotherapies and targeted treatments between these two melanoma subtypes. For these reasons, mucosal melanoma was not included in the following analysis, and will analysed separately.

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Student ID Number	1704667	**Title**	Mrs
First Name(s)	Veronica		
Surname/Family Name	Di Carlo		
Thesis Title	What explains global variation in population-based survival from malignant melanoma of the skin?		
Primary Supervisor	Prof Claudia Allemani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JNCI Cancer Spectrum		
When was the work published?	14 September 2020		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Veronica Di Carlo (VDC) was the lead author of the paper. VDC, Prof Claudia Allemani and Prof Michel Coleman designed the study. VDC carried out the literature review, produced the statistical analyses, tables and graphics and drafted the manuscript. All co-authors commented on the drafted manuscript. VDC integreted the comments to the manuscript. All co-authors reviewed and approved the final version of the manuscript.

SECTION E

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2. Trends in short-term survival among 18,601 patients diagnosed during 2001-2013 with distant-stage cutaneous melanoma in the United States (CONCORD-3) (Research paper 1)

2.1 Introduction

The incidence of cutaneous melanoma has been rising in most Caucasian populations over the past 50 years.[99] In the United States, the age-standardised incidence rate rose from 8 per 100,000 person-years in 1975 to 25 in 2016.[100] Cutaneous melanoma was the 4th and 5th most common cancer in men and women, respectively, in the US in 2016, with a total of 82,476 new cases.[101]

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3) highlighted increasing trends in age-standardised 5-year net survival from cutaneous melanoma in most countries during 2000-2014; 5-year net survival exceeded 90% for patients diagnosed during 2010-2014 in the United States, Australia, New Zealand and most Nordic and Western European countries, but was below 60% in Ecuador, China and Taiwan.[102] Stage at diagnosis is an important predictor of prognosis, and survival for disease diagnosed at an advanced stage is much lower than for localised disease. If detected at a localised stage (Tumour Node Metastasis Stage I-II and resectable Stage III), cutaneous melanoma can be surgically treated with a favourable outcome. Five-year relative survival for localised melanoma of the skin diagnosed in the last 20 years was higher than 90% in Germany,[103] Denmark,[20] Estonia,[21] Sweden,[104] and the United States.[105]

Until about 2010, when advanced disease (TNM stage III unresectable melanoma and stage IV disease) was mainly treated with chemotherapy (e.g. dacarbazine) and cytokines (e.g. interleukin-2), the prognosis for metastatic melanoma was generally poor, with survival as low as 16% at 5 years after diagnosis for patients diagnosed in the US.[105,106] In recent years, significant improvements in treatment, involving the use of targeted therapies and immunotherapy, have led to unprecedented clinical benefit. Ipilimumab, the first immunotherapy, and vemurafenib, the first targeted treatment for metastatic and unresectable melanoma, were approved by the US Food and Drug Administration (FDA) in 2011.

The aim of this study is to describe the characteristics of patients diagnosed with cutaneous melanoma during 2001-2013, using data provided by 34 US population-based

cancer registries included in CONCORD-3, and to assess trends in short-term (1-year) survival for distant-stage disease.

2.2 Materials and methods

CONCORD-3 obtained anonymised individual tumour records from 322 population-based cancer registries in 71 countries worldwide, for patients who had been diagnosed with one of 18 common cancers, including melanoma, during 2000-2014 and followed up to 31 December 2014. Data acquisition, ethical approval and data quality control for the CONCORD programme have been described elsewhere.[102] Cancer registries submitted records on all patients diagnosed with a melanoma, defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision [ICD-O-3].[46] We restricted survival analysis to malignant melanoma (ICD-O-3 behaviour code 3) arising in the skin (ICD-O-3 topography codes C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9), and scrotum (C63.2).

Records with incomplete data, or for tumours that were benign, *in situ*, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or on patients with age outside the range 15-99 years, were considered ineligible for analysis. We excluded tumours registered only from a death certificate or discovered at autopsy, since their duration of survival was unknown, as well as records for which the vital status or sex was unknown, and those with an invalid date or sequence of dates. If two or more invasive primary malignant melanomas were detected in the same person but with different dates of diagnosis, the record with the earliest date of diagnosis was retained. Registry data sets in which 15% or more of patients were lost to follow-up were excluded from the survival analyses.

Patients diagnosed in 2014 were included in CONCORD-3 but were not included in this study, because a full year of follow-up was not available by the study closure date (31 December 2014). To assess trends in survival for the same registries, we retained only registries that submitted data on patients diagnosed up to and including 2013, with follow-up to 31 December 2014.

The CONCORD protocol required information on stage of disease at the time of diagnosis for patients diagnosed from 2001 onward, because the completeness of data on stage in many countries and US states was known to be much lower before 2001.

Stage was categorised as localised, regional and distant, according to the SEER Summary Stage 2000 classification.[107] “Distant stage” includes melanoma with distant lymph

node involvement, metastatic skin lesions, further contiguous extension or metastasis to other organs. Age at diagnosis was grouped into 15-44, 45-54, 55-64, 65-74 and 75-99 years. Race was categorised as white, black and other race/ethnicities (Asian/Pacific Islander; American Indian/Alaska Native; other, unspecified or unknown race). Melanoma was categorised by anatomic location as arising in the skin of the head and neck (C44.0-C44.4), the trunk (C44.5), the limbs (C44.6-C44.7) or the genital organs (C51.0, C51.9, C60.9, C63.2), or as lesions overlapping the used categories, or of the skin with anatomic location not otherwise specified (C44.8-C44.9). Morphological sub-types were grouped according to the first revision of ICD-O-3,[46] as malignant melanoma, not otherwise specified (NOS, 8720), superficial spreading (8743), lentigo maligna (8742), nodular (8721), acral (8744) and all other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8743, 8745-8746, 8750, 8760-8761, 8770-8774, 8780, 8790).

We explored the distribution of stage at diagnosis by sex, age, race, topography and morphology. Survival analyses were restricted to patients diagnosed with distant-stage melanoma. One-year net survival for patients diagnosed in each of the 13 years 2001-2013 was estimated with the non-parametric Pohar Perme estimator,[108] using the STATA[109] command *stns*.[110] Net survival is the cumulative probability of surviving after a given time since diagnosis after correcting for background mortality. It deploys life tables of all-cause mortality rates in the general population to control for other causes of death. To account for differences in background mortality between states, geographical areas and racial groups, and over time, we used life tables of all-cause mortality in the general population by single year of age, sex, single calendar year, race (blacks, whites and others) and county within each state. These were provided by the National Cancer Institute.[111]

We estimated trends in one-year net survival for five age groups. We then obtained age-standardised estimates for all ages combined, using the second of the three sets of International Cancer Survival Standard weights (0.28, 0.17, 0.21, 0.20 and 0.14), designed for cancers with broadly constant incidence by age.[112] Survival was estimated for men and women, and for both sexes combined.

We fitted a flexible parametric survival model on the log-hazard scale, to estimate the effect of race on the hazard of death due to distant-stage melanoma; excess mortality and net survival by race were also estimated,[113] with race as a categorical variable. Restricted cubic splines for the effect of age at diagnosis (3 degrees of freedom) and year of diagnosis (4 degrees of freedom) were included with the command *rcsgen,*[114] including time-dependent effects.

2.3 Results

We examined individual records for 1,040,814 adults (15-99 years) diagnosed with a primary, malignant cutaneous melanoma in 41 state-wide cancer registries in the US. Data quality was generally high. The proportion of patients excluded for incomplete dates or for other reasons ranged from 0 to 4% (Table 1). Overall, 36% of patients were diagnosed with an *in situ* tumour.

Of the 632,861 patients eligible for inclusion in survival analyses, we excluded 3,045 (<1%) because the cancer was registered only from a death certificate or discovered at autopsy. Less than 3% of the remaining 629,816 patients were lost to follow-up or censored within 5 years from diagnosis, but this proportion was much lower among patients with distant-stage disease (<1%). The diagnosis was histologically confirmed in 99.3% of tumours (data not shown).

New Jersey was excluded because of the high proportion of patients lost to follow-up (48%). A further 118,239 patients were excluded from six state-wide registries (Arkansas, California, Massachusetts, Oklahoma, Tennessee and Washington), because data were not available for patients diagnosed up to and including 2013.

Finally, we explored the distribution of 425,915 patients by sex, age, race, topography, morphology and stage at diagnosis.

Most patients diagnosed during 2001-2013 were men (57%) and they were generally older than women (median age at diagnosis: 64 *vs*. 57 years old, respectively). Only 4% of patients were black (Table 2). Data on stage at diagnosis were available for 386,885 (91%) patients.

Seventy-seven percent of patients were diagnosed with localised disease. The proportion was stable over time (4-5%, data not shown), slightly higher in women (79% *vs*. 75%) and in younger patients (80% *vs*. 74% in patients aged 15-44 and 75-99 years, respectively). Four percent of melanomas were diagnosed at a distant stage, with a slightly higher proportion in men than women in all years (4% *vs.* 3% respectively, in 2001; 6% *vs.* 5% in 2013, data not shown). Fifteen percent of blacks were diagnosed with distant-stage disease, compared to only 4% in whites and 1% in the “other race” category. Patients with distant-stage melanoma were generally older (median age: 65 years) than those diagnosed with localised (61 years) or regional (62 years) disease (data not shown).

Melanomas arose mostly on the skin of the limbs (42%), the trunk (32%) and the head and neck (21%) and were diagnosed at a distant-stage in less than 3% of those cases (Table 2). Melanomas arising in overlapping or unspecified locations only accounted for 5% of all cases, but half of these (50%) were diagnosed at an advanced stage. The proportion of melanomas registered with an unspecified morphology was higher than 50%, followed by superficial spreading (30%) and nodular melanoma (7%). Distant-stage melanomas represented less than 1% of the superficial spreading and lentigo maligna morphologies, but up to 7% of those classified as malignant melanoma, NOS.

We restricted survival analysis to 18,601 patients diagnosed with distant-stage disease (Figure 1). In 2001, age-standardised 1-year net survival was 43% [95% confidence interval 39-46%] and remained stable until 2010 (Table 3). Survival improved rapidly from 2010 onwards, reaching 59% [57-61%] for patients diagnosed in 2013. Short-term survival improved for men and women from 2010, and was slightly but consistently higher in women (Table 3).

One-year net survival increased for all ages (Figure 2, Table 3). The youngest patients (15-44 years) experienced the largest absolute improvement, particularly from 2010, rising from 44% [36-53%] in 2001 to 68% [62-74%] in 2013. For patients aged 45-54 years, one-year survival increased from 46% [38-53%] in 2001 to 63% [58-68%] in 2013. We observed similar trends in patients aged 55-64 and 65-74 years, starting from 2011; both survival curves reached 56% in 2013. One-year survival for patients aged 75 years or more remained at 45% or lower throughout the period 2001-2013.

Age-standardised 1-year net survival increased for both whites and blacks with distant-stage melanoma (Figure 3). Short-term survival for whites rose from 42% [39-44] in 2001 to 56% [55-58] in 2013; it improved from 37% [32-43] to 51% [46-56] in blacks over the same period. The excess hazard of death due to melanoma within one year of diagnosis was 12% higher in blacks than whites (excess hazard ratio: 1.13 [1.00-1.27]; data not shown).

2.4 Discussion

This study includes data from 34 state-wide cancer registries covering 57% of the US population, and is the largest population-based analysis of trends in 1-year survival for distant-stage cutaneous melanoma. It shows a dramatic improvement in survival, particularly between 2010 and 2013.

The proportion of melanomas diagnosed at a distant stage remained stable over time (4-5%), and was slightly lower in women than men. Sex inequalities in stage at diagnosis are

well known;[115-117] they are commonly attributed to differences in health-seeking behaviour.[28] Traditionally, women tend to visit their health-care provider and perform skin checks more frequently than men; this can translate to a higher proportion of women diagnosed with localised disease.

Blacks were more likely to be diagnosed with distant-stage melanoma than whites. The perception that melanoma risk in African Americans is low is considered a major cause for delayed diagnosis.[118,119] Consistent with previous studies,[90,120-122] patients diagnosed at a distant stage were generally older.

One-year net survival improved noticeably for men and women, and in both blacks and whites. This improvement may reflect the recent introduction of new treatments for metastatic and unresectable disease.

The first immune checkpoint inhibitor approved by the FDA, in March 2011, ipilimumab,[123] showed a one-year overall survival for patients diagnosed with metastatic melanoma in a phase III randomized clinical trial as high as 46%, compared with less than 30% for patients treated with the standard therapy.[40]

Vemurafenib, the first licensed targeted treatment for patients with metastatic disease and the BRAF V600E mutation, was also shown to increase short-term survival. A phase III randomized clinical trial of 675 patients diagnosed with metastatic melanoma showed an overall 6-month survival of 84% [78-89%] in those treated with vemurafenib compared to 64% [56- 73%] in those treated with dacarbazine.[44] The FDA approved the drug on this evidence in August 2011.[124]

The current study has shown a substantial improvement in short-term survival for patients diagnosed with distant-stage melanoma of the skin, particularly for younger patients. Most of the improvement occurred from 2010, one year before the approval of the new lines of treatment. Some of these patients may have been recruited to clinical trials, which started well before 2010.[40,84,125,126] Additionally, they may have received the newer treatments through the FDA expanded access programs,[127] which provide access to investigational drugs, before their official approval, to patients with life-threatening conditions who cannot be enrolled in clinical trials.

Data on whether the patients were recruited to a clinical trial or received systemic therapy for compassionate use were not available to explore these hypotheses. However, a population-based study of the impact of targeted and immune-based therapies for metastatic

or unresectable melanoma in Ontario found that about 5% of patients were already being treated with the new therapies in 2007; this percentage increased to more than 82% in 2015.[128] The study confirmed the use of immunotherapy well before the approval of ipilimumab by Health Canada in 2012, and highlighted its widespread use in recent years. A similar study in the US showed that the use of immunotherapy in patients under 65 years improved rapidly after 2010, from 8-12% during 2004-2010 to 30% in 2014.[129]

Patients aged 75 years or more with distant-stage disease experienced considerably less improvement in short-term survival. This may be due to less frequent use of the newer therapies. A recent study designed to identify factors associated with the treatment of metastatic melanoma in the US[130] found that older patients were less likely to receive ipilimumab or to be tested for the BRAF mutation. This may have resulted from concerns about how they would tolerate the new treatments. Previous studies on solid tumours have shown that age can act as a barrier to receipt of optimal treatment, due to a higher prevalence of comorbidity, absence of data on treatment efficacy from clinical trials, and more frequent adverse effects.[131,132] A US study showed that only 46% of patients aged 80 years or more received imatinib, a highly effective treatment for chronic myeloid leukaemia, compared with 90% of those aged 20-59 years.[133]

The CONCORD-3 study protocol did not require detailed information on specific type of treatment, so it was not possible to estimate the proportion of patients who received immune-checkpoint inhibitors or targeted treatments. Data on socio-economic status and type of health insurance were also not collected. This information might have helped to explain the disparities in the stage distribution and stage-specific survival by age and race. An analysis of 61,650 melanoma patients aged 18-64 years diagnosed in the United States during 2007-2012 estimated that the proportion of patients with metastatic disease ranged from only 3% in the non-Medicaid insurance group to 15% among Medicaid and uninsured patients.[134] A recent systematic review of the cost-effectiveness of immune-checkpoint inhibitors in the US estimated that the individual cost of treatment for metastatic melanoma ranged from US$152,000 to US$303,000 for a patient with a median survival time.[135] The cost of targeted therapies for metastatic melanomas with the BRAF V600E mutation was estimated at between US$149,000 and US$319,000.[136] Recent analyses have shown that patients were less likely to receive immunotherapy if they had no insurance or Medicaid insurance, perceived a lower income, or received care at a community practice rather than an academic centre.[129,137,138] Such differences in access to treatment may partly explain the disparities in the recent trends in short-term survival reported in this study.

One-year net survival was consistently lower in blacks than whites. Survival was not estimated for other races. Previous studies have shown that the proportion of patients lost to follow-up, including those whose deaths were missed by the cancer registries, was generally higher among Asian/Pacific Islanders (API) than whites and blacks.[139,140] Incomplete follow-up among API and other minority groups could therefore produce an overestimation of survival and lead to biased comparisons.

Several studies have shown a survival disadvantage for blacks diagnosed with melanoma in the US. A study of more than 260,000 people diagnosed during 1988-2011 estimated an absolute gap of almost 20% between blacks and whites in 5-year relative survival for all stages combined.[120] Among whites and blacks of non-Hispanic origin, the difference in 5-year overall survival was almost 30% [82% *vs.* 53%] during 1982-2011.[90] The racial disparities were commonly ascribed to a less favourable stage distribution of black patients.[120,141-143] However, we have shown that while the proportion of distant-stage melanoma was higher among blacks than whites, one-year survival for distant-stage melanoma was also consistently lower among blacks than among whites. This gap suggests racial differences in treatment and access to care.

Despite the exclusion of about 2,500 patients registered with a distant-stage melanoma in cancer registries for which incidence data was not complete for the period 2001-2013, this is the largest population-based analysis on trends in one-year net survival for distant-stage disease. Although selection bias could not be completely rule out, the excluded cancer registries presented with similar characteristics, proportion of distant-stage melanoma and distributions of main risk factors compared to the registries retained in the analysis.

In conclusion, this is the first population-based study to show a recent improvement in short-term survival from distant-stage cutaneous melanoma in the United States. This may be due to the availability of new and more effective therapies for the treatment of metastatic or unresectable disease. The dramatic improvement since 2010 in short-term survival for melanoma of the skin diagnosed at the metastatic or unresectable stage is important, because for most other solid tumours, survival for metastatic disease has not changed for several decades.[144-146] More detailed population-based studies would help evaluate access to novel treatments, and their longer-term survival benefit for patients diagnosed with distant-stage melanoma.

Table 2.1: Data quality indicators, patients diagnosed with malignant melanoma of the skin during 2000-2014 in the United States

			Ineligible (%) ¶				Excluded (%) ‖			Data quality indicators (%) †	
	Calendar period	Patients submitted	Incomplete dates	In situ	Other	Eligible patients	DCO	Other	Patients included	Lost to follow-up	Censored
US registries	2000-2014	**1,040,814**	0.6	36.0	2.6	**632,861**	0.5	0.0	**629,816**	2.6	0.1
Alabama	2000-2014	**23,564**	0.9	41.3	2.3	**13,084**	0.6	0.0	**13,012**	0.0	0.0
Alaska	2000-2013	**1,533**	4.4	30.6	3.5	**944**	0.4	0.0	**940**	0.0	0.0
Arkansas	2000-2011	**7,592**	0.3	31.9	3.3	**4,897**	0.3	0.0	**4,879**	0.0	0.0
California	2000-2011	**127,043**	1.1	36.9	2.3	**75,851**	0.2	0.0	**75,712**	0.0	0.0
Colorado	2000-2013	**21,135**	0.3	33.1	3.1	**13,427**	0.7	0.0	**13,338**	0.0	0.0
Connecticut	2000-2014	**21,602**	0.4	40.9	2.2	**12,211**	0.2	0.0	**12,185**	5.5	0.0
Delaware	2000-2014	**6,283**	0.2	44.0	1.4	**3,413**	0.2	0.0	**3,406**	0.0	0.0
Florida	2000-2013	**89,847**	0.1	35.4	2.7	**55,590**	0.7	0.1	**55,134**	0.0	0.0
Georgia	2000-2014	**43,981**	0.0	35.6	2.0	**27,451**	0.4	0.0	**27,350**	0.0	0.0
Hawaii	2000-2014	**5,753**	0.3	33.7	1.5	**3,710**	0.2	0.0	**3,704**	7.5	0.0
Idaho	2000-2014	**9,032**	0.6	40.8	2.2	**5,095**	0.7	0.0	**5,059**	0.0	0.0
Indiana	2000-2014	**25,599**	0.6	32.3	3.3	**16,347**	0.5	0.0	**16,269**	0.0	0.0
Iowa	2000-2014	**15,612**	0.6	32.6	3.7	**9,846**	0.2	0.0	**9,822**	2.8	0.0
Kentucky	2000-2014	**23,097**	0.0	33.3	2.8	**14,764**	0.2	0.0	**14,729**	6.4	0.0
Louisiana	2000-2014	**15,105**	0.5	37.1	2.8	**9,000**	0.2	0.0	**8,982**	6.4	0.1
Maine	2000-2013	**7,860**	0.3	38.4	3.0	**4,581**	0.3	0.0	**4,565**	0.0	0.0
Maryland	2000-2014	**29,516**	0.4	40.2	1.8	**16,981**	0.6	0.1	**16,868**	0.0	0.0
Massachusetts	2000-2009	**23,194**	0.0	34.5	3.0	**14,483**	0.4	0.0	**14,420**	0.0	0.0
Michigan	2000-2013	**41,986**	0.2	36.5	2.5	**25,505**	0.6	0.0	**25,335**	0.0	0.0
Minnesota	2000-2013	**27,449**	0.0	38.1	1.9	**16,472**	0.3	0.0	**16,421**	0.0	0.0
Mississippi	2002-2014	**9,214**	0.8	31.6	2.8	**5,968**	0.6	0.0	**5,931**	0.0	0.0
Montana	2000-2014	**5,595**	0.6	37.8	2.9	**3,289**	0.5	0.0	**3,272**	0.0	0.0
Nebraska	2000-2014	**7,894**	0.6	33.4	3.5	**4,930**	0.5	0.0	**4,906**	0.0	0.0
New Hampshire	2000-2014	**9,727**	0.1	40.3	2.3	**5,575**	0.3	0.0	**5,560**	0.0	0.0
New Jersey	2000-2014	**49,568**	0.8	42.7	1.9	**27,024**	0.4	0.0	**26,910**	48.2	0.0
New Mexico	2000-2014	**8,720**	0.0	40.1	2.2	**5,030**	0.6	0.0	**5,000**	8.7	0.4
North Carolina	2000-2014	**47,654**	0.0	39.5	2.4	**27,727**	0.4	0.0	**27,602**	0.0	0.0
Ohio	2000-2014	**54,382**	0.1	35.7	3.0	**33,292**	0.6	0.0	**33,079**	0.0	0.0
Oklahoma	2000-2010	**9,135**	0.4	24.8	3.9	**6,479**	1.1	0.0	**6,407**	0.0	0.0
Oregon	2000-2013	**24,301**	0.1	40.9	2.6	**13,703**	0.5	0.0	**13,637**	0.0	0.0
Pennsylvania	2000-2014	**62,912**	2.4	32.9	2.7	**39,052**	0.4	0.0	**38,904**	0.0	0.0
Rhode Island	2000-2014	**6,363**	0.4	39.0	2.4	**3,703**	0.4	0.0	**3,688**	0.0	0.0
South Carolina	2000-2014	**24,940**	0.0	40.8	1.8	**14,309**	0.5	0.0	**14,230**	0.0	0.0
Tennessee	2000-2011	**19,264**	0.5	28.5	3.3	**13,047**	0.3	0.0	**13,003**	0.0	0.0
Texas	2000-2013	**59,374**	0.9	28.4	3.5	**39,862**	0.8	0.0	**39,555**	0.0	0.0
Utah	2000-2014	**14,946**	0.1	38.2	2.1	**8,893**	0.1	0.0	**8,885**	0.0	0.2
Vermont	2000-2013	**4,537**	0.1	38.8	1.9	**2,688**	0.3	0.0	**2,679**	0.0	0.0
Washington	2000-2008	**22,317**	0.8	39.2	2.2	**12,876**	0.2	0.0	**12,843**	0.0	0.0
West Virginia	2000-2014	**8,894**	1.3	31.1	3.4	**5,707**	0.4	0.0	**5,682**	0.0	0.0
Wisconsin	2000-2013	**21,636**	0.9	28.4	3.6	**14,507**	1.0	0.0	**14,366**	0.0	0.0
Wyoming	2000-2013	**2,658**	0.2	38.6	2.9	**1,548**	0.1	0.0	**1,547**	0.0	0.1

¶ **Incomplete dates**: records in which the year of birth is unknown; or the month and/or year of diagnosis is unknown; or the year of last known vital status is unknown. **Other**: records with incomplete data, or for tumours that are benign (behaviour code 0), of uncertain behaviour (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or for patients with age outside the range 15-99

‖ **Other**: vital status or sex unknown; invalid date or sequence of dates

† **Censored**: patients whose last known vital status is "alive" and who were censored within five years of diagnosis or, if diagnosed in 2010 or later, before 31 December 2014

Table 2.2: Adults (15-99 years) diagnosed with primary malignant melanoma of the skin during 2001-2013 in 34 US registries: distribution (no., %) by sex, age at diagnosis and stage

	Localised		Regional		Distant		Unknown		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sex										
Men	**182,150**	75.3	**24,747**	10.2	**12,443**	5.1	**22,470**	9.3	**241,810**	56.8
Women	**146,022**	79.3	**15,365**	8.3	**6,158**	3.3	**16,560**	9.0	**184,105**	43.2
Age group										
15-44	**61,321**	79.7	**7,039**	9.1	**2,074**	2.7	**6,510**	8.5	**76,944**	18.1
45-54	**58,041**	78.2	**6,857**	9.2	**2,942**	4.0	**6,386**	8.6	**74,226**	17.4
55-64	**69,434**	77.4	**8,296**	9.2	**4,131**	4.6	**7,848**	8.7	**89,709**	21.1
65-74	**66,251**	76.8	**7,739**	9.0	**4,204**	4.9	**8,116**	9.4	**86,310**	20.3
75-99	**73,125**	74.1	**10,181**	10.3	**5,250**	5.3	**10,170**	10.3	**98,726**	23.2
Race										
Whites	**315,166**	77.3	**39,200**	9.6	**18,052**	4.4	**35,550**	8.7	**407,968**	95.8
Blacks	**1,286**	51.8	**500**	20.1	**363**	14.6	**333**	13.4	**2,482**	0.6
Others	**11,720**	75.8	**412**	2.7	**186**	1.2	**3,147**	20.3	**15,465**	3.6
Anatomic location										
Head and neck	**67,980**	77.6	**9,140**	10.4	**2,036**	2.3	**8,405**	9.6	**87,561**	20.6
Trunk	**111,247**	81.3	**12,071**	8.8	**2,817**	2.1	**10,754**	7.9	**136,889**	32.1
Limbs	**146,001**	81.5	**16,259**	9.1	**3,314**	1.9	**13,561**	7.6	**179,135**	42.1
Overlapping region or NOS	**2,014**	9.7	**2,297**	11.0	**10,321**	49.6	**6,191**	29.7	**20,823**	4.9
Skin of genital organs	**930**	61.7	**345**	22.9	**113**	7.5	**119**	7.9	**1,507**	0.4
Morphology										
Malignant melanoma, NOS	**156,892**	71.8	**17,992**	8.2	**14,538**	6.7	**29,031**	13.3	**225,635**	51.9
Superficial spreading	**115,022**	89.0	**7,906**	6.1	**1,077**	0.8	**5,285**	4.1	**129,782**	29.8
Lentigo maligna	**23,590**	88.0	**808**	3.0	**162**	0.6	**2,258**	8.4	**27,163**	6.2
Nodular	**19,161**	62.1	**8,963**	29.1	**1,653**	5.4	**1,064**	3.4	**31,329**	7.2
Acral lentiginous	**2,990**	68.2	**1,017**	23.2	**189**	4.3	**186**	4.2	**4,428**	1.0
Others	**10,517**	65.2	**3,426**	21.2	**982**	6.1	**1,206**	7.5	**16,518**	3.8
Total	**328,172**	77.1	**40,112**	9.4	**18,601**	4.4	**39,030**	9.2	**425,915**	100.1

Table 2.3: Age-standardised and age-specific 1-year net survival (%) for patients diagnosed with distant cutaneous melanoma during 2001-2013 in 34 US registries by sex

	All			Men			Women			Age (years) 15-44			45-54			55-64			65-74			75-99		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
2001	**921**	**42.8**	39.3 - 46.3	**626**	**39.9**	35.7 - 44.1	**295**	**48.7**	42.5 - 54.9	**132**	**44.4**	35.9 - 52.8	**178**	**45.7**	38.4 - 53.1	**169**	**50.2**	42.6 - 57.8	**198**	**32.7**	26.1 - 39.4	**244**	**39.7**	33.0 - 46.3
2002	**1,009**	**38.5**	35.2 - 41.7	**673**	**36.8**	32.9 - 40.7	**336**	**41.6**	35.9 - 47.2	**162**	**46.4**	38.7 - 54.0	**186**	**34.0**	27.2 - 40.8	**198**	**37.3**	30.5 - 44.0	**208**	**36.1**	29.5 - 42.7	**255**	**33.2**	27.1 - 39.3
2003	**1,070**	**44.1**	40.7 - 47.4	**733**	**42.3**	38.3 - 46.3	**337**	**48.0**	42.1 - 53.9	**133**	**49.7**	41.3 - 58.2	**185**	**44.5**	37.4 - 51.7	**230**	**45.3**	38.8 - 51.7	**244**	**42.8**	36.5 - 49.2	**278**	**32.3**	26.5 - 38.1
2004	**1,226**	**42.9**	39.8 - 46.0	**807**	**40.0**	36.2 - 43.9	**419**	**48.6**	43.4 - 53.8	**163**	**46.7**	39.1 - 54.3	**207**	**38.8**	32.2 - 45.4	**250**	**42.4**	36.3 - 48.6	**256**	**42.9**	36.7 - 49.1	**350**	**40.8**	35.2 - 46.3
2005	**1,244**	**42.8**	39.6 - 46.0	**855**	**42.5**	38.5 - 46.4	**389**	**43.2**	37.8 - 48.7	**137**	**43.9**	35.6 - 52.1	**195**	**44.3**	37.3 - 51.3	**266**	**45.4**	39.3 - 51.4	**288**	**40.5**	34.7 - 46.2	**358**	**38.5**	33.0 - 43.9
2006	**1,359**	**45.6**	42.5 - 48.7	**879**	**44.0**	40.2 - 47.8	**480**	**48.5**	43.4 - 53.7	**146**	**51.5**	43.4 - 59.5	**232**	**47.6**	41.2 - 54.0	**312**	**44.4**	38.8 - 49.9	**297**	**41.7**	36.0 - 47.4	**372**	**38.7**	33.4 - 44.0
2007	**1,319**	**44.5**	41.3 - 47.7	**855**	**44.2**	40.1 - 48.2	**464**	**45.6**	40.3 - 50.8	**130**	**45.5**	37.0 - 54.0	**209**	**43.7**	37.0 - 50.5	**281**	**45.3**	39.4 - 51.1	**317**	**48.4**	42.8 - 54.1	**382**	**37.0**	31.8 - 42.1
2008	**1,381**	**42.8**	39.7 - 45.9	**935**	**41.1**	37.2 - 45.0	**446**	**46.6**	41.5 - 51.8	**142**	**43.0**	34.9 - 51.1	**225**	**47.2**	40.7 - 53.7	**336**	**40.3**	35.0 - 45.5	**290**	**45.2**	39.4 - 51.0	**388**	**37.2**	32.1 - 42.3
2009	**1,486**	**42.0**	39.1 - 45.0	**988**	**40.5**	36.8 - 44.1	**498**	**45.0**	40.0 - 49.9	**159**	**44.7**	37.0 - 52.4	**230**	**38.9**	32.6 - 45.2	**346**	**43.2**	37.9 - 48.4	**341**	**43.8**	38.4 - 49.2	**410**	**36.2**	31.3 - 41.2
2010	**1,678**	**45.7**	43.0 - 48.3	**1,151**	**44.5**	41.2 - 47.8	**527**	**47.9**	43.3 - 52.5	**207**	**57.1**	50.4 - 63.8	**277**	**46.1**	40.2 - 51.9	**385**	**41.4**	36.5 - 46.4	**366**	**41.4**	36.3 - 46.5	**443**	**34.9**	30.2 - 39.6
2011	**1,725**	**51.9**	49.2 - 54.6	**1,168**	**49.0**	45.4 - 52.6	**557**	**56.8**	52.5 - 61.1	**168**	**66.1**	58.9 - 73.2	**265**	**51.7**	45.7 - 57.8	**430**	**45.8**	41.1 - 50.5	**388**	**47.4**	42.4 - 52.5	**474**	**39.3**	34.6 - 44.0
2012	**2,012**	**56.7**	54.3 - 59.2	**1,355**	**54.6**	51.4 - 57.7	**657**	**60.3**	56.4 - 64.1	**226**	**70.3**	64.4 - 76.3	**297**	**58.2**	52.5 - 63.8	**485**	**51.0**	46.5 - 55.5	**486**	**51.1**	46.6 - 55.7	**518**	**44.5**	39.9 - 49.1
2013	**2,171**	**58.9**	56.6 - 61.2	**1,418**	**57.4**	54.4 - 60.5	**753**	**61.4**	57.7 - 65.1	**251**	**67.8**	62.0 - 73.6	**349**	**62.7**	57.6 - 67.8	**484**	**56.1**	51.6 - 60.6	**541**	**56.7**	52.4 - 60.9	**546**	**43.9**	39.4 - 48.3

Figure 2.1: Trends in age-specific 1−year net survival (%) for patients diagnosed with distant cutaneous melanoma during 2001-2013 in the United States

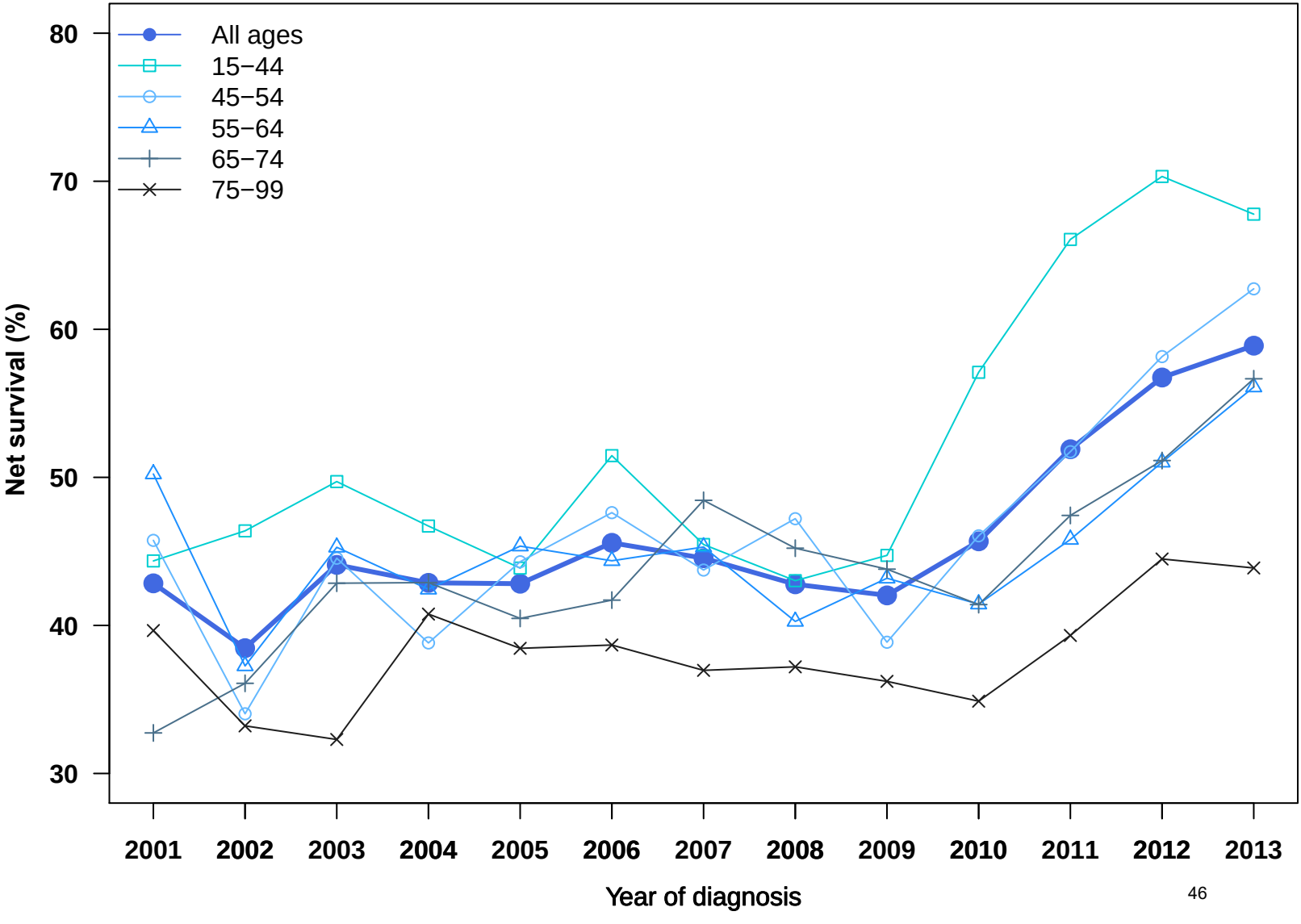
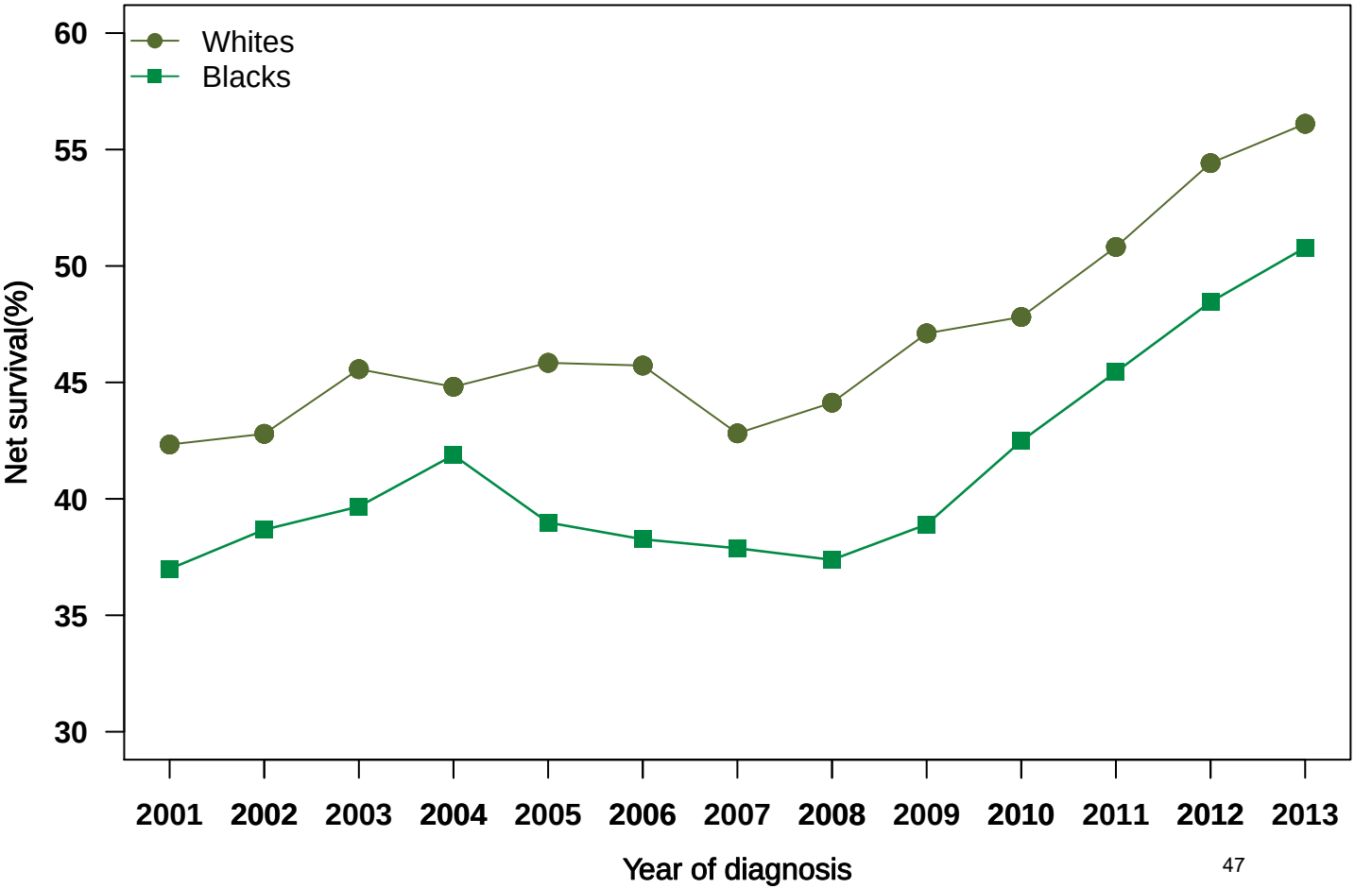
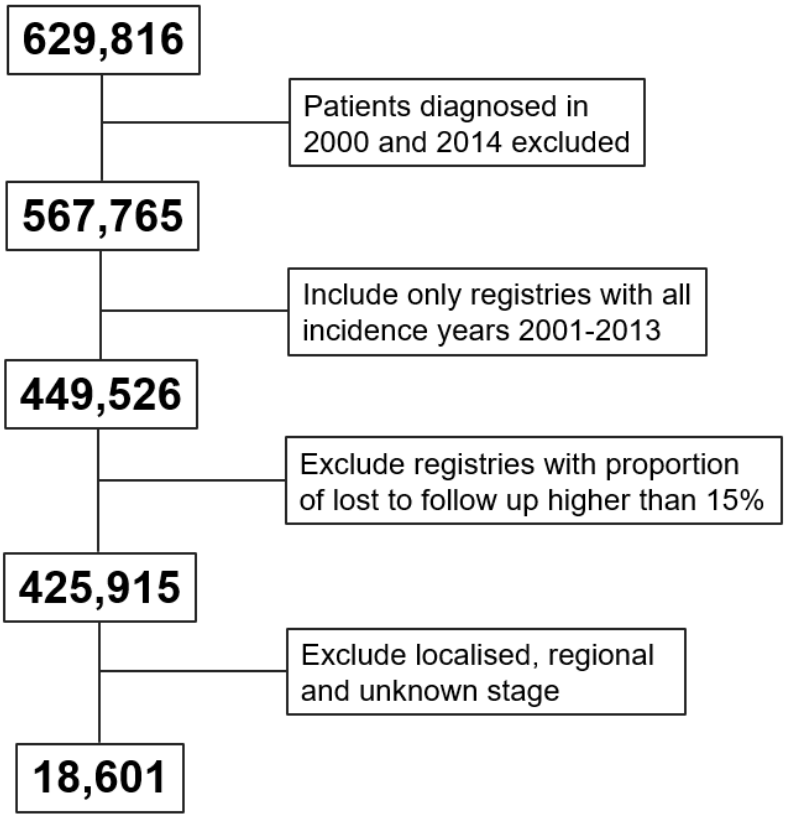


Figure 2.2: Trends in age-standardised 1−year net survival (%) for patients diagnosed with distant cutaneous melanoma during 2001-2013 in the United States by race



Supplementary figure 2.1: Patients included in survival analysis



Preface to Chapter 3

The following chapter addresses the second and third objectives of the thesis, i.e., the impact that the different morphological distribution and survival by morphological subtypes may have on the international differences in prognosis, which are usually reported for all melanomas combined.

While the prognostic role of stage at diagnosis for cutaneous melanoma is well established, as discussed in Chapters 1 and 2, the prognostic role of morphology is still controversial. National and international clinical guidelines generally indicate stage at diagnosis as the most relevant prognostic factor. The prevalent idea is that melanomas of different histologic subtypes converge in their biologic behaviour once they metastasise.[147] Recommended treatment options do not differ between morphological subtypes of disease at the same stage of diagnosis, so clinical guidelines only indicate histology as an optional item for inclusion in pathology reports. However, the international guidelines are based on the conclusions from small single-centre or multi-centre studies that were conducted more than 20 years ago.[148-150]

Clinical evidence suggests marked international differences in the proportion of the more lethal acral and nodular subtypes of cutaneous melanoma. Two population-based studies in Colombia[151] and Brazil[152] showed that the proportion of nodular and acral lentiginous melanoma is higher than that observed in European countries. These studies also highlighted the poorer prognosis for nodular and acral lentiginous melanoma than the more common superficial spreading melanoma. To my knowledge, population-based studies exploring the morphological distribution and survival by subtype in Asian countries are not available. The annual report of the Japanese Skin Cancer Society estimated the proportion of acral lentiginous melanoma to be 40% of the total 4,239 cases diagnosed within 26 institutes in 2016. This proportion is extremely high, when compared with the roughly 2% of all cases experienced in Europe. The report did not provide survival estimates for any specific subtype, or for all subtypes combined.

Chapter 3 aims to assess the extent to which differences in morphological distribution and survival by morphology may explain international variation in survival when all histological subtypes are combined. This study provides, for the first time, international comparisons of age-standardised five-year net survival estimates for the main histologic sub-types of melanoma, for over 1.5 million adults diagnosed during 2000-2014, using data from 228 population-based cancer registries in 59 countries.

In discussing the results, I have emphasised the data from Asia and Central and South America, where population-based studies of survival are scant, and clinical studies suggest a different morphological distribution from that seen in Europe, North America or Oceania.

The results of this study highlight a high proportion of more aggressive acral lentiginous and nodular melanoma in Asia and Latin America. The prognosis for both subtypes is poorer than that for superficial spreading melanoma in all countries.

The poorer survival for nodular melanoma has commonly been ascribed to aggressive clinicopathological and prognostic features.[53,153] Nodular melanoma is most likely to penetrate into the deeper layers of the skin if not removed, rather than growing in size laterally, as with superficial spreading melanoma, and it is more common on the back, head and neck, areas of the body that are less often scrutinized than the legs or arms. However, after controlling for major confounders, i.e., sex, age and stage at diagnosis, patients with nodular melanoma still had a much higher excess hazard of death than those with superficial spreading melanoma.

The lack of information on detailed TNM stage in most cancer registries did not allow me to produce more detailed analysis by stage. Rather, a simple binary variable, i.e. non-metastatic *vs.* metastatic melanoma was used to model the excess hazard of death for nodular and acral lentiginous melanoma compared to superficial spreading melanoma. This approach is certainly a limitation because nodular and acral lentiginous melanomas are known to have higher clinical stage than superficial spreading melanoma even if they are non-metastatic.[52,54,154,155]

The poor survival for acral lentiginous melanoma has also been attributed to aggressive prognostic features. Acral lentiginous melanoma mostly occurs in sun-protected areas of the body, such as the palms, the sole of the foot and underneath the nails. The hidden location of the lesion, the unusual clinical presentation, the low public awareness, and the misdiagnosis by healthcare professionals, especially when the lesion is not pigmented, have been deemed the main factor responsible for its poor prognosis. The perception that the risk of melanoma is lower among dark-skinned people and people of Asian origin is considered to be one reason for delayed diagnosis. Healthcare professionals may often be less suspicious of melanoma, and less likely to offer regular, full-body skin examinations.

Awareness campaigns aiming at educating GPs and the general public in recognising the early signs of acral lentiginous melanoma should be implemented, particularly in countries in Southeast Asia and Latin America, where the proportion of this lethal subtype is higher. Public health efforts to increase awareness of this rare but aggressive form of melanoma, together

with specific training in diagnosis aimed at clinicians, may reduce the time between the first consultation and a definitive diagnosis, and would be expected to lead to a better prognosis.

Chapter 3 may serve as the basis to persuade clinicians, dermatologists, pathologists and melanoma experts of the importance of morphology as a relevant prognostic factor. Future studies should include data from cancer registries in Asia and Latin America, which have been disregarded for far too long because of the lower incidence of melanoma in the populations they cover.

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Student ID Number	1704667	**Title**	Mrs
First Name(s)	Veronica		
Surname/Family Name	Di Carlo		
Thesis Title	What explains global variation in population-based survival from malignant melanoma of the skin?		
Primary Supervisor	Prof Claudia Allemani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Journal of Dermatology		
When was the work published?	27 March 2022		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Veronica Di Carlo (VDC) was the lead author of the paper. VDC, Prof Claudia Allemani and Prof Michel Coleman designed the study and analysis plan. VDC carried out the literature review, produced the statistical analyses, tables and graphics and drafted the manuscript. All co-authors commented on the drafted manuscript. VDC integreted the comments to the manuscript. All co-authors reviewed and approved the final version of the manuscript.

SECTION E

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Date	25/10/2023

3. Does the morphology of cutaneous melanoma help explain the international differences in survival? Results from 1,578,482 adults diagnosed during 2000-2014 in 59 countries (CONCORD-3)

3.1 Introduction

The incidence of cutaneous melanoma has been rising steadily in most populations of Caucasian origin over the past 50 years.[156,157] It is now one of the 10 most common malignancies in Oceania, North America and Europe, with age-standardised incidence rates in the range 7.0 to 36.6 per 100,000 person-years. By contrast, melanoma is rare in populations of Asian and African origin, where incidence rates are in the range 0.4–3.0.[99]

The histopathologic features of cutaneous melanoma vary markedly world-wide. The proportion of melanomas with the more aggressive acral lentiginous or nodular histologic types is higher in populations with predominantly dark skin than in those with predominantly fair skin.[24,25]

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3)[64] highlighted wide disparities in 5-year net survival from cutaneous melanoma, which was lower in Asian populations than in the rest of the world. Age-standardised 5-year net survival for adults (15-99 years) diagnosed during 2010-2014 was 90% or higher in the US, Australia, New Zealand and most Nordic countries, but 60% or lower in Ecuador, China, Korea, Singapore and Taiwan.

Stage at diagnosis is recognised as the most important predictor of survival.[79,103,158,159] Age at diagnosis is also a prognostic factor, and several studies have shown much higher survival for younger patients.[80,83,160-162]

The prognostic role of morphology in cutaneous melanoma is controversial, however. Traditionally, melanomas of the skin have been classified into three fairly well-defined sub-groups, characterised by different patterns of growth: superficial spreading and lentigo maligna melanoma, which is characterised by a long period of superficial growth; nodular melanoma, which is more likely to penetrate into the deeper layers of the skin if not removed, and acral lentiginous melanoma, which mostly develops on the extremities but displays similar biological behaviour to that of nodular melanoma.[51] Despite the advent of high-resolution genomics and other proposed approaches for the classification of melanocytic tumours, the

diagnosis of the different subtypes should continue to be based on the pathologist's interpretation of the histology and how it fits into the WHO Classification of Tumours, commonly known as the WHO `Blue Books'.[163]

However, the morphology classification has not been considered useful for prognostic purposes, because of the idea that the clinical development of all melanomas is similar, whatever the histologic subtype, spreading horizontally within the epidermis and then extending vertically into the dermis, and that they converge in their biologic behaviour once they metastasise.[147]

In this study, we aimed to describe the histologic distribution of cutaneous melanoma in 59 countries that contributed data to CONCORD-3, for adults diagnosed during 2000-2014, and to produce the first international comparison of trends in population-based age-standardised 5-year net survival by morphology sub-type. We also aimed to examine the role of morphology sub-type on the prognosis of cutaneous melanoma.

3.2 Materials and Methods

Anonymised individual tumour registrations for patients diagnosed during 2000-2014 with one of 18 cancers or groups of malignancies, including melanoma, were provided for CONCORD-3 by 322 population-based cancer registries in 71 countries worldwide. Patients were followed up for their vital status to 31 December 2014. Data acquisition, ethical approval and data quality control have been described elsewhere.[64]

We asked participating registries to submit all registrations for malignant melanoma, regardless of anatomic site. Melanoma was defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision [ICD-O-3].[46] We focused this analysis of survival on melanomas arising in the skin (ICD-O-3 topography C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9) and scrotum (C63.2). Survival from melanomas arising in internal organs and in the eye will be examined in a subsequent analysis. To facilitate quality control and comparison of the intensity of early diagnostic and screening activity, we requested all melanoma registrations, regardless of behaviour, whether benign (behaviour code 0), uncertain (1), *in situ* (2) or invasive (3). However, survival analyses included only primary, invasive melanomas.

Records with incomplete data, or of tumours that were benign, *in situ*, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or for patients with age outside the range 15-99 years, were not included in survival analyses. We excluded tumours

registered only from a death certificate or discovered at autopsy, since their survival is unknown, as well as records for which the sex or vital status was unknown, and those with an invalid date or sequence of dates.

Patients were grouped into seven morphology categories with the ICD-O-3 classification: malignant melanoma, not otherwise specified (NOS; morphology code 8720), superficial spreading melanoma (8743), lentigo maligna melanoma (8742), nodular melanoma (8721), acral lentiginous melanoma (8744), desmoplastic melanoma (8745) and other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8746, 8761, 8770-8774, 8780).

Patients were grouped by calendar period of diagnosis: 2000-2004, 2005-2009, 2010-2014. We examined time trends in the morphology distribution in each country. We also estimated trends in age-standardised 5-year net survival by country and morphology with the non-parametric Pohar Perme estimator,[72] using the STATA[109] command *stns*.[164] The cohort approach was used for patients diagnosed during 2000-2004 and 2005-2009, because they had all been followed up for at least five years. We used the period approach[78] to estimate survival for patients diagnosed during 2010-2014, because 5 years of follow-up for vital status were not available for all patients by 31 December 2014.

To control for wide differences in background mortality between geographical areas, men and women, and over time, we constructed life tables of all-cause mortality in the general population for each country or registry by single year of age, sex, calendar year and, where possible, by race/ethnicity (Israel, Singapore, United States, Australian Northern Territory, and New Zealand).

We estimated five-year net survival by morphology in each of five age groups (15-44, 45-54, 55-64, 65-74 and 75-99 years). We obtained age-standardised estimates for all age-groups combined using the International Cancer Survival Standard type 2 weights for the five age groups (0.28, 0.17, 0.21, 0.20 and 0.14).[77] We did not estimate survival if fewer than ten patients were available for analysis in a given combination of morphology group and calendar period. If 10-49 patients were available for analysis in a given calendar period, we only estimated survival for all ages combined. If 50 or more patients were diagnosed during 2000-2004 and 2005-2009, we attempted survival estimation for each age group in each calendar period. For 2010-2014, we estimated net survival using the period approach, i.e., including in analysis patients diagnosed during the 5 years 2010-2014, plus those diagnosed earlier than 2010 who survived longer than the start of 2010. Therefore, for 2010-2014 the threshold of 50 or more patients for age-standardization applies to the combination of those cohort of patients. If a single age-specific estimate could not be obtained, we merged the data for adjacent age

groups and assigned the combined estimate to both age groups before standardisation for age. If two or more age-specific estimates could not be obtained, we present only the unstandardised estimate for all ages combined. The pooled estimates for countries with more than one registry do not include data from registries for which the estimates were less reliable. Less reliable estimates are shown with a flag (§) in Table 2 when they are the only available information from a given country or territory (see footnote in Table 2 for the definition of less reliable estimates). We comment in the text only on reliable, age-standardised survival estimates. Continental regions were defined using the United Nations Geoscheme.[165]

To estimate the effect of morphology on the hazard of death due to melanoma, we fitted a flexible parametric model on the log cumulative hazard scale, using *stpm2*[166] in STATA. We restricted this analysis to registries where at least 65% of registrations had a specific morphology code, i.e., not malignant melanoma, NOS. Among these registries, we further selected those for which data on stage were available for at least 75% of registrations in one of the following classifications: UICC Tumour-Node-Metastasis staging system, 7th edition,[36] Condensed TNM,[167] or SEER Summary Stage 2000.[107] With this constraint, we were able to include data from one regional cancer registry in Germany (Lower Saxony), two registries in Spain (Basque Country and Granada) and the Norwegian national cancer registry.

For each country, we first fitted a model with only morphology as a covariable (model 1). We then included, as additional covariables, sex, a restricted cubic spline for the effect of age at diagnosis (4 degrees of freedom) and stage at diagnosis (metastatic *vs.* non metastatic) (model 2). We excluded patients for which stage at diagnosis was unknown (complete case analysis).

3.3 Results

We obtained data from 284 registries in 59 countries on 2,303,095 adults who were diagnosed with melanoma during 2000-2014 (Table 1). Among these, 49% were diagnosed in North America, 37% in Europe, 12% in Oceania, and only 2% in Asia and less than 1% in both Africa and in Central and South America.

We excluded from survival analysis 637,957 patients (28%) who were diagnosed with an *in situ* tumour, ranging from 11% in Central and South America to 35% in North America. The proportion of *in situ* melanoma was 20% or higher in 10 countries (Table 1), suggesting a highly effective approach to early diagnosis. We additionally excluded 78,587 patients for other reasons (see footnote in Table 1). The proportion of melanomas of benign or uncertain

behaviour was particularly high in Norway (22%), highlighting intensive activity of monitoring atypical naevi and pre-malignant lesions.

Of the 1,586,551 eligible patients, we further excluded 7,139 patients (0.5%) who were diagnosed only from a death certificate or discovered at autopsy and 930 patients (less than 0.1%) for other reasons. Finally, 1,578,482 patients diagnosed with a primary, invasive melanoma of the skin were available for survival analysis (99.5% of those eligible). More than 99% of these tumours were microscopically confirmed, either cytologically or histologically.

About 42% of the tumours were registered as malignant melanoma, NOS. The proportion was generally high in countries in Asia (76%), Central and South America (63%), North America (51%) and Africa (46%) and much lower in Oceania (33%). In Europe, the proportion of melanomas with a non-specific morphology was higher in Eastern European countries (57%) than in Southern (37%), Northern (32%) and Western European countries (27%). The proportion of melanomas diagnosed with a non-specific morphology fell substantially in Australia (from 40% in 2000-2004 to 26% in 2010-2014), Denmark (from 42% to 11%), Iceland (from 36% to 18%), Italy (from 32% to 19%), Lithuania (from 85% to 35%), Portugal (from 70% to 35%) and the United Kingdom (from 39% to 23%) (Table A1).

Overall, superficial spreading melanoma was the second most common histology (36% of all cases). It accounted for more than half the patients in Denmark, France, Iceland, the Netherlands, Norway, Sweden and Switzerland (Figure 1). Nodular melanoma accounted for 7% of all cases in North America and Asia, 9% in Oceania and 13% in Central and South America. In Europe, 12% of the cases were registered as nodular melanoma, with higher proportions in Czech Republic, Ireland, Norway, Romania, Slovakia and Sweden. About 6% of adults were diagnosed with lentigo maligna melanoma, ranging from 2% in Asia to 8% in Oceania. Acral lentiginous melanoma was very rare in North America, Europe and Oceania (less than 2% of all cases) but the proportion was higher in Central and South America (more than 10% in Colombia, Costa Rica, Guadeloupe and Martinique) and Asia (more than 10% in Korea, Singapore and Taiwan). Desmoplastic melanoma represented less than 1% of the patients. The proportion of patients diagnosed with other morphologies was higher than 20% in Estonia, Italy and Latvia.

Malignant melanoma, not otherwise specified

Age-standardised 5-year net survival varied widely between world regions (Table 2). It was in the range 85-89% in Oceania and North America during 2010-2014. It was higher than 80% in all Western European countries and ranged from 54% to 79% in Eastern Europe. In Central

and South America, age-standardised 5-year net survival ranged from 57% in Ecuador to 76% in Costa Rica and Puerto Rico. Five-year survival was lower than 70% in all Asian countries except Israel (88%), and as low as 47% in Taiwan.

Five-year survival increased between 2000-04 and 2010-14 by 10% or more in China (from 36 to 48%), Bulgaria (from 52 to 62%), Croatia (from 66 to 77%) and Estonia (from 71 to 83%).

Superficial spreading melanoma

Age-standardised 5-year net survival for patients diagnosed during 2010-2014 was 90% or higher in North America, Oceania and almost all European countries; survival was lower than 90% only in Slovakia, Poland, Lithuania, Portugal and Bulgaria. In Asia, survival ranged from 71% in Taiwan to 98% in Israel (Figure 2).

Lentigo maligna melanoma

This sub-type of melanoma had the most favourable prognosis: age-standardised 5-year net survival was close to 100% in North America, Australia and most European countries. Estimates were not available for most countries in Central and South America and Asia because of the small numbers of patients diagnosed with this specific sub-type.

Nodular melanoma

The prognosis for nodular melanoma was the poorest in all continents. Age-standardised 5-year net survival for patients diagnosed during 2010-2014 reached 72% in Canada and United States, 77% in New Zealand and 80% in Australia. In Central and South America, it ranged from 58% in Costa Rica to 72% in Argentina, and in Europe, from 58% in Poland to 80% in Ireland. Survival improved dramatically in Bulgaria (from 46% in 2000-2004 to 64% in 2010-2014) and in Portugal (from 59% to 76%).

Acral lentiginous melanoma

Five-year net survival for adults diagnosed during 2010-2014 was in the range 77-82% in North America and Oceania and 70-95% in Europe. Most of the estimates for countries in Asia and Central and South America were not age-standardised because of the small numbers of patients available for survival analysis.

Five-year net survival for adults diagnosed with desmoplastic melanoma during 2010-2014 ranged between 76% and 91%. Estimates were not available for Central and South America or for most countries in Asia because of the small numbers of patients available for analysis.

With the excess hazard of death for patients with superficial spreading melanoma taken as the reference category, the excess hazard ratio for patients diagnosed with nodular melanoma was 21.8 (95%CI 14.7-32.3) in Germany, 12.1 (8.1-18.1) in Spain and 6.7 (5.7-7.9) in Norway (Table 3). The excess hazard ratios were lower after controlling for sex, age and stage at diagnosis, but the excess hazard of death for patients with nodular melanoma was still 13.5 (9.6-18.9) times higher in Germany, 6.7 (4.8-9.3) times higher in Spain and 4.1 (3.6-4.8) times higher in Norway, than for patients in the same country diagnosed with superficial spreading melanoma.

The excess hazard ratio for patients diagnosed with acral lentiginous melanoma *vs*. superficial spreading melanoma was 15.2 (9.0-25.5), 9.0 (5.2-15.5) and 1.7 (0.5-5.1) in Germany, Spain, and Norway, respectively. After controlling for sex, age and stage at diagnosis, the excess hazard of death for patients with acral lentiginous melanoma was still 10.8-fold (6.8-17.1) in Germany, 5.0-fold (3.1-8.1) in Spain and 2.2-fold (1.0-4.9) higher in Norway, than in patients diagnosed with superficial spreading melanoma.

3.4 Discussion

This study of over 1.5 million adults diagnosed with cutaneous melanoma world-wide during 2000-2014 has highlighted wide international differences in the distribution of histologic sub-types as well as in survival by sub-type. The prognosis is poorest everywhere for nodular and acral lentiginous melanoma.

The prognostic role of the morphology of cutaneous melanomas is controversial. Clinical guidelines indicate that stage at diagnosis is the most important prognostic factor. The prevalent idea is that melanomas of different morphologies converge in their biologic behaviour once they metastasize,[61] so the recommended treatment options do not differ between morphological sub-types at a given stage at diagnosis. Clinical guidelines even indicate that the histologic sub-type is only an optional item for inclusion in pathology reports.[168]

Probably for this reason, the primary histologic sub-types of melanoma are often poorly specified, if at all, in pathology reports.[80,160] In turn, this determines the high proportion of melanomas that are coded as “malignant melanoma, not otherwise specified (NOS)” in cancer

registry data.[161] In this global study, 43% of melanomas were registered as malignant melanoma NOS. The proportion varied widely, and was higher in Asia, Central and South America and Eastern Europe, as has been shown elsewhere.[161,169] However, our study shows that the proportion of melanomas with poorly specified morphology has fallen in most countries over the last 15 years, suggesting improvements in pathological practice.[170]

Overall, superficial spreading melanoma was the most frequent of the specific morphologies, and the proportion has been increasing over time. It is generally associated with an excellent prognosis in Europe, North America and Oceania, as has been shown in previous studies.[61,80,161,171] Several international studies have shown an increasing incidence of thinner melanomas (1mm or less),[27,162,172-177] as a result of raised public awareness and earlier detection, especially for superficial spreading melanomas. The result is an increasing number of people with melanoma who are less likely to die because of their tumours. This phenomenon may help explain the improvement in the already high 5-year net survival from superficial spreading melanoma.

Acral lentiginous melanoma represented less 1% of the patients in Europe, North America and Oceania, but almost 6% of the patients in Asia and 7% in Central and South America. Very few studies have focused on survival from cutaneous melanoma in Asia and Central and South America, perhaps because the overall incidence is much lower than in fairer-skinned populations. In Singapore, acral lentiginous melanoma accounted for 16% of all cases diagnosed during 2008-2017.[178] In a study of 915 patients diagnosed during 1997-2011 in Brazil, the acral sub-type accounted for 7% of all cases and that 5-year cause-specific survival was much lower (51%) than for superficial spreading melanoma (82%).[152] A study of 142 patients in China confirmed the poor prognosis for patients with acral lentiginous melanoma; 5-year cause-specific survival was 53%.[179] By contrast, an analysis of 252 patients diagnosed in a single institution in Japan during 2001-2014 showed no difference between 5-year survival for acral and non-acral lentiginous subtypes (59% *vs.* 62% in men and 71% *vs*. 85% in women),[180] although the numbers of patients were too small to derive definitive conclusions.

Our study found that age-standardised five-year net survival for acral lentiginous melanoma was generally lower than for other morphologies, with the only exception of nodular melanoma, and globally in the range 66-95%. The poorer prognosis for acral lentiginous melanoma, which usually develops on the palms, the sole of the foot or underneath the nails, is commonly ascribed to delayed diagnosis, because these areas are not routinely examined by patients or primary care physicians.[181] Moreover, the proportion of the acral sub-type is higher in Blacks

than Caucasians;[182] but because the risk of melanoma in black populations is perceived to be low, the lack of secondary prevention is also considered a major cause of late diagnosis.[183,184]

Nodular melanoma had the poorest prognosis in all countries, as has been reported elsewhere.[53,185,186] Forty years ago, a multivariable analysis of 339 patients diagnosed in a single institution in the US during 1960-1977 found that the increased risk associated with nodular histology was confounded by an increase in thickness and ulceration; in other words, the higher risk of death was due to more advanced stage at diagnosis, not intrinsic to the morphologic sub-type.[148] On the basis of this conclusion from a small study, the American Joint Committee on Cancer did not include histologic sub-type in the cutaneous melanoma staging system, because it was not considered to be a significant prognostic factor.[187] Thirty years later, however, a very large population-based study of 118,508 patients diagnosed in the US with superficial spreading or nodular melanoma during 1973-2012 showed that morphology is in fact an independent predictor of survival.[61] After controlling for thickness, ulceration, mitotic index and stage at diagnosis, nodular sub-type remained an independent risk factor for death from melanoma (HR 1.55, 95% CI 1.41 to 1.70). Another population-based study of 82,901 patients diagnosed in Germany during 1997-2013 showed that differences in 5-year survival by histologic subtype were partially explained by tumour size.[188]

Our population-based study confirms these findings. The multivariable analysis of data from four population-based registries with complete information on stage and morphology highlights a much higher excess risk of death with nodular or acral lentiginous melanoma than for superficial spreading melanoma, after controlling for major confounders. Sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes. The different magnitude of the excess hazard ratios in Germany, Spain and Norway may be due to the low baseline hazard for superficial spreading melanoma in Germany, where national skin cancer screening for people aged 35 years or more with health insurance was introduced in 2008. This may have improved early detection of the generally slow-growing, less aggressive superficial spreading melanomas.[188]

Our study has also shown that while five-year survival from cutaneous melanoma in Eastern Europe has been increasing in recent years, survival continues to lag behind the rest of Europe for each morphologic sub-type of melanoma. A study of seven common malignancies diagnosed in Europe during 2000-2007 found that late stage at diagnosis alone did not explain the lower survival for melanoma of the skin in Eastern Europe.[189] In the current study, data on stage at diagnosis in Eastern European countries were only available for Russia and Slovakia, where the proportion of metastatic disease (6% and 7%) was higher than in Norway (2%) and

Denmark (3%) (data not shown). More detailed information on morphology would have helped investigate the reasons for the persistent gap in survival.

The high proportion of melanomas registered with poorly specified morphology was the major limitation of our study, because it limited the interpretation of net survival estimates for melanomas with specific morphological sub-types in all countries. Information on stage at diagnosis was also limited; complete data could have contributed disentangling the prognostic role of morphology at international level. Additionally, we were not able to control for surgical margins, a relevant prognostic factor, because these data were not available.

Our study is the largest analysis to date of survival from cutaneous melanoma. It provides, for the first time, international comparisons of population-based survival for the main histologic sub-types of melanoma in more than 50 countries. The higher frequency and poorer survival of nodular acral lentiginous melanomas in Asia and in Central and South America suggest the need for health policies in these populations that are designed to improve public awareness, and especially to facilitate earlier diagnosis and prompt access to optimal treatment.

Table 3.1: Data quality indicators, patients diagnosed with melanoma of the skin during 2000-2014, by continent and country

			Ineligible (%)				Exclusions (%)			Data quality indicators (%)			
	Calendar period	Patients submitted	Incomplete dates	In situ	Other	Eligible patients	DCO	Other	Available for analysis	MV	Non-specific morphology	Lost to follow-up	Censored
AMERICA (Central and South)		**10,610**	**3.2**	**10.7**	**5.1**	**8,599**	**1.4**	**0.3**	**8,452**	**99.0**	**62.4**	**0.5**	**6.8**
Argentinian registries	2000-2013	**1,196**	4.7	0.8	3.3	**1,092**	0.7	0.0	**1,084**	99.6	67.7	0.0	0.0
Brazilian registries	2000-2014	**2,169**	0.7	12.7	5.6	**1,758**	4.8	0.0	**1,674**	99.2	73.1	0.0	2.0
Chilean registries	2000-2012	**569**	0.0	0.0	2.5	**555**	0.2	0.0	**554**	99.5	60.1	0.0	19.3
Colombian registries	2000-2014	**1,698**	3.8	5.2	10.0	**1,376**	0.2	0.0	**1,373**	98.8	49.4	0.0	25.0
Costa Rica *	2002-2014	**1,448**	0.0	0.0	0.8	**1,436**	0.0	0.3	**1,432**	98.3	44.7	0.0	0.0
Ecuadorian registries	2000-2013	**1,483**	11.2	8.4	6.5	**1,096**	0.4	1.1	**1,080**	98.8	78.0	0.2	5.3
Guadeloupe (France)	2008-2013	**60**	0.0	13.3	0.0	**52**	0.0	0.0	**52**	100.0	0.0	0.0	71.2
Martinique (France)	2000-2012	**177**	0.0	0.0	2.8	**172**	0.0	4.7	**164**	100.0	23.2	25.0	0.0
Puerto Rico *	2000-2011	**1,810**	2.2	34.6	4.5	**1,062**	2.2	0.0	**1,039**	99.3	75.6	0.0	0.0
AMERICA (North)		**1,367,036**	**0.6**	**35.2**	**2.7**	**841,101**	**0.4**	**0.0**	**837,593**	**99.2**	**51.1**	**3.8**	**0.1**
Canadian registries	2000-2014	**94,011**	0.1	17.2	4.5	**73,496**	0.3	0.0	**73,278**	95.6	41.8	0.0	0.0
US registries	2000-2014	**1,273,025**	0.6	36.6	2.5	**767,605**	0.4	0.0	**764,315**	99.5	52.0	4.2	0.1
ASIA		**41,718**	**0.5**	**14.9**	**8.4**	**31,768**	**1.1**	**0.3**	**31,337**	**98.2**	**76.4**	**0.4**	**2.0**
Chinese registries	2003-2013	**1,733**	0.2	0.0	16.1	**1,450**	0.1	0.0	**1,449**	99.0	95.4	4.8	0.2
Cyprus *	2004-2014	**687**	3.6	3.1	6.1	**599**	1.7	0.0	**589**	99.7	32.8	0.0	53.7
Indian registries	2000-2014	**61**	0.0	0.0	8.2	**56**	0.0	7.1	**52**	98.1	94.2	3.8	5.8
Israel *	2000-2013	**18,303**	0.0	28.3	4.2	**12,348**	0.7	0.0	**12,265**	98.0	78.1	0.0	0.0
Japanese registries	2000-2014	**6,462**	1.3	10.4	22.3	**4,263**	5.7	0.0	**4,018**	95.3	88.1	0.0	2.4
Jordan *	2000-2014	**306**	0.3	1.0	27.8	**217**	0.0	1.4	**214**	99.5	84.1	14.0	0.0
Korea * ‡	2000-2014	**5,824**	0.9	0.0	0.0	**5,771**	0.0	0.0	**5,771**	98.6	74.9	0.0	0.0
Kuwait *	2000-2013	**21**	0.0	0.0	14.3	**18**	0.0	0.0	**18**	100.0	72.2	0.0	0.0
Qatar *	2000-2014	**61**	0.0	1.6	8.2	**55**	0.0	0.0	**55**	98.2	87.3	0.0	70.9
Singapore *	2000-2014	**521**	0.0	9.0	20.3	**368**	0.3	0.0	**367**	100.0	56.1	0.0	0.0
Taiwan *	2000-2014	**3,123**	0.3	3.4	0.6	**2,988**	0.0	0.0	**2,988**	100.0	64.0	0.0	0.0
Thai registries	2000-2014	**817**	0.0	0.0	5.9	**769**	0.0	9.6	**695**	99.7	95.0	0.3	3.9
Turkish registries	2000-2013	**3,799**	1.4	4.8	18.4	**2,866**	0.3	0.0	**2,856**	99.3	64.8	0.2	4.8
EUROPE		**825,792**	**0.1**	**16.8**	**5.3**	**641,814**	**0.5**	**0.1**	**637,956**	**99.3**	**34.1**	**1.7**	**3.9**
Austria *	2000-2014	**28,233**	0.0	24.2	5.9	**19,742**	2.9	0.1	**19,150**	97.5	65.4	0.0	0.0
Belgium *	2004-2014	**29,278**	0.0	22.8	2.4	**21,905**	0.0	0.0	**21,905**	99.9	36.3	1.9	0.0
Bulgaria *	2000-2014	**6,057**	0.0	0.0	0.0	**6,056**	3.0	0.0	**5,875**	100.0	73.7	0.0	0.0
Croatia *	2000-2014	**8,602**	0.0	2.0	3.5	**8,126**	3.4	0.0	**7,848**	99.9	90.4	0.0	0.0
Czech Republic *	2000-2014	**33,285**	0.0	16.0	0.5	**27,802**	0.0	0.0	**27,800**	100.0	31.8	0.0	0.0
Denmark *	2000-2014	**24,683**	0.0	0.0	0.2	**24,630**	0.0	0.0	**24,630**	99.7	21.6	0.6	0.0
Estonia *	2000-2012	**2,556**	0.0	11.8	9.9	**2,002**	0.9	0.0	**1,983**	98.4	31.1	1.2	0.0
Finland *	2000-2014	**15,873**	0.4	0.0	5.3	**14,968**	0.1	0.0	**14,949**	100.0	90.8	0.3	0.0
French registries	2000-2010	**14,962**	0.3	0.0	6.0	**14,017**	0.0	2.4	**13,677**	100.0	11.4	3.4	0.0
German registries	2000-2014	**99,363**	0.3	16.2	2.6	**80,338**	2.0	0.0	**78,713**	99.4	28.4	0.6	28.7
Gibraltar *	2000-2010	**39**	0.0	12.8	7.7	**31**	0.0	0.0	**31**	100.0	19.4	0.0	51.6
Iceland *	2000-2014	**715**	0.0	0.0	0.3	**713**	0.0	0.0	**713**	99.9	29.3	0.0	0.0
Ireland *	2000-2013	**14,683**	0.0	35.3	0.1	**9,475**	0.1	0.0	**9,470**	99.8	36.9	0.0	0.0
Italian registries	2000-2014	**53,776**	0.0	7.8	5.4	**46,634**	0.1	0.0	**46,607**	98.2	26.5	1.2	1.5
Latvia *	2000-2014	**7,521**	0.0	0.0	0.2	**7,509**	0.1	0.0	**7,503**	99.8	47.5	0.0	0.0
Lithuania *	2000-2012	**4,129**	0.0	6.3	13.4	**3,317**	0.0	0.0	**3,317**	100.0	55.8	0.0	0.9
Malta *	2000-2013	**725**	0.0	14.2	10.9	**543**	0.4	0.0	**541**	99.6	36.4	0.0	0.0
Netherlands *	2000-2014	**80,641**	0.0	20.0	6.6	**59,141**	0.0	0.1	**59,088**	100.0	13.2	1.1	0.0
Norway *	2000-2014	**31,469**	0.0	8.6	27.9	**19,997**	0.0	0.0	**19,994**	99.9	21.0	0.3	0.0
Poland *	2000-2014	**38,834**	0.0	0.2	7.3	**35,932**	0.0	0.3	**35,834**	100.0	77.1	0.0	0.0
Portugal *	2000-2014	**10,897**	0.3	11.3	2.5	**9,358**	0.0	0.0	**9,358**	99.3	54.6	2.1	0.1
Romania (Cluj)	2006-2012	**515**	0.0	3.9	11.5	**436**	0.0	0.0	**436**	98.9	50.9	0.0	0.0
Russian registries ‡	2000-2014	**5,081**	0.0	0.1	2.9	**4,927**	0.1	0.2	**4,914**	99.5	79.0	2.5	0.7
Slovakia *	2000-2010	**7,933**	0.0	11.1	7.3	**6,478**	1.4	0.0	**6,389**	100.0	21.9	0.0	0.0
Slovenia *	2000-2013	**7,442**	0.0	18.8	5.9	**5,605**	0.0	0.0	**5,603**	100.0	36.3	0.1	0.0
Spanish registries	2000-2013	**14,567**	0.5	18.8	3.2	**11,292**	0.3	0.1	**11,242**	99.7	25.8	0.6	0.1
Sweden *	2000-2014	**58,528**	0.0	30.2	6.7	**36,925**	0.0	0.0	**36,921**	100.0	20.8	0.3	0.1
Swiss registries	2000-2014	**19,030**	0.0	19.4	2.1	**14,923**	0.1	0.1	**14,893**	99.9	20.0	7.2	7.9
United Kingdom *	2000-2014	**206,375**	0.1	22.9	4.8	**148,992**	0.2	0.0	**148,572**	98.5	30.8	4.3	0.0
OCEANIA		**273,076**	**0.2**	**29.6**	**1.5**	**187,846**	**0.2**	**0.0**	**187,512**	**99.0**	**32.8**	**0.0**	**0.0**
Australia *	2000-2014	**241,133**	0.2	33.5	1.4	**156,531**	0.1	0.0	**156,302**	98.9	32.3	0.0	0.0
New Zealand *	2000-2014	**31,943**	0.0	0.0	2.0	**31,315**	0.3	0.0	**31,210**	99.7	35.3	0.0	0.0
Total		**2,518,232**	**0.4**	**28.1**	**3.5**	**1,711,128**	**0.4**	**0.0**	**1,702,850**	**99.2**	**43.2**	**2.5**	**1.6**

Table 3.2: Age-standardised 5-year net survival (NS, %): adults (15-99 years) diagnosed with melanoma of the skin by morphology and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AMERICA (CENTRAL AND SOUTH)																						
Argentina	2000-2004							**30**	*71.2*	*50.7 - 91.7*							**131**	**66.7**	57.8 - 75.5	**10**	*44.8*	*14.6 - 75.0*
	2005-2009	**31**	*98.5*	*92.3 - 100.0*	**24**	*100.0*	*85.9 - 100.0*	**76**	**58.1**	45.8 - 70.4							**320**	**62.9**	57.0 - 68.8	**44**	*72.6*	*55.6 - 89.5*
	2010-2014	**26**	**100.0**	90.0 - 100.0	**21**	*100.0*	*85.7 - 100.0*	**44**	**71.9**	61.3 - 82.6							**277**	**65.2**	58.5 - 71.9	**11**	*52.0*	*26.6 - 77.5*
Brazil	2000-2004				**18**	*100.0*	*81.5 - 100.0*	**64**	**70.6**	60.0 - 81.3	**12**	*65.9*	*36.0 - 95.7*				**298**	**76.9**	70.7 - 83.0			
	2005-2009	**41**	*84.4*	*65.0 - 100.0*	**21**	*96.5*	*77.2 - 100.0*	**78**	**68.8**	56.7 - 80.8	**10**	*32.1*	*3.4 - 60.7*				**437**	**76.3**	71.5 - 81.1	**12**	*67.8*	*40.8 - 94.8*
	2010-2014	**43**	**92.2**	78.3 - 100.0	**10**	*95.3*	*72.8 - 100.0*	**43**	**64.8**	51.5 - 78.1							**251**	**69.7**	64.4 - 75.1	**13**	*33.7*	*5.6 - 61.8*
Chile	2000-2004							**12**	*19.0*	*0.0 - 39.7*							**59**	*57.0*	*42.6 - 71.4*			
	2005-2009	**11**	*100.0*	*100.0 - 100.0*	**10**	*95.2*	*61.5 - 100.0*	**28**	*50.8*	*30.2 - 71.4*	**18**	*64.1*	*38.2 - 89.9*				**57**	*55.8*	*36.6 - 75.1*			
	2010-2014	**16**	*100.0 §*	*100.0 - 100.0*	**20**	*87.9 §*	*48.1 - 100.0*	**36**	*63.5 §*	*39.0 - 88.0*	**25**	*80.5 §*	*46.8 - 100.0*				**154**	**55.6** §	43.1 - 68.1			
Colombia	2000-2004	**29**	*85.0 §*	*70.0 - 100.0*	**16**	*100.0 §*	*85.1 - 100.0*	**53**	*41.8 §*	*24.8 - 58.8*	**45**	*81.6 §*	*62.1 - 100.0*				**196**	**54.9** §	46.9 - 62.9			
	2005-2009	**49**	*84.8 §*	*71.0 - 98.5*	**53**	*99.6 §*	*79.6 - 100.0*	**83**	**63.4** §	51.3 - 75.4	**73**	*75.6 §*	*61.4 - 89.7*				**219**	**64.7** §	57.1 - 72.4	**15**	*42.3 §*	*9.0 - 75.6*
	2010-2014				**17**	**96.0** §	86.4 - 100.0	**23**	**56.7** §	43.7 - 69.7	**21**	**70.6** §	56.9 - 84.4				**43**	**55.8** §	46.6 - 65.0	**10**	*35.0 §*	*7.2 - 62.8*
Costa Rica *	2000-2004	**47**	*100.0*	*95.8 - 100.0*	**33**	*100.0*	*100.0 - 100.0*	**34**	*72.6*	*55.2 - 90.1*	**46**	*75.3*	*59.0 - 91.5*				**104**	**75.6**	67.0 - 84.2			
	2005-2009	**71**	**86.3**	78.9 - 93.7	**51**	**97.5**	89.9 - 100.0	**63**	**58.9**	49.3 - 68.5	**70**	**74.2**	62.1 - 86.2				**183**	**69.9**	62.5 - 77.4			
	2010-2014	**90**	**83.9**	74.4 - 93.4	**103**	**93.6**	85.3 - 100.0	**49**	**58.2**	44.6 - 71.9	**65**	**70.5**	58.8 - 82.2				**318**	**75.9**	69.2 - 82.6	**23**	*88.2*	*59.1 - 100.0*
Ecuador	2000-2004							**24**	*69.1*	*46.1 - 92.2*	**12**	*47.5*	*17.8 - 77.2*				**146**	**56.2**	47.3 - 65.1			
	2005-2009							**45**	*61.0*	*44.3 - 77.7*	**12**	*27.6*	*2.9 - 52.3*				**319**	**60.1**	53.5 - 66.6	**13**	*54.7*	*23.2 - 86.3*
	2010-2014							**53**	**67.6**	52.3 - 82.9	**17**	*27.1*	*1.4 - 52.8*				**332**	**57.0**	50.2 - 63.8			
Guadeloupe *	2000-2004																					
	2005-2009																					
	2010-2014	**16**	*0.1 §*	*0.0 - 0.2*				**11**	*38.5 §*	*0.0 - 90.8*												
Martinique *	2000-2004	**12**	*92.6 §*	*76.2 - 100.0*							**14**	*78.0 §*	*42.3 - 100.0*				**28**	*92.1 §*	*76.0 - 100.0*			
	2005-2009	**18**	*100.0 §*	*89.5 - 100.0*							**20**	*84.0 §*	*62.1 - 100.0*									
	2010-2014	**18**	*100.0 §*	*90.0 - 100.0*																		
Puerto Rico *	2000-2004	**12**	*62.4*	*28.2 - 96.6*	**22**	*100.0*	*92.9 - 100.0*	**25**	*50.9*	*27.4 - 74.5*	**27**	*56.4*	*33.4 - 79.5*				**296**	**72.4**	66.4 - 78.4	**15**	*68.1*	*34.7 - 100.0*
	2005-2009	**19**	*71.9*	*50.4 - 93.3*				**36**	*38.9*	*20.8 - 56.9*	**14**	*35.3*	*7.7 - 62.8*				**340**	**79.9**	74.9 - 85.0	**11**	*57.8*	*26.7 - 88.9*
	2010-2014	**20**	*70.8*	*41.0 - 100.0*				**17**	*62.0*	*31.3 - 92.8*	**10**	*50.5*	*18.2 - 82.8*				**149**	**76.2**	68.5 - 83.9			
AMERICA (NORTH)																						
Canada	2000-2004	**6,720**	**95.1**	94.1 - 96.1	**1,219**	**97.6**	95.9 - 99.4	**2,076**	**72.1**	69.8 - 74.4	**297**	**86.1**	81.6 - 90.5	**131**	*79.6*	*69.4 - 89.8*	**8,737**	**83.9**	*82.9 - 84.9*	**661**	**75.6**	*71.7 - 79.4*
	2005-2009	**8,352**	**96.2**	95.4 - 97.0	**1,492**	**97.8**	96.4 - 99.3	**2,661**	**69.7**	67.6 - 71.8	**366**	**81.6**	77.0 - 86.2	**194**	**90.4**	85.3 - 95.5	**10,731**	**83.7**	82.9 - 84.6	**926**	**80.6**	77.6 - 83.6
	2010-2014	**10,737**	**96.8**	96.0 - 97.5	**2,301**	**96.8**	94.6 - 99.0	**3,119**	**72.3**	70.3 - 74.3	**391**	**77.9**	72.8 - 83.0	**266**	**91.8**	87.3 - 96.4	**11,139**	**84.8**	84.0 - 85.6	**762**	**80.9**	77.7 - 84.2
United States	2000-2004	**51,276**	**96.8**	96.5 - 97.2	**10,760**	**98.7**	98.0 - 99.5	**12,341**	**69.5**	68.6 - 70.5	**1,771**	**82.2**	79.9 - 84.6	**2,082**	**87.3**	85.3 - 89.3	**96,459**	**86.4**	86.1 - 86.7	**6,317**	**84.1**	82.9 - 85.3
	2005-2009	**66,456**	**97.5**	97.1 - 97.8	**13,531**	**99.3**	98.7 - 99.9	**15,772**	**71.2**	70.3 - 72.0	**2,229**	**82.6**	80.6 - 84.6	**2,442**	**89.1**	87.3 - 91.0	**111,496**	**88.2**	87.9 - 88.4	**6,469**	**85.3**	84.1 - 86.4
	2010-2014	**64,285**	**97.6**	97.3 - 97.9	**13,989**	**99.6**	98.9 - 100.0	**14,881**	**71.6**	70.7 - 72.4	**2,265**	**81.6**	79.6 - 83.7	**2,204**	**89.7**	87.8 - 91.5	**98,703**	**88.5**	88.2 - 88.8	**4,872**	**84.2**	83.0 - 85.5
ASIA																						
China	2000-2004																**110**	**36.0**	26.0 - 46.0			
	2005-2009																**538**	**44.7**	39.8 - 49.5	**15**	*63.2*	*37.1 - 89.4*
	2010-2014																**623**	**48.4**	43.2 - 53.6	**17**	*69.9*	*41.1 - 98.7*
Cyprus *	2000-2004																**15**	*84.7 §*	*59.6 - 100.0*			
	2005-2009	**72**	*96.2 §*	*88.9 - 100.0*				**59**	**73.8** §	62.8 - 84.7							**86**	**75.1** §	64.6 - 85.5	**13**	*83.6 §*	*34.4 - 100.0*
	2010-2014	**101**	**87.3** §	78.8 - 95.8				**94**	**71.4** §	59.9 - 82.9							**92**	**69.7** §	58.9 - 80.5	**20**	*63.6 §*	*36.8 - 90.5*
Israel *	2000-2004	**585**	**93.3**	90.1 - 96.5	**141**	**97.6**	92.2 - 100.0	**251**	**69.6**	63.0 - 76.2	**22**	*66.6*	*41.0 - 92.2*				**2,648**	**84.8**	83.1 - 86.5	**58**	*50.7*	*35.4 - 66.1*
	2005-2009	**407**	**94.2**	90.4 - 98.0	**110**	*97.5*	*88.4 - 100.0*	**316**	**68.9**	62.5 - 75.3	**23**	*80.8*	*51.6 - 100.0*				**3,614**	**89.3**	87.9 - 90.6	**42**	*51.1*	*34.3 - 67.9*
	2010-2014	**335**	**97.7**	93.8 - 100.0	**74**	**98.7**	93.6 - 100.0	**208**	**65.3**	57.4 - 73.2	**26**	*79.3*	*56.6 - 100.0*	**11**	*51.0*	*20.7 - 81.2*	**3,314**	**87.8**	86.3 - 89.3	**64**	**64.6**	52.9 - 76.2
Japan	2000-2004																**703**	**68.7**	64.7 - 72.7			
	2005-2009	**36**	*84.8*	*69.6 - 99.9*	**31**	*90.1*	*59.0 - 100.0*	**53**	*52.3*	*36.2 - 68.4*	**78**	*82.4*	*68.5 - 96.2*				**1,605**	**67.2**	64.3 - 70.1	**14**	*35.8*	*7.9 - 63.6*
	2010-2014	**42**	**88.4**	77.8 - 98.9	**25**	*89.0*	*57.8 - 100.0*	**57**	**56.5**	44.3 - 68.7	**71**	**93.2**	81.7 - 100.0				**999**	**68.0**	64.7 - 71.2	**14**	*46.2*	*16.5 - 75.9*
Korea *	2000-2004	**17**	*83.1*	*61.5 - 100.0*				**87**	**50.4**	39.2 - 61.6	**156**	**73.1**	64.6 - 81.6				**982**	**47.2**	43.8 - 50.6	**22**	*41.6*	*20.9 - 62.3*
	2005-2009	**27**	*84.0*	*66.5 - 100.0*	**16**	*94.2*	*72.2 - 100.0*	**113**	**38.0**	29.5 - 46.6	**247**	**80.3**	74.1 - 86.4				**1,548**	**51.3**	48.5 - 54.1	**38**	*64.2*	*47.9 - 80.5*
	2010-2014	**39**	**86.3**	63.0 - 100.0	**20**	*100.0*	*85.9 - 100.0*	**192**	**41.5**	32.1 - 50.9	**399**	**79.4**	73.9 - 84.9	**16**	*53.7*	*26.2 - 81.3*	**1,790**	**56.2**	53.5 - 59.0	**43**	**60.8**	48.5 - 73.2
Singapore *	2000-2004										**11**	*71.2*	*35.8 - 100.0*				**59**	**53.4**	40.8 - 66.1			
	2005-2009	**17**	*66.9*	*41.3 - 92.5*				**15**	*39.8*	*13.2 - 66.3*	**19**	*62.2*	*34.6 - 89.8*				**71**	**55.5**	45.2 - 65.9			
	2010-2014	**14**	*100.0*	*100.0 - 100.0*				**27**	*25.2*	*8.8 - 41.6*	**28**	*65.2*	*38.9 - 91.5*				**76**	**55.6**	43.5 - 67.6			

Table 3.2: Age-standardised 5-year net survival (NS, %): adults (15-99 years) diagnosed with melanoma of the skin by morphology and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Taiwan *	2000-2004	**10**	*93.3*	*73.8 - 100.0*				**62**	**40.9**	29.1 - 52.8	**87**	**66.9**	56.5 - 77.3				**612**	**46.1**	41.6 - 50.7	**23**	*51.0*	*26.8 - 75.1*
	2005-2009	**33**	*81.3*	*66.0 - 96.6*				**81**	**41.8**	31.4 - 52.2	**167**	**68.2**	59.4 - 77.0				**667**	**49.6**	45.2 - 54.0	**34**	*33.5*	*15.1 - 51.8*
	2010-2014	**49**	**71.4**	54.6 - 88.2				**154**	**36.7**	27.0 - 46.5	**306**	**65.6**	57.4 - 73.8				**634**	**46.7**	42.1 - 51.3	**33**	**35.9**	21.2 - 50.6
Thailand	2000-2004																**103**	**44.9**	34.4 - 55.4			
	2005-2009																**248**	**35.9** §	28.6 - 43.2			
	2010-2014																**151**	**28.0** §	21.5 - 34.4			
Turkey	2000-2004	**21**	*79.9* §	*59.2 - 100.0*	**20**	*84.8* §	*67.1 - 100.0*	**48**	*59.9* §	*42.1 - 77.7*	**10**	*61.6* §	*26.3 - 96.9*				**181**	**51.9** §	42.9 - 60.8			
	2005-2009	**67**	**77.7**	66.4 - 88.9	**58**	*97.3*	*85.8 - 100.0*	**187**	**52.3**	44.3 - 60.4	**67**	**73.8**	62.3 - 85.3				**810**	**52.5**	48.6 - 56.4	**36**	*63.2*	*45.2 - 81.3*
	2010-2014	**91**	**80.1**	68.7 - 91.5	**94**	**96.4**	90.5 - 100.0	**192**	**53.9**	46.2 - 61.6	**65**	**72.5**	60.2 - 84.9				**858**	**56.4**	52.6 - 60.1	**33**	**55.9**	41.8 - 69.9
EUROPE																						
Austria *	2000-2004	**1,433**	**98.2**	96.1 - 100.0	**258**	*97.3*	*88.3 - 100.0*	**384**	**75.0**	70.0 - 80.1	**48**	*60.9*	*45.6 - 76.1*	**11**	*70.3*	*40.7 - 99.9*	**3,306**	**77.9**	*76.3 - 79.6*	**89**	**60.2**	*48.7 - 71.7*
	2005-2009	**1,236**	**95.6**	93.3 - 97.9	**245**	**99.6**	96.7 - 100.0	**405**	**67.2**	61.7 - 72.7	**55**	*71.3*	*56.4 - 86.3*	**22**	*100.0*	*85.2 - 100.0*	**4,044**	**81.9**	*80.5 - 83.4*	**97**	**68.6**	*59.4 - 77.9*
	2010-2014	**1,522**	**94.9**	92.4 - 97.3	**290**	**98.7**	95.5 - 100.0	**383**	**62.9**	57.3 - 68.6	**54**	**72.4**	59.2 - 85.6	**23**	*100.0*	*100.0 - 100.0*	**5,180**	**87.1**	*85.8 - 88.4*	**65**	**70.5**	*59.7 - 81.2*
Belgium *	2000-2004																					
	2005-2009																					
	2010-2014	**5,590**	**94.9**	92.0 - 97.7	**725**	**98.7**	95.3 - 100.0	**940**	**77.8**	72.9 - 82.8	**190**	**94.8**	88.6 - 100.0	**43**	*74.4*	*49.2 - 99.5*	**4,128**	**89.5**	87.2 - 91.8	**250**	**86.1**	78.0 - 94.1
Bulgaria *	2000-2004	**20**	*85.0*	*45.5 - 100.0*				**151**	**46.2**	36.6 - 55.7							**1,245**	**51.6**	48.3 - 54.9	**180**	**45.4**	36.7 - 54.0
	2005-2009	**27**	*76.8*	*55.1 - 98.5*				**271**	**57.9**	50.8 - 65.0							**1,421**	**57.1**	54.1 - 60.2	**186**	**35.0**	27.2 - 42.8
	2010-2014	**90**	**86.6**	75.4 - 97.8				**379**	**64.0**	57.2 - 70.9							**1,661**	**61.6**	58.8 - 64.4	**210**	**39.9**	32.0 - 47.8
Croatia *	2000-2004																**2,174**	**66.3**	63.8 - 68.7			
	2005-2009	**39**	*90.6*	*75.2 - 100.0*				**122**	**70.4**	61.2 - 79.6							**2,622**	**74.6**	72.5 - 76.6			
	2010-2014	**288**	**89.6**	81.6 - 97.7				**174**	**58.9**	49.8 - 68.1	**25**	*67.9*	*33.9 - 100.0*				**2,298**	**77.1**	75.0 - 79.1	**57**	*80.8*	*66.6 - 95.0*
Czech Republic *	2000-2004	**2,214**	**97.0**	95.1 - 98.9	**361**	**97.9**	93.9 - 100.0	**2,016**	**71.2**	68.8 - 73.7	**53**	*86.3*	*67.5 - 100.0*	**46**	*59.1*	*41.7 - 76.5*	**2,546**	**71.3**	*69.2 - 73.4*	**507**	**77.5**	*72.6 - 82.3*
	2005-2009	**3,142**	**98.1**	96.7 - 99.6	**438**	**97.0**	93.3 - 100.0	**2,080**	**73.0**	70.6 - 75.3	**93**	**83.5**	75.2 - 91.9	**106**	**77.9**	68.8 - 87.0	**2,964**	**77.2**	75.4 - 79.1	**540**	**80.1**	75.8 - 84.3
	2010-2014	**4,082**	**98.2**	96.9 - 99.6	**442**	**99.0**	96.3 - 100.0	**2,033**	**73.0**	70.7 - 75.3	**93**	**82.3**	72.9 - 91.7	**142**	**80.2**	72.4 - 87.9	**3,335**	**78.9**	77.2 - 80.7	**567**	**81.5**	77.3 - 85.6
Denmark *	2000-2004																					
	2005-2009	**5,384**	**95.3**	94.1 - 96.4	**218**	*88.6*	*78.8 - 98.4*	**757**	**72.4**	68.8 - 76.0	**66**	**84.3**	73.9 - 94.7				**1,778**	**78.1**	75.8 - 80.3	**61**	*90.4*	*80.0 - 100.0*
	2010-2014	**8,123**	**96.0**	95.1 - 97.0	**329**	**92.1**	85.5 - 98.7	**943**	**74.8**	71.5 - 78.1	**77**	**75.3**	61.8 - 88.8	**43**	*100.0*	*87.7 - 100.0*	**1,229**	**77.1**	*74.7 - 79.5*	**69**	**90.9**	*79.9 - 100.0*
Estonia *	2000-2004	**27**	*100.0*	*93.0 - 100.0*	**28**	*100.0*	*85.5 - 100.0*	**24**	*82.7*	*58.1 - 100.0*							**109**	**71.0**	62.0 - 80.1	**410**	**66.3**	60.8 - 71.8
	2005-2009	**32**	*100.0*	*100.0 - 100.0*	**15**	*95.0*	*71.3 - 100.0*	**14**	*71.6*	*45.3 - 97.8*							**203**	**70.0**	63.4 - 76.7	**500**	**73.7**	69.2 - 78.1
	2010-2014	**28**	**100.0**	100.0 - 100.0	**11**	*100.0*	*96.1 - 100.0*	**29**	**56.2**	34.4 - 78.0	**17**	*64.0*	*17.3 - 100.0*				**305**	**82.7**	74.0 - 91.4	**207**	**78.2**	72.5 - 83.8
Finland *	2000-2004																**3,576**	**84.8**	83.3 - 86.4			
	2005-2009	**137**	**92.8**	87.0 - 98.5	**102**	*100.0*	*93.8 - 100.0*	**76**	**72.0**	62.6 - 81.5	**10**	*79.1*	*42.8 - 100.0*				**4,452**	**87.0**	85.7 - 88.3			
	2010-2014	**539**	**93.9**	89.9 - 98.0	**260**	**100.0**	97.3 - 100.0	**216**	**76.0**	69.0 - 83.1	**16**	*93.1*	*68.4 - 100.0*				**5,539**	**88.1**	86.9 - 89.3			
France	2000-2004	**2,552**	**94.6**	93.0 - 96.2	**375**	**92.7**	87.6 - 97.8	**518**	**70.1**	65.5 - 74.8	**114**	**76.5**	67.7 - 85.3	**16**	*69.6*	*37.9 - 100.0*	**565**	**82.8**	79.2 - 86.5	**352**	**87.7**	83.3 - 92.1
	2005-2009	**4,419**	**95.7**	94.5 - 96.9	**640**	**95.9**	92.9 - 99.0	**706**	**70.9**	66.5 - 75.2	**155**	**83.1**	75.2 - 91.0	**42**	*75.5*	*56.1 - 94.9*	**817**	**83.5**	79.7 - 87.4	**483**	**90.6**	87.1 - 94.2
	2010-2014	**1,109**	**94.9**	92.4 - 97.4	**115**	**94.5**	88.6 - 100.0	**158**	**74.6**	65.4 - 83.7	**38**	**82.4**	73.1 - 91.7				**167**	**83.3**	76.4 - 90.1	**62**	**89.1**	80.7 - 97.4
Germany	2000-2004	**6,566**	**99.2**	98.2 - 100.0	**1,235**	**99.4**	98.0 - 100.0	**2,415**	**74.4**	72.3 - 76.4	**319**	**85.4**	80.4 - 90.4	**39**	*91.4*	*77.2 - 100.0*	**3,734**	**83.8**	82.3 - 85.3	**481**	**78.3**	73.9 - 82.7
	2005-2009	**11,019**	**98.8**	98.1 - 99.5	**2,057**	**99.4**	97.9 - 100.0	**3,394**	**77.7**	76.0 - 79.5	**478**	**83.7**	79.4 - 88.0	**56**	*80.9*	*63.6 - 98.3*	**5,649**	**84.6**	83.4 - 85.9	**649**	**79.8**	75.9 - 83.7
	2010-2014	**11,676**	**99.0**	98.4 - 99.7	**1,990**	**99.4**	97.9 - 100.0	**3,188**	**77.2**	75.3 - 79.0	**450**	**84.7**	80.5 - 89.0	**78**	**91.6**	82.5 - 100.0	**6,095**	**86.6**	85.4 - 87.8	**625**	**82.7**	78.8 - 86.7
Iceland *	2000-2004																					
	2005-2009	**132**	**87.4**	79.7 - 95.2	**16**	*82.3*	*55.9 - 100.0*	**17**	*61.6*	*31.3 - 91.9*							**80**	*87.7*	*78.8 - 96.6*			
	2010-2014	**134**	**91.7**	85.6 - 97.8				**26**	*56.0*	*29.6 - 82.5*							**37**	**82.7**	71.1 - 94.4			
Ireland *	2000-2004																					
	2005-2009																					
	2010-2014	**1,427**	**94.5**	87.9 - 100.0	**359**	**94.3**	88.0 - 100.0	**494**	**82.9**	76.8 - 89.0	**69**	*77.3*	*58.7 - 95.8*	**48**	*83.4*	*67.0 - 99.8*	**1,121**	**85.0**	79.9 - 90.0	**61**	**90.1**	80.9 - 99.3
Italy	2000-2004	**5,044**	**94.4**	93.2 - 95.6	**435**	**98.7**	96.4 - 100.0	**1,411**	**68.5**	65.7 - 71.2	**155**	**84.1**	77.7 - 90.5	**54**	*78.0*	*65.8 - 90.3*	**4,548**	**78.9**	77.6 - 80.3	**2,515**	**79.4**	77.6 - 81.3
	2005-2009	**8,677**	**94.6**	93.8 - 95.5	**626**	**99.2**	97.6 - 100.0	**2,170**	**68.5**	66.2 - 70.8	**250**	**85.4**	80.3 - 90.6	**79**	*77.1*	*62.8 - 91.4*	**5,983**	**81.8**	80.6 - 82.9	**5,130**	**83.0**	81.8 - 84.2
	2010-2014	**3,636**	**95.2**	94.1 - 96.2	**202**	**99.3**	97.0 - 100.0	**904**	**66.4**	63.3 - 69.5	**96**	**85.0**	78.0 - 92.0	**25**	**78.9**	64.7 - 93.1	**1,768**	**79.7**	78.0 - 81.5	**2,554**	**82.8**	81.3 - 84.3
Latvia *	2000-2004	**12**	*100.0*	*76.7 - 100.0*				**36**	*44.5*	*26.3 - 62.7*							**353**	**60.7**	54.7 - 66.8	**291**	**72.7**	66.2 - 79.1
	2005-2009							**45**	*60.8*	*43.3 - 78.2*							**424**	**64.1**	58.6 - 69.6	**357**	**66.0**	59.9 - 72.1
	2010-2014							**32**	**76.6**	63.9 - 89.2							**410**	**69.8**	64.3 - 75.3	**527**	**73.2**	67.8 - 78.5
Lithuania *	2000-2004	**73**	**78.6**	67.3 - 89.9	**15**	*87.8*	*62.9 - 100.0*	**70**	**61.0**	49.8 - 72.2							**938**	**66.4**	62.8 - 70.0			
	2005-2009	**336**	**85.2**	80.1 - 90.3	**39**	*100.0*	*85.8 - 100.0*	**273**	**66.7**	60.0 - 73.4	**13**	*93.7*	*68.4 - 100.0*				**573**	**59.5**	54.8 - 64.2	**12**	*83.5*	*56.5 - 100.0*
	2010-2014	**331**	**88.3**	82.6 - 94.0	**41**	*100.0*	*100.0 - 100.0*	**226**	**65.5**	57.4 - 73.6	**13**	*77.8*	*45.1 - 100.0*				**339**	**63.3**	57.0 - 69.7			

Table 3.2: Age-standardised 5-year net survival (NS, %): adults (15-99 years) diagnosed with melanoma of the skin by morphology and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Malta *	2000-2004	**59**	*100.0*	*92.5 - 100.0*				**29**	*73.0*	*54.0 - 91.9*							**54**	**83.8**	73.8 - 93.8			
	2005-2009	**85**	**87.6**	81.1 - 94.1				**15**	*61.2*	*35.8 - 86.6*							**72**	**76.5**	68.0 - 85.1			
	2010-2014	**88**	**90.1**	81.7 - 98.5	**11**	*100.0*	*100.0 - 100.0*	**25**	*61.0*	*37.1 - 84.9*							**71**	**72.4**	62.6 - 82.2			
Netherlands *	2000-2004	**8,326**	**93.9**	92.7 - 95.0	**509**	**97.2**	93.4 - 100.0	**2,046**	**76.3**	74.1 - 78.6	**132**	**79.8**	71.9 - 87.8	**34**	*86.4*	*68.3 - 100.0*	**2,630**	**82.5**	*80.5 - 84.5*	**499**	**79.4**	*75.2 - 83.5*
	2005-2009	**12,494**	**94.7**	93.9 - 95.5	**663**	**97.9**	95.4 - 100.0	**2,473**	**73.0**	71.0 - 75.0	**138**	**80.3**	72.5 - 88.1	**60**	*76.8*	*60.4 - 93.2*	**2,781**	**83.6**	*81.9 - 85.4*	**517**	**88.0**	*84.3 - 91.8*
	2010-2014	**18,354**	**95.1**	94.4 - 95.8	**1,317**	**98.0**	95.0 - 100.0	**2,931**	**74.2**	72.2 - 76.1	**229**	**87.5**	80.9 - 94.2	**115**	**83.6**	76.4 - 90.7	**2,385**	**84.3**	82.6 - 86.1	**455**	**85.8**	81.9 - 89.8
Norway *	2000-2004	**2,780**	**93.7**	92.2 - 95.3	**158**	*100.0*	*87.0 - 100.0*	**1,103**	**74.1**	71.0 - 77.2	**40**	*93.6*	*76.3 - 100.0*	**33**	*71.9*	*49.8 - 94.1*	**967**	**78.3**	*75.2 - 81.4*	**29**	*85.1*	*56.3 - 100.0*
	2005-2009	**3,143**	**93.7**	92.3 - 95.1	**197**	*97.1*	*85.4 - 100.0*	**1,304**	**74.0**	71.2 - 76.9	**32**	*84.4*	*68.6 - 100.0*	**44**	*100.0*	*85.2 - 100.0*	**1,428**	**83.4**	*81.0 - 85.8*	**34**	*64.2*	*45.2 - 83.3*
	2010-2014	**4,853**	**94.5**	93.2 - 95.8	**266**	**97.4**	93.6 - 100.0	**1,642**	**77.2**	74.5 - 79.9	**38**	**85.5**	77.3 - 93.6	**46**	**75.9**	61.8 - 89.9	**1,798**	**87.0**	84.9 - 89.0	**59**	**76.5**	63.9 - 89.1
Poland *	2000-2004	**509**	**84.2**	79.4 - 88.9	**205**	**98.4**	94.4 - 100.0	**566**	**63.2**	58.5 - 67.9	**37**	*84.3*	*70.4 - 98.2*				**7,413**	**60.5**	59.2 - 61.8	**687**	**62.6**	58.4 - 66.8
	2005-2009	**847**	**88.9**	85.6 - 92.2	**259**	**99.0**	95.4 - 100.0	**956**	**59.0**	55.4 - 62.6	**48**	*90.1*	*77.4 - 100.0*				**9,291**	**64.9**	63.7 - 66.0	**545**	**67.0**	62.5 - 71.6
	2010-2014	**1,380**	**88.6**	85.7 - 91.6	**193**	**98.7**	94.6 - 100.0	**1,216**	**58.3**	54.8 - 61.9	**60**	**84.0**	73.5 - 94.5	**19**	*53.0*	*21.4 - 84.7*	**10,938**	**68.1**	*67.1 - 69.1*	**655**	**66.5**	*62.1 - 70.9*
Portugal	2000-2004	**323**	**92.6**	88.2 - 97.0	**81**	*100.0*	*100.0 - 100.0*	**233**	**59.2**	52.1 - 66.3	**80**	*85.9*	*74.5 - 97.3*				**1,766**	**76.2**	73.8 - 78.5	**45**	*72.1*	*56.5 - 87.6*
	2005-2009	**748**	**91.7**	88.4 - 94.9	**157**	*97.9*	*88.4 - 100.0*	**355**	**63.0**	57.2 - 68.9	**136**	**82.4**	74.2 - 90.6	**12**	*69.2*	*29.1 - 100.0*	**2,283**	**79.8**	77.9 - 81.8	**66**	*82.8*	*71.5 - 94.1*
	2010-2014	**1,214**	**88.0**	80.3 - 95.7	**151**	**97.7**	90.9 - 100.0	**425**	**75.8**	65.3 - 86.2	**107**	**69.8**	58.6 - 81.0	**15**	*45.5*	*3.4 - 87.6*	**1,064**	**81.8**	77.7 - 85.9	**92**	**74.4**	62.3 - 86.4
Romania (Cluj)	2000-2004																					
	2005-2009	**17**	*75.5*	*52.7 - 98.3*				**33**	*61.2*	*40.3 - 82.1*							**137**	**64.6**	56.1 - 73.0	**27**	*89.5*	*73.5 - 100.0*
	2010-2014	**58**	*90.0*	*80.6 - 99.3*				**53**	*61.7*	*42.4 - 81.0*							**85**	**63.3**	51.9 - 74.7	**19**	*84.0*	*57.1 - 100.0*
Russia	2000-2004							**21**	*87.9*	*64.2 - 100.0*							**943**	**62.1**	58.3 - 65.9	**377**	**70.2**	63.4 - 77.0
	2005-2009	**16**	*85.4*	*56.2 - 100.0*				**41**	*56.7*	*39.2 - 74.2*							**1,316**	**61.5**	58.3 - 64.8	**210**	**69.9**	61.7 - 78.1
	2010-2014	**16**	*86.0*	*58.9 - 100.0*				**115**	**58.8**	47.0 - 70.6							**1,623**	**66.4**	63.3 - 69.5	**216**	**66.6**	58.6 - 74.6
Slovakia *	2000-2004	**1,141**	**88.3**	85.1 - 91.5	**130**	**86.4**	77.5 - 95.3	**553**	**59.5**	54.6 - 64.4	**38**	*81.3*	*64.1 - 98.6*				**542**	**63.0**	58.1 - 67.8	**115**	**61.9**	51.8 - 72.0
	2005-2009	**1,494**	**91.0**	88.4 - 93.5	**138**	**93.5**	86.0 - 100.0	**689**	**69.3**	64.7 - 74.0	**31**	*67.4*	*46.3 - 88.5*	**11**	*100.0*	*37.5 - 100.0*	**720**	**63.5**	*58.8 - 68.2*	**77**	**48.8**	*36.1 - 61.5*
	2010-2014	**363**	**89.5**	83.5 - 95.4	**22**	**98.9**	90.9 - 100.0	**164**	**69.2**	60.2 - 78.2							**137**	**54.3**	44.3 - 64.4			
Slovenia *	2000-2004	**492**	**90.5**	86.5 - 94.6	**60**	*90.2*	*75.0 - 100.0*	**277**	**65.6**	59.4 - 71.8	**19**	*72.5*	*43.8 - 100.0*				**525**	**74.9**	70.3 - 79.4	**109**	**71.3**	61.8 - 80.8
	2005-2009	**882**	**95.1**	92.3 - 97.9	**74**	*89.6*	*76.0 - 100.0*	**284**	**71.8**	65.8 - 77.8	**18**	*78.8*	*54.0 - 100.0*				**724**	**78.5**	75.0 - 82.1	**114**	**71.5**	62.2 - 80.7
	2010-2014	**899**	**95.0**	92.1 - 97.9	**48**	**89.0**	77.0 - 100.0	**224**	**73.1**	66.6 - 79.5	**21**	**65.2**	51.1 - 79.3				**783**	**79.7**	76.0 - 83.3	**34**	**68.9**	57.1 - 80.8
Spain	2000-2004	**1,465**	**92.9**	90.3 - 95.6	**268**	**95.4**	90.8 - 100.0	**501**	**68.9**	64.3 - 73.5	**144**	**71.9**	63.0 - 80.8	**20**	*58.6*	*33.7 - 83.4*	**1,049**	**81.1**	78.3 - 84.0	**274**	**81.0**	75.2 - 86.8
	2005-2009	**1,996**	**95.3**	93.5 - 97.0	**364**	**97.8**	94.7 - 100.0	**652**	**67.3**	63.3 - 71.3	**164**	**79.0**	71.9 - 86.1	**35**	*65.5*	*46.1 - 84.9*	**1,167**	**82.8**	80.3 - 85.4	**300**	**85.6**	80.6 - 90.7
	2010-2014	**1,181**	**96.8**	94.3 - 99.3	**179**	**97.8**	93.5 - 100.0	**398**	**60.4**	54.0 - 66.8	**80**	**82.8**	74.0 - 91.5	**27**	*39.2*	*10.1 - 68.3*	**644**	**84.6**	80.5 - 88.6	**126**	**80.6**	72.3 - 88.9
Sweden *	2000-2004	**4,549**	**93.7**	92.6 - 94.9	**496**	**99.2**	96.7 - 100.0	**1,509**	**71.9**	69.0 - 74.8	**103**	**84.0**	76.5 - 91.5	**32**	*59.6*	*36.4 - 82.9*	**2,477**	**87.5**	85.8 - 89.2	**45**	*87.5*	*66.8 - 100.0*
	2005-2009	**6,319**	**95.7**	94.8 - 96.6	**732**	**99.3**	97.4 - 100.0	**2,077**	**71.4**	68.8 - 74.0	**125**	**81.1**	74.3 - 88.0	**67**	*76.7*	*61.0 - 92.4*	**2,566**	**88.9**	87.3 - 90.5	**50**	*75.6*	*57.6 - 93.6*
	2010-2014	**9,437**	**95.9**	95.1 - 96.7	**1,041**	**96.3**	92.6 - 99.9	**2,375**	**74.2**	71.8 - 76.6	**155**	**84.6**	78.4 - 90.7	**90**	**86.1**	75.1 - 97.0	**2,620**	**90.8**	89.4 - 92.3	**56**	**83.0**	71.5 - 94.5
Switzerland	2000-2004	**1,022**	**96.9**	94.6 - 99.3	**157**	*91.8*	*75.5 - 100.0*	**213**	**70.8**	62.8 - 78.7	**48**	*86.9*	*61.5 - 100.0*				**259**	**80.4**	74.6 - 86.2	**41**	*62.2*	*45.7 - 78.7*
	2005-2009	**2,134**	**97.6**	96.1 - 99.2	**369**	**98.6**	96.0 - 100.0	**442**	**69.8**	64.6 - 74.9	**132**	**90.1**	84.3 - 96.0	**23**	*78.8*	*57.5 - 100.0*	**852**	**90.2**	87.5 - 93.0	**107**	**81.8**	74.0 - 89.7
	2010-2014	**1,725**	**98.1**	96.6 - 99.5	**268**	**100.0**	97.8 - 100.0	**256**	**72.6**	66.7 - 78.5	**122**	**91.1**	85.6 - 96.5				**542**	**88.7**	85.7 - 91.6	**84**	**83.6**	75.6 - 91.7
United Kingdom *	2000-2004	**2,466**	**97.5**	95.5 - 99.5	**532**	**98.0**	94.7 - 100.0	**559**	**73.1**	68.6 - 77.6	**116**	**81.7**	73.8 - 89.5	**12**	*36.5*	*1.9 - 71.1*	**1,180**	**79.2**	76.1 - 82.2	**125**	**70.3**	61.1 - 79.5
	2005-2009	**25,047**	**97.4**	96.8 - 97.9	**3,254**	**98.0**	96.1 - 99.8	**6,925**	**74.5**	73.2 - 75.8	**714**	**79.7**	75.9 - 83.5	**225**	**83.3**	76.8 - 89.8	**17,094**	**82.1**	81.4 - 82.8	**1,189**	**84.4**	81.8 - 87.1
	2010-2014	**37,002**	**97.5**	97.1 - 98.0	**4,940**	**97.4**	95.6 - 99.3	**8,735**	**74.9**	73.7 - 76.2	**1,033**	**78.5**	74.8 - 82.1	**373**	**82.3**	75.3 - 89.3	**15,586**	**84.3**	83.6 - 85.1	**895**	**85.0**	82.1 - 87.9
OCEANIA																						
Australia *	2000-2004	**18,244**	**97.4**	96.8 - 97.9	**3,523**	**98.6**	97.5 - 99.7	**3,930**	**79.3**	77.8 - 80.8	**230**	**78.1**	71.5 - 84.6	**805**	**84.6**	81.3 - 87.8	**19,244**	**88.5**	87.9 - 89.1	**2,574**	**93.2**	91.8 - 94.7
	2005-2009	**24,151**	**97.5**	97.0 - 97.9	**5,186**	**97.9**	96.9 - 98.9	**4,574**	**79.5**	78.0 - 81.0	**274**	**82.3**	76.6 - 88.0	**918**	**84.9**	81.8 - 88.1	**17,740**	**87.9**	87.3 - 88.5	**2,384**	**93.2**	91.7 - 94.7
	2010-2014	**26,279**	**97.5**	97.1 - 98.0	**4,376**	**98.3**	97.3 - 99.2	**4,643**	**80.2**	78.6 - 81.8	**288**	**81.2**	75.6 - 86.8	**894**	**84.8**	81.4 - 88.2	**13,506**	**87.2**	86.4 - 87.9	**2,539**	**94.1**	92.6 - 95.6
New Zealand *	2000-2004	**3,633**	**96.9**	95.6 - 98.2	**563**	**94.8**	91.9 - 97.7	**889**	**75.3**	71.7 - 78.8	**68**	**90.4**	82.5 - 98.4	**105**	**79.7**	70.4 - 89.1	**3,617**	**86.3**	84.8 - 87.8	**146**	**84.9**	77.9 - 91.8
	2005-2009	**4,998**	**97.2**	96.3 - 98.2	**488**	**95.4**	92.1 - 98.8	**1,034**	**78.0**	74.7 - 81.2	**65**	**80.7**	71.2 - 90.3	**122**	**88.5**	82.3 - 94.8	**3,891**	**86.6**	85.2 - 88.0	**70**	*81.2*	*67.7 - 94.8*
	2010-2014	**5,786**	**97.9**	97.0 - 98.9	**617**	**90.0**	79.3 - 100.0	**1,232**	**77.4**	74.2 - 80.6	**100**	**77.4**	68.5 - 86.3	**134**	**89.9**	83.9 - 95.8	**3,523**	**87.0**	85.6 - 88.5	**129**	**81.6**	73.9 - 89.3

* Data with 100% coverage of the national population

[§] Survival estimate considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), ***or*** (b) registered only from a death certificate or at autopsy, ***or*** (c) registered with incomplete dates, i.e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status

Italics denote survival estimates that are not age-standardised

Table 3.3. Crude and adjusted estimates of the association (OR) between cutaneous malignant melanoma and death due to any cause, by histological subtype

	German registries		Norway		Spanish registries	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Superficial spreading	**1**	**1**	**1**	**1**	**1**	**1**
Lentigo maligna	**2.6** (2.3-3.0)	**1.4** (1.2-1.7)	**2.7** (2.3-3.2)	**1.2** (1.0-1.4)	**3.6** (2.7-4.8)	**1.6** (1.2-2.3)
Nodular	**4.6** (4.1-5.1)	**3.3** (2.9-3.7)	**3.7** (3.5-4.0)	**2.9** (2.6-3.1)	**6.5** (5.2-8.0)	**5.2** (4.1-6.5)
Acral lentiginous	**4.2** (3.4-5.3)	**2.9** (2.3-3.7)	**2.3** (1.6-3.5)	**1.8** (1.2-2.8)	**6** (4.2-8.6)	**3.4** (2.0-3.0)
Malignant melanoma, NOS	**2.1** (2.9-1.4)	**1.9** (1.7-2.2)	**2.3** (2.1-2.4)	**2** (1.8-2.1)	**2.8** (2.3-3.4)	**2.4** (2.0-3.8)

*corrected for sex, age and stage at diagnosis

Figure 3.1: Morphology distribution by continent and country, all periods combined

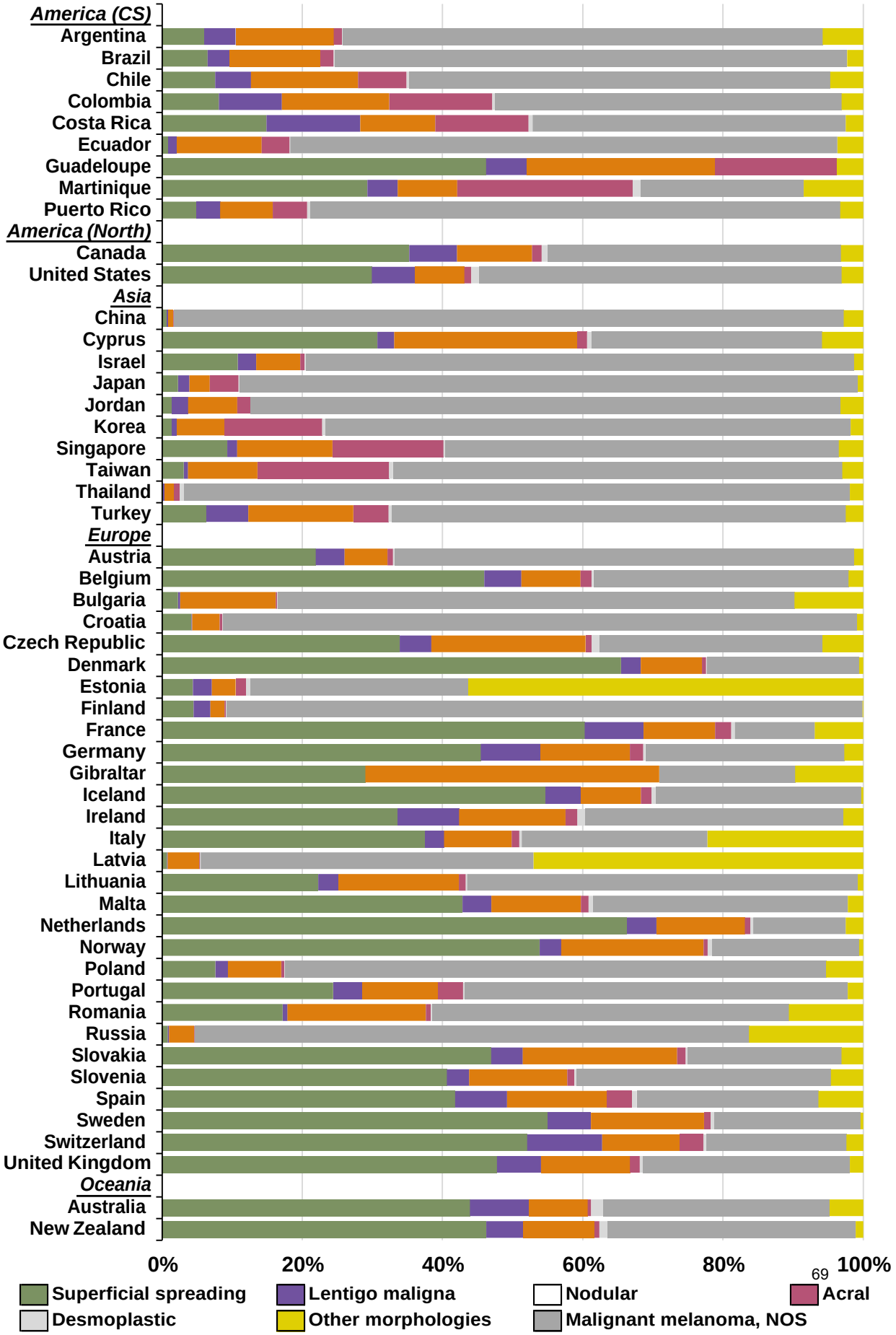
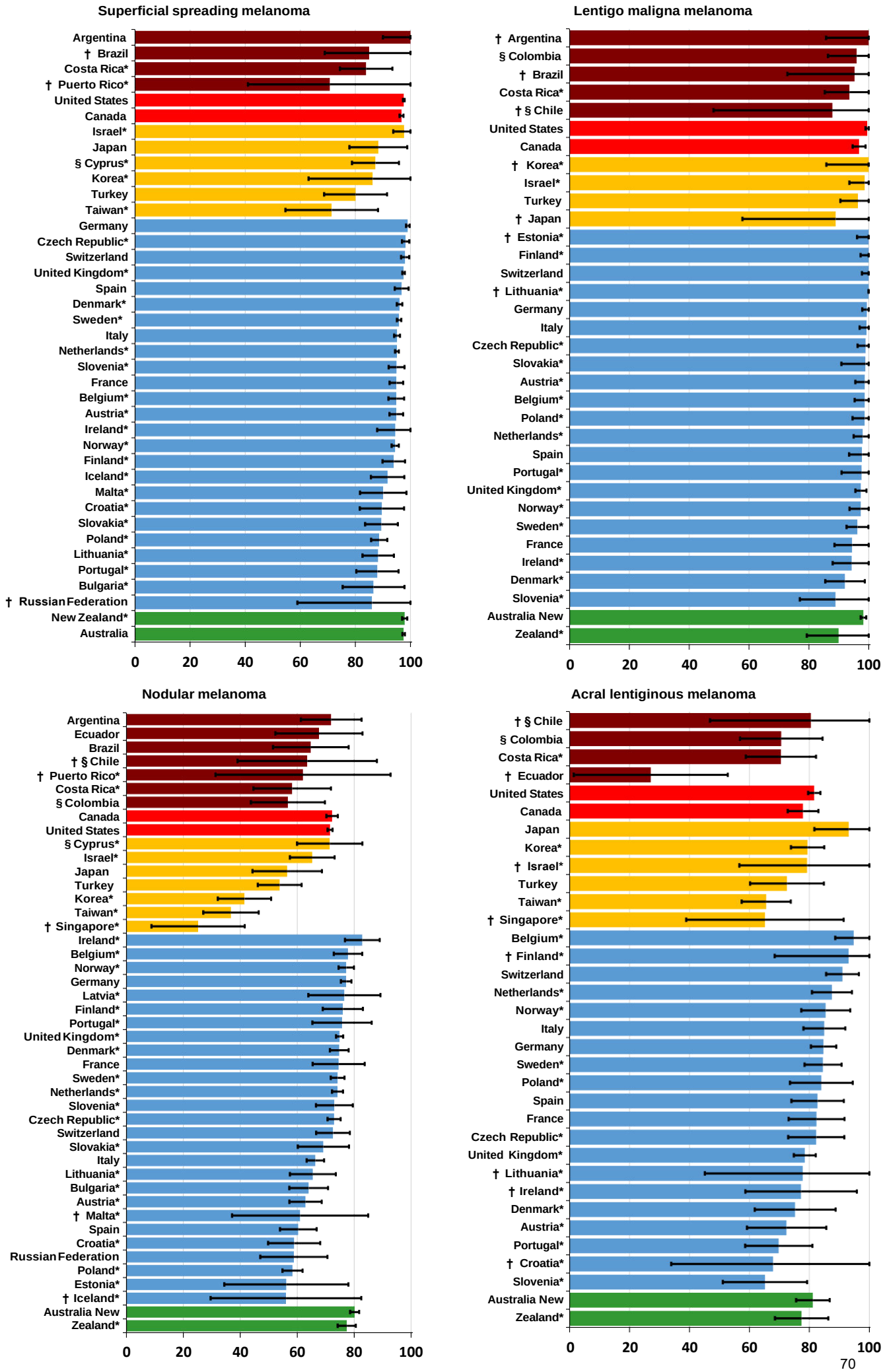


Figure 3.2: Age-standardised 5-year net survival for patients diagnosed with cutaneous melanoma during 2010- 2014 by continent, country and morphology group



* Data with 100% coverage of the national population

† Survival estimate is not age-standardised

§ Survival estimate considered less reliable

Supplementary table 3.1: Malignant melanoma of the skin - distribution by morphology group, country and calendar period of diagnosis

	Period of diagnosis	Superficial spreading melanoma		Lentigo maligna melanoma		Nodular melanoma		Acral lentiginous melanoma		Desmoplastic melanoma		Malignant melanoma, NOS		Others		Total
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
AFRICA				**1**	**0.3**	**4**	**1.1**	**11**	**3.0**	**1**	**0.3**	**169**	**45.9**	**182**	**49.5**	**368**
Algeria	2000-2004					1	**3.6**	2	**7.1**			7	**25.0**	18	**64.3**	28
	2005-2009											13	**11.0**	105	**89.0**	118
	2010-2014					3	**2.9**	1	**1.0**			42	**41.2**	56	**54.9**	102
Mauritius	2000-2004															
	2005-2009															
	2010-2014											4	**100.0**			4
Nigeria	2000-2004															
	2005-2009			1	**2.9**							32	**91.4**	2	**5.7**	35
	2010-2014									1	**2.9**	32	**94.1**	1	**2.9**	34
South Africa	2000-2004							4	**20.0**			16	**80.0**			20
	2005-2009							1	**11.1**			8	**88.9**			9
	2010-2014							3	**16.7**			15	**83.3**			18
AMERICA (CENTRAL AND SOUTH)		**675**	**8.0**	**505**	**6.0**	**1,058**	**12.5**	**618**	**7.3**	**28**	**0.3**	**5,294**	**62.6**	**274**	**3.2**	**8,452**
Argentina	2000-2004	6	**3.1**	4	**2.1**	31	**16.2**	2	**1.0**			138	**72.3**	10	**5.2**	191
(4 registries)	2005-2009	34	**6.4**	25	**4.7**	79	**14.8**	6	**1.1**	1	**0.2**	343	**64.5**	20	**8.3**	508
	2010-2014	27	**6.8**	21	**5.3**	47	**11.8**	5	**1.3**			274	**72.1**	11	**2.8**	385
Brazil	2000-2004	12	**2.3**	21	**3.9**	82	**15.4**	14	**2.6**			393	**73.7**	11	**2.1**	533
(4 registries)	2005-2009	41	**6.0**	22	**3.2**	85	**12.5**	10	**1.5**	1	**0.1**	507	**74.6**	14	**2.1**	680
	2010-2014	56	**12.1**	10	**2.2**	49	**10.6**	7	**1.5**	2	**0.4**	323	**70.1**	14	**3.0**	461
Chile	2000-2004	4	**4.3**	8	**8.5**	12	**12.8**	9	**9.6**			59	**62.8**	2	**2.1**	94
(4 registries)	2005-2009	37	**11.0**	16	**4.8**	55	**16.4**	22	**6.5**	2	**0.6**	184	**54.8**	20	**6.0**	336
	2010-2014	1	**0.8**	4	**3.2**	18	**14.5**	7	**5.6**			90	**72.6**	4	**3.2**	124
Colombia	2000-2004	29	**7.1**	19	**4.6**	55	**13.4**	50	**12.2**	1	**0.2**	244	**59.5**	12	**2.9**	410
(4 registries)	2005-2009	50	**9.5**	56	**10.6**	87	**16.5**	76	**14.4**	3	**0.6**	241	**45.6**	15	**2.8**	528
	2010-2014	32	**7.4**	49	**11.3**	68	**15.6**	76	**17.5**	2	**0.5**	193	**44.4**	15	**3.4**	435
Costa Rica	2000-2004	49	**16.4**	34	**11.4**	38	**12.7**	50	**16.7**	3	**1.0**	117	**39.1**	8	**2.7**	299
	2005-2009	74	**15.4**	55	**11.4**	66	**13.7**	75	**15.6**	2	**0.4**	205	**42.5**	5	**1.0**	482
	2010-2014	90	**13.8**	103	**15.8**	49	**7.5**	65	**10.0**	3	**0.5**	318	**48.8**	23	**3.5**	651
Ecuador	2000-2004	1	**0.5**	1	**0.5**	27	**13.7**	12	**6.1**			152	**77.2**	4	**2.0**	197
(5 registries)	2005-2009	1	**0.2**	5	**1.2**	46	**11.1**	12	**2.9**			333	**80.6**	16	**3.9**	413
	2010-2014	8	**1.7**	7	**1.5**	58	**12.3**	19	**4.0**	1	**0.2**	357	**76.0**	20	**4.3**	470
Guadeloupe (France) *	2000-2004															
	2005-2009	8	**47.1**	1	**5.9**	3	**17.6**	4	**23.5**					1	**5.9**	17
	2010-2014	16	**45.7**	2	**5.7**	11	**31.4**	5	**14.3**					1	**2.9**	35
Martinique (France) *	2000-2004	12	**18.8**	2	**3.1**	5	**7.8**	14	**21.9**	1	**1.6**	28	**43.8**	2	**3.1**	64
	2005-2009	18	**28.6**	4	**6.3**	8	**12.7**	20	**31.7**			9	**14.3**	4	**6.3**	63
	2010-2014	18	**48.6**	1	**2.7**	1	**2.7**	7	**18.9**	1	**2.7**	1	**2.7**	8	**21.6**	37
Puerto Rico *	2000-2004	12	**3.0**	22	**5.5**	25	**6.3**	27	**6.8**	3	**0.8**	296	**74.0**	15	**3.8**	400
	2005-2009	19	**4.4**	8	**1.9**	36	**8.4**	14	**3.3**	1	**0.2**	340	**79.3**	11	**2.6**	429
	2010-2014	20	**9.5**	5	**2.4**	17	**8.1**	10	**4.8**	1	**0.5**	149	**71.0**	8	**3.8**	210
AMERICA (NORTH)		**212,215**	**30.2**	**43,662**	**6.2**	**52,461**	**7.5**	**7,482**	**1.1**	**7,528**	**1.1**	**358,887**	**51.0**	**20,859**	**3.0**	**703,094**
Canada	2000-2004	6,720	**33.9**	1,219	**6.1**	2,076	**10.5**	297	**1.5**	131	**0.7**	8,737	**44.0**	661	**3.3**	19,841
(10 registries)	2005-2009	8,352	**33.8**	1,492	**6.0**	2,661	**10.8**	366	**1.5**	194	**0.8**	10,731	**43.4**	926	**3.7**	24,722
	2010-2014	10,737	**37.4**	2,301	**8.0**	3,119	**10.9**	391	**1.4**	266	**0.9**	11,139	**38.8**	762	**2.7**	28,715
United States	2000-2004	53,051	**27.4**	11,152	**5.8**	12,881	**6.6**	1,852	**1.0**	2,180	**1.1**	106,076	**54.7**	6,725	**3.5**	193,917
(41 registries)	2005-2009	69,539	**29.7**	14,051	**6.0**	16,731	**7.1**	2,336	**1.0**	2,583	**1.1**	122,226	**52.1**	6,980	**3.0**	234,446
	2010-2014	63,816	**31.7**	13,447	**6.7**	14,993	**7.4**	2,240	**1.1**	2,174	**1.1**	99,978	**49.6**	4,805	**2.4**	201,453
ASIA		**2,001**	**6.4**	**654**	**2.1**	**2,253**	**7.2**	**1,820**	**5.8**	**104**	**0.3**	**23,932**	**76.4**	**573**	**1.8**	**31,337**
China	2000-2004											196	**97.5**	5	**2.5**	201
(21 registries)	2005-2009			1	**0.2**	4	**0.7**					542	**96.4**	15	**2.7**	562
	2010-2014	9	**1.3**	4	**0.6**	6	**0.9**	2	**0.3**			645	**94.0**	20	**2.9**	686
Cyprus *	2000-2004	8	**28.6**	2	**7.1**	1	**3.6**					15	**53.6**	2	**7.1**	28
	2005-2009	72	**30.0**	8	**3.3**	59	**24.6**	2	**0.8**			86	**35.8**	13	**5.4**	240
	2010-2014	101	**31.5**	4	**1.2**	94	**29.3**	6	**1.9**	4	**1.2**	92	**28.7**	20	**6.2**	321
India	2000-2004											4	**80.0**	1	**20.0**	5
(2 registries)	2005-2009											25	**100.0**			25
	2010-2014			1	**4.5**							20	**90.9**	1	**4.5**	22
Israel *	2000-2004	585	**15.8**	141	**3.8**	251	**6.8**	22	**0.6**	7	**0.2**	2,648	**71.3**	58	**1.6**	3,712
	2005-2009	407	**9.0**	110	**2.4**	316	**7.0**	23	**0.5**	9	**0.2**	3,614	**79.9**	42	**0.9**	4,521
	2010-2014	335	**8.3**	74	**1.8**	208	**5.2**	26	**0.6**	11	**0.3**	3,314	**82.2**	64	**1.6**	4,032
Japan	2000-2004	13	**1.5**	7	**0.8**	7	**0.8**	13	**1.5**	2	**0.2**	816	**94.7**	4	**0.5**	862
(16 registries)	2005-2009	36	**2.0**	31	**1.7**	53	**2.9**	78	**4.3**	2	**0.1**	1,605	**88.2**	14	**0.8**	1,819
	2010-2014	42	**3.1**	26	**1.9**	58	**4.3**	72	**5.4**	4	**0.3**	1,120	**83.8**	15	**1.1**	1,337
Jordan *	2000-2004	1	**1.1**	1	**1.1**	6	**6.7**	3	**3.3**			75	**83.3**	4	**4.4**	90
	2005-2009			2	**2.9**	4	**5.8**	1	**1.4**			61	**88.4**	1	**1.4**	69
	2010-2014	2	**3.6**	2	**3.6**	5	**9.1**					44	**80.0**	2	**3.6**	55
Korea *	2000-2004	17	**1.3**	7	**0.5**	87	**6.8**	156	**12.2**	3	**0.2**	982	**77.1**	22	**1.7**	1,274
	2005-2009	27	**1.4**	16	**0.8**	113	**5.7**	247	**12.4**	9	**0.5**	1,548	**77.5**	38	**1.9**	1,998
	2010-2014	39	**1.6**	20	**0.8**	192	**7.7**	399	**16.0**	16	**0.6**	1,790	**71.6**	43	**1.7**	2,499
Kuwait *	2000-2004					2	**40.0**					3	**60.0**			5
	2005-2009							1	**14.3**			6	**85.7**			7
	2010-2014	1	**16.7**			1	**16.7**					4	**66.7**			6
Qatar *	2000-2004					2	**20.0**					8	**80.0**			10
	2005-2009					1	**7.1**	3	**21.4**			9	**64.3**	1	**7.1**	14
	2010-2014											31	**100.0**			31

Supplementary table 3.1: Malignant melanoma of the skin - distribution by morphology group, country and calendar period of diagnosis

	Period of diagnosis	Superficial spreading melanoma		Lentigo maligna melanoma		Nodular melanoma		Acral lentiginous melanoma		Desmoplastic melanoma		Malignant melanoma, NOS		Others		Total
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Singapore *	2000-2004	3	**3.4**	1	**1.1**	8	**9.2**	11	**12.6**	1	**1.1**	59	**67.8**	4	**4.6**	87
	2005-2009	17	**13.1**	2	**1.5**	15	**11.5**	19	**14.6**			71	**54.6**	6	**4.6**	130
	2010-2014	14	**9.3**	2	**1.3**	27	**18.0**	28	**18.7**			76	**50.7**	3	**2.0**	150
Taiwan *	2000-2004	10	**1.2**	6	**0.7**	62	**7.7**	87	**10.8**	5	**0.6**	612	**76.0**	23	**2.9**	805
	2005-2009	33	**3.3**	5	**0.5**	81	**8.1**	167	**16.8**	8	**0.8**	667	**67.0**	34	**3.4**	995
	2010-2014	49	**4.1**	7	**0.6**	154	**13.0**	306	**25.8**	5	**0.4**	634	**53.4**	33	**2.8**	1,188
Thailand	2000-2004					3	**1.8**					166	**97.1**	2	**1.2**	171
(6 registries)	2005-2009	1	**0.4**	1	**0.4**	3	**1.2**	1	**0.4**			248	**96.1**	4	**1.6**	258
	2010-2014			1	**0.4**	3	**1.1**	5	**1.9**	4	**1.5**	246	**92.5**	7	**2.6**	266
Turkey	2000-2004	21	**7.4**	20	**7.1**	48	**17.0**	10	**3.5**			181	**64.0**	3	**1.1**	283
(9 registries)	2005-2009	67	**5.4**	58	**4.7**	187	**15.2**	67	**5.4**	7	**0.6**	810	**65.7**	36	**2.9**	1,232
	2010-2014	91	**6.8**	94	**7.0**	192	**14.3**	65	**4.8**	7	**0.5**	859	**64.1**	33	**2.5**	1,341
EUROPE		**278,225**	**43.0**	**34,048**	**5.3**	**78,728**	**12.2**	**8,281**	**1.3**	**2,591**	**0.4**	**217,463**	**33.6**	**28,392**	**4.4**	**647,728**
Austria *	2000-2004	1,433	**25.9**	258	**4.7**	384	**6.9**	48	**0.9**	11	**0.2**	3,306	**59.8**	89	**1.6**	5,529
	2005-2009	1,236	**20.2**	245	**4.0**	405	**6.6**	55	**0.9**	22	**0.4**	4,044	**66.3**	97	**1.6**	6,104
	2010-2014	1,522	**20.2**	290	**3.9**	383	**5.1**	54	**0.7**	23	**0.3**	5,180	**68.9**	65	**0.9**	7,517
Belgium *	2000-2004	619	**41.5**	50	**3.3**	121	**8.1**	23	**1.5**	4	**0.3**	645	**43.2**	31	**2.1**	1,493
	2005-2009	3,852	**45.1**	380	**4.4**	785	**9.2**	146	**1.7**	25	**0.3**	3,181	**37.2**	177	**2.1**	8,546
	2010-2014	5,590	**47.1**	725	**6.1**	940	**7.9**	190	**1.6**	43	**0.4**	4,128	**34.8**	250	**2.1**	11,866
Bulgaria *	2000-2004	**20**	**1.3**	**1**	**0.1**	**151**	**9.4**	**1**	**0.1**			**1,245**	**77.9**	**180**	**11.3**	1,598
	2005-2009	**27**	**1.4**	**6**	**0.3**	**271**	**14.1**	**3**	**0.2**	**4**	**0.2**	**1,421**	**74.1**	**186**	**9.7**	1,918
	2010-2014	**90**	**3.8**	**8**	**0.3**	**379**	**16.1**	**7**	**0.3**	**4**	**0.2**	**1,661**	**70.4**	**210**	**8.9**	2,359
Croatia *	2000-2004	2	**0.1**	1	**0.0**	9	**0.4**	5	**0.2**	1	**0.0**	2,174	**99.0**	5	**0.2**	2,197
	2005-2009	39	**1.4**			122	**4.4**	3	**0.1**	1	**0.0**	2,622	**93.8**	9	**0.3**	2,796
	2010-2014	288	**10.1**	9	**0.3**	174	**6.1**	25	**0.9**	4	**0.1**	2,298	**80.5**	57	**2.0**	2,855
Czech Republic *	2000-2004	2,214	**28.6**	361	**4.7**	2,016	**26.0**	53	**0.7**	46	**0.6**	2,546	**32.9**	507	**6.5**	7,743
	2005-2009	3,142	**33.6**	438	**4.7**	2,080	**22.2**	93	**1.0**	106	**1.1**	2,964	**31.7**	540	**5.8**	9,363
	2010-2014	4,082	**38.2**	442	**4.1**	2,033	**19.0**	93	**0.9**	142	**1.3**	3,335	**31.2**	567	**5.3**	10,694
Denmark *	2000-2004	2,597	**46.8**	136	**2.5**	444	**8.0**	17	**0.3**	9	**0.2**	2,318	**41.8**	27	**0.5**	5,548
	2005-2009	5,384	**65.1**	218	**2.6**	757	**9.2**	66	**0.8**	5	**0.1**	1,778	**21.5**	61	**0.7**	8,269
	2010-2014	8,123	**75.1**	329	**3.0**	943	**8.7**	77	**0.7**	43	**0.4**	1,229	**11.4**	69	**0.6**	10,813
Estonia *	2000-2004	27	**4.4**	28	**4.6**	24	**4.0**	5	**0.8**	4	**0.7**	109	**18.0**	410	**67.5**	607
	2005-2009	32	**4.1**	15	**1.9**	14	**1.8**	8	**1.0**	5	**0.6**	203	**26.1**	500	**64.4**	777
	2010-2014	28	**4.7**	11	**1.8**	29	**4.8**	17	**2.8**	2	**0.3**	305	**50.9**	207	**34.6**	599
Finland *	2000-2004	2	**0.1**									3,576	**99.9**			3,578
	2005-2009	137	**2.9**	102	**2.1**	76	**1.6**	10	**0.2**	4	**0.1**	4,452	**93.0**	4	**0.1**	4,785
	2010-2014	539	**8.2**	260	**3.9**	216	**3.3**	16	**0.2**	8	**0.1**	5,539	**84.1**	8	**0.1**	6,586
France	2000-2004	2,552	**56.8**	375	**8.3**	518	**11.5**	114	**2.5**	16	**0.4**	565	**12.6**	352	**7.8**	4,492
(11 registries)	2005-2009	4,419	**60.9**	640	**8.8**	706	**9.7**	155	**2.1**	42	**0.6**	817	**11.3**	483	**6.7**	7,262
	2010-2014	1,265	**65.8**	140	**7.3**	176	**9.2**	46	**2.4**	7	**0.4**	180	**9.4**	109	**5.7**	1,923
Germany	2000-2004	8,389	**42.2**	1,691	**8.5**	2,691	**13.5**	387	**1.9**	49	**0.2**	6,100	**30.7**	590	**3.0**	19,897
(10 registries)	2005-2009	13,714	**45.6**	2,674	**8.9**	3,873	**12.9**	570	**1.9**	77	**0.3**	8,375	**27.8**	806	**2.7**	30,089
	2010-2014	13,691	**47.7**	2,295	**8.0**	3,539	**12.3**	513	**1.8**	87	**0.3**	7,897	**27.5**	705	**2.5**	28,727
Gibraltar *	2000-2004	4	**30.8**			4	**30.8**					4	**30.8**	1	**7.7**	13
	2005-2009	5	**29.4**			8	**47.1**					2	**11.8**	2	**11.8**	17
	2010-2014					1	**100.0**									1
Iceland *	2000-2004	124	**48.6**	13	**5.1**	18	**7.1**	7	**2.7**	1	**0.4**	92	**36.1**			255
	2005-2009	132	**52.8**	16	**6.4**	17	**6.8**	3	**1.2**	1	**0.4**	80	**32.0**	1	**0.4**	250
	2010-2014	134	**64.4**	7	**3.4**	26	**12.5**	1	**0.5**	2	**1.0**	37	**17.8**	1	**0.5**	208
Ireland *	2000-2004	771	**30.7**	184	**7.3**	418	**16.6**	36	**1.4**	20	**0.8**	1,007	**40.1**	78	**3.1**	2,514
	2005-2009	980	**29.0**	294	**8.7**	527	**15.6**	52	**1.5**	35	**1.0**	1,365	**40.4**	124	**3.7**	3,377
	2010-2014	1,427	**39.9**	359	**10.0**	494	**13.8**	69	**1.9**	48	**1.3**	1,121	**31.3**	61	**1.7**	3,579
Italy	2000-2004	5,044	**35.6**	435	**3.1**	1,411	**10.0**	155	**1.1**	54	**0.4**	4,548	**32.1**	2,515	**17.8**	14,162
(43 registries)	2005-2009	8,769	**37.8**	626	**2.7**	2,185	**9.4**	254	**1.1**	79	**0.3**	6,016	**26.0**	5,246	**22.6**	23,175
	2010-2014	3,664	**39.5**	202	**2.2**	907	**9.8**	97	**1.0**	26	**0.3**	1,773	**19.1**	2,601	**28.1**	9,270
Latvia *	2000-2004	12	**1.7**	1	**0.1**	36	**5.2**	2	**0.3**	1	**0.1**	353	**50.7**	291	**41.8**	696
	2005-2009	2	**0.2**	1	**0.1**	45	**5.4**					424	**51.1**	357	**43.1**	829
	2010-2014	4	**0.4**			32	**3.3**	1	**0.1**	2	**0.2**	410	**42.0**	527	**54.0**	976
Lithuania *	2000-2004	73	**6.6**	15	**1.4**	70	**6.3**	7	**0.6**			938	**84.7**	4	**0.4**	1,107
	2005-2009	336	**26.9**	39	**3.1**	273	**21.9**	13	**1.0**	3	**0.2**	573	**45.9**	12	**1.0**	1,249
	2010-2014	331	**34.4**	41	**4.3**	226	**23.5**	13	**1.4**	2	**0.2**	339	**35.3**	9	**0.9**	961
Malta *	2000-2004	59	**37.8**	5	**3.2**	29	**18.6**	1	**0.6**	1	**0.6**	54	**34.6**	7	**4.5**	156
	2005-2009	85	**46.2**	6	**3.3**	15	**8.2**	1	**0.5**	1	**0.5**	72	**39.1**	4	**2.2**	184
	2010-2014	88	**43.8**	11	**5.5**	25	**12.4**	4	**2.0**	1	**0.5**	71	**35.3**	1	**0.5**	201
Netherlands *	2000-2004	8,326	**58.7**	509	**3.6**	2,046	**14.4**	132	**0.9**	34	**0.2**	2,630	**18.6**	499	**3.5**	14,176
	2005-2009	12,494	**65.3**	663	**3.5**	2,473	**12.9**	138	**0.7**	60	**0.3**	2,781	**14.5**	517	**2.7**	19,126
	2010-2014	18,354	**71.2**	1,317	**5.1**	2,931	**11.4**	229	**0.9**	115	**0.4**	2,385	**9.2**	455	**1.8**	25,786
Norway *	2000-2004	2,780	**54.4**	158	**3.1**	1,103	**21.6**	40	**0.8**	33	**0.6**	967	**18.9**	29	**0.6**	5,110
	2005-2009	3,143	**50.8**	197	**3.2**	1,304	**21.1**	32	**0.5**	44	**0.7**	1,428	**23.1**	34	**0.5**	6,182
	2010-2014	4,853	**55.8**	266	**3.1**	1,642	**18.9**	38	**0.4**	46	**0.5**	1,798	**20.7**	59	**0.7**	8,702
Poland *	2000-2004	509	**5.4**	205	**2.2**	566	**6.0**	37	**0.4**	5	**0.1**	7,413	**78.7**	687	**7.3**	9,422
	2005-2009	847	**7.1**	259	**2.2**	956	**8.0**	48	**0.4**	5	**0.0**	9,291	**77.7**	545	**4.6**	11,951
	2010-2014	1,380	**9.5**	193	**1.3**	1,216	**8.4**	60	**0.4**	19	**0.1**	10,938	**75.6**	655	**4.5**	14,461
Portugal *	2000-2004	323	**12.8**	81	**3.2**	233	**9.2**	80	**3.2**	5	**0.2**	1,766	**69.7**	45	**1.8**	2,533
	2005-2009	748	**19.9**	157	**4.2**	355	**9.4**	136	**3.6**	12	**0.3**	2,283	**60.8**	66	**1.8**	3,757
	2010-2014	1,214	**39.6**	151	**4.9**	425	**13.9**	107	**3.5**	15	**0.5**	1,064	**34.7**	92	**3.0**	3,068

Supplementary table 3.1: Malignant melanoma of the skin - distribution by morphology group, country and calendar period of diagnosis

	Period of diagnosis	Superficial spreading melanoma		Lentigo maligna melanoma		Nodular melanoma		Acral lentiginous melanoma		Desmoplastic melanoma		Malignant melanoma, NOS		Others		Total
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Romania (Cluj)	2000-2004															
	2005-2009	17	**7.9**	1	**0.5**	33	**15.3**					137	**63.7**	27	**12.6**	215
	2010-2014	58	**26.2**	2	**0.9**	53	**24.0**	3	**1.4**	1	**0.5**	85	**38.5**	19	**8.6**	221
Russia	2000-2004	5	**0.4**	2	**0.1**	21	**1.6**	1	**0.1**			943	**69.9**	377	**27.9**	1,349
(3 registries)	2005-2009	16	**1.0**	5	**0.3**	41	**2.6**	1	**0.1**	1	**0.1**	1,316	**82.8**	210	**13.2**	1,590
	2010-2014	16	**0.8**	1	**0.1**	115	**5.8**	4	**0.2**			1,623	**82.2**	216	**10.9**	1,975
Slovakia *	2000-2004	1,141	**45.2**	130	**5.2**	553	**21.9**	38	**1.5**	4	**0.2**	542	**21.5**	115	**4.6**	2,523
	2005-2009	1,494	**47.3**	138	**4.4**	689	**21.8**	31	**1.0**	11	**0.3**	720	**22.8**	77	**2.4**	3,160
	2010-2014	363	**51.4**	22	**3.1**	164	**23.2**	9	**1.3**	4	**0.6**	137	**19.4**	7	**1.0**	706
Slovenia *	2000-2004	492	**33.1**	60	**4.0**	277	**18.6**	19	**1.3**	5	**0.3**	525	**35.3**	109	**7.3**	1,487
	2005-2009	882	**42.0**	74	**3.5**	284	**13.5**	18	**0.9**	4	**0.2**	724	**34.5**	114	**5.4**	2,100
	2010-2014	899	**44.6**	48	**2.4**	224	**11.1**	21	**1.0**	7	**0.3**	783	**38.8**	34	**1.7**	2,016
Spain	2000-2004	1,486	**39.2**	272	**7.2**	521	**13.8**	145	**3.8**	20	**0.5**	1,064	**28.1**	278	**7.3**	3,786
(10 registries)	2005-2009	2,024	**42.4**	370	**7.8**	676	**14.2**	166	**3.5**	36	**0.8**	1,188	**24.9**	308	**6.5**	4,768
	2010-2014	1,198	**44.4**	188	**7.0**	411	**15.2**	83	**3.1**	28	**1.0**	659	**24.4**	130	**4.8**	2,697
Sweden *	2000-2004	4,549	**49.4**	496	**5.4**	1,509	**16.4**	103	**1.1**	32	**0.3**	2,477	**26.9**	45	**0.5**	9,211
	2005-2009	6,319	**52.9**	732	**6.1**	2,077	**17.4**	125	**1.0**	67	**0.6**	2,566	**21.5**	50	**0.4**	11,936
	2010-2014	9,437	**59.8**	1,041	**6.6**	2,375	**15.1**	155	**1.0**	90	**0.6**	2,620	**16.6**	56	**0.4**	15,774
Switzerland	2000-2004	2,014	**49.3**	433	**10.6**	559	**13.7**	157	**3.8**	22	**0.5**	797	**19.5**	105	**2.6**	4,087
(9 registries)	2005-2009	2,686	**51.0**	497	**9.4**	584	**11.1**	149	**2.8**	27	**0.5**	1,191	**22.6**	135	**2.6**	5,269
	2010-2014	3,048	**55.0**	661	**11.9**	517	**9.3**	192	**3.5**	15	**0.3**	985	**17.8**	119	**2.1**	5,537
United Kingdom *	2000-2004	15,962	**39.6**	2,142	**5.3**	5,109	**12.7**	521	**1.3**	155	**0.4**	15,485	**38.4**	951	**2.4**	40,325
	2005-2009	25,047	**46.0**	3,254	**6.0**	6,925	**12.7**	714	**1.3**	225	**0.4**	17,094	**31.4**	1,189	**2.2**	54,448
	2010-2014	37,002	**54.0**	4,940	**7.2**	8,735	**12.7**	1,033	**1.5**	373	**0.5**	15,586	**22.7**	895	**1.3**	68,564
OCEANIA		**83,091**	**44.3**	**14,753**	**7.9**	**16,302**	**8.7**	**1,025**	**0.5**	**2,978**	**1.6**	**61,521**	**32.8**	**7,842**	**4.2**	**187,512**
Australia *	2000-2004	18,244	**37.6**	3,523	**7.3**	3,930	**8.1**	230	**0.5**	805	**1.7**	19,244	**39.6**	2,574	**5.3**	48,550
	2005-2009	24,151	**43.7**	5,186	**9.4**	4,574	**8.3**	274	**0.5**	918	**1.7**	17,740	**32.1**	2,384	**4.3**	55,227
	2010-2014	26,279	**50.0**	4,376	**8.3**	4,643	**8.8**	288	**0.5**	894	**1.7**	13,506	**25.7**	2,539	**4.8**	52,525
New Zealand *	2000-2004	3,633	**40.3**	563	**6.2**	889	**9.9**	68	**0.8**	105	**1.2**	3,617	**40.1**	146	**1.6**	9,021
	2005-2009	4,998	**46.9**	488	**4.6**	1,034	**9.7**	65	**0.6**	122	**1.1**	3,891	**36.5**	70	**0.7**	10,668
	2010-2014	5,786	**50.2**	617	**5.4**	1,232	**10.7**	100	**0.9**	134	**1.2**	3,523	**30.6**	129	**1.1**	11,521
Total		**576,207**	**36.5**	**93,623**	**5.9**	**150,806**	**19.1**	**19,237**	**1.2**	**13,230**	**0.0**	**667,266**	**42.3**	**58,122**	**3.7**	**1,578,482**

* Data with 100% coverage of the national population

Preface to Chapter 4

In *Research Paper 2,* I highlight the global variation in the distribution of morphological subtypes of melanoma of the skin, because countries in Asia and Central and South America show a higher proportion of the nodular and acral lentiginous subtypes. These subtypes are also characterised by the lowest five-year net survival everywhere. I underline the difficulties in early detection and diagnosis of these aggressive subtypes, their hidden location, and the low public awareness, which may help to explain the poor prognosis, even after adjustment for the main prognostic factors, i.e., sex, age and stage at diagnosis.

This chapter (*Research Paper 3*) addresses the fourth and fifth objectives of my thesis, i.e., to explain the reasons for the higher survival in women than in men, in all countries. I examine the differences in the distribution of relevant prognostic factors between men and women, i.e., age at diagnosis, anatomic location and stage at diagnosis, and I estimate five-year net survival by the main prognostic factors for both women and men, in each country.

Several studies in Europe and the United States have shown a survival advantage for women with melanoma.[80,117] A biological difference in the oestrogen receptor β expression (Erβ) has been suggested as a possible explanation. Erβ is postulated to have a protective effect against tumour formation because it reduces uncontrolled cell proliferation. The loss of Erβ expression was more pronounced in melanoma tissue than in adjacent healthy skin. It is also more pronounced in men than in women, and in post-menopausal than in pre-menopausal women.[190]

Differences in help-seeking behaviour may also play a role in the survival benefit for women. Traditionally, women tend to visit their healthcare provider more often and to perform skin checks more frequently than men. This can translate to a higher percentage of disease diagnosed at an early stage in women than in men, which could explain part of the survival gap.[83,159]

In this chapter, I show that the differences in survival between men and women are particularly pronounced in Brazil, Bulgaria, Ecuador, Lithuania, Poland, Romania, Russia and Türkiye. Overall, men with melanoma were generally older than women. Survival is lower at older ages in most countries, for both men and women. However, older age at diagnosis among men is only one of the possible explanations for the lower prognosis.

Men are more frequently diagnosed with a melanoma on the scalp or neck, which is also associated with a worse prognosis. The proportion of men diagnosed with metastatic

melanoma is also slightly higher in men than women, and five-year net survival for metastatic melanoma is substantially lower than for localised disease.

It was not possible to produce a robust international comparison of survival by morphologic subtype in both men and women, because of the high proportion of tumours coded with a non-specific morphology code (malignant melanoma, NOS, ICD-O-3 code 8720), as documented in *Research Paper 2*.

In summary, several factors contribute to explain the poorer prognosis for men with cutaneous melanoma. Men tend to be older, with a higher proportion of lesions in more lethal locations, and are more often diagnosed with metastatic disease.

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SECTION A – Student Details

Student ID Number	1704667	**Title**	Mrs
First Name(s)	Veronica		
Surname/Family Name	Di Carlo		
Thesis Title	What explains global variation in population-based survival from malignant melanoma of the skin?		
Primary Supervisor	Prof Claudia Allemani		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	British Journal of Dermatology
Please list the paper's authors in the intended authorship order:	Veronica Di Carlo, Michel P Coleman, Claudia Allemani
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Veronica Di Carlo (VDC) was the lead author of the paper. VDC built the conceptual framework of the study and designed the analysis. VDC carried out the literature review, produced the statistical analyses, tables and graphics and drafted the manuscript. Prof Michel Coleman and Prof Claudia Allemani reviewed the drafted manuscript.

SECTION E

Student Signature	[redacted]
Date	24/11/2023

Supervisor Signature	[redacted]
Date	24/11/2023

4. Sex differences in survival from melanoma of the skin: the role of age, anatomic location and stage at diagnosis: a CONCORD-3 study in 59 countries

4.1 Introduction

Over the last few decades,[191] the incidence of melanoma of the skin has increased for both men and women world-wide. In 2020, the age-standardised incidence rates reached their highest level for men in Australia (42.9 per 100,000 person-year) and for women in Denmark (33.6).[192]

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3)[64] highlighted wide disparities in five-year net survival for 18 common cancers in adults (15–99 years), including cutaneous melanoma. Age-standardised five-year net survival for adults diagnosed with melanoma during 2010–2014 was 90% or higher in the USA, Australia, New Zealand and most Nordic countries, but 60% or lower in Ecuador, China, Korea, Singapore and Taiwan. The more detailed analysis presented in Chapter 3 of the distribution of histological subtypes, and survival for each subtype, using melanoma data contributed to CONCORD-3, has shown that the frequency of more aggressive nodular and acral lentiginous melanomas is higher in Asia and in Central and South America.[193] The prognosis for these two subtypes is poorer than for superficial spreading melanoma, which partially explains the global inequalities in survival for all melanoma subtypes combined.

Population-based studies in Europe, the United States and Oceania have shown a survival advantage in women with cutaneous melanoma.[83,103,117,160,171] A biological difference in the oestrogen receptor β (Erβ) expression has been suggested as an explanation, with Erβ postulated to have a protective effect against tumour formation because it reduces uncontrolled cell proliferation. The loss of Erβ expression was more pronounced in melanoma than in adjacent healthy skin, in men than in women, and in post-menopausal than in pre-menopausal women.[194] The survival gap between men and women is therefore postulated to be less marked at older ages, because Erβ expression declines in women after the menopause.

However, there are conflicting findings about the influence of age on the sex differences in survival from melanoma. Some studies have shown an advantage only for younger women,[159,195] or for all age groups,[83,174,196] while other studies have shown gender differences in survival only for the elderly, and not for younger patients.[21,197]

A higher proportion of advanced melanoma in men than women has also been postulated as accounting for lower survival in men.[83,159] However, as with the role of age, there are conflicting results. A survival advantage for women at all stages of disease has been found in Australia, in the Netherlands and in the USA,[198-201] whereas the female survival advantage was limited to earlier stage of disease in the USA for patients diagnosed during 1992-2011.[83] No findings on this point were available from African, Asian or Latin American countries.

We set out to examine the differences in the distribution of age at diagnosis, anatomic location and stage at diagnosis for women and men diagnosed with cutaneous melanoma during 2000–2014 in the 59 countries from which population-based data were contributed to CONCORD-3. We estimated trends in age-standardised five-year net survival by sex, further stratifying by age, anatomic location and stage at diagnosis, to examine the role of each variable on the survival advantage for women.

4.2 Methods

For CONCORD-3, data were contributed by 322 population-based cancer registries in 71 countries for 37,513,025 patients diagnosed with one of 18 cancers or groups of malignancies during 2000-2014, including 2,303,095 patients with melanoma. Patients were followed up for their vital status to 31 December 2014. Data acquisition, ethical approvals and data quality control have been described.[64]

Cancer registries were invited to contribute all registrations for melanoma, defined by morphology codes in the range 8720-8790 of the International Classification of Diseases for Oncology, third revision [ICD-O-3].[46] We focused this analysis on melanomas arising in the skin (ICD-O-3 topography C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9) and scrotum (C63.2). We requested data on all melanoma registrations, regardless of tumour behaviour, whether benign (behaviour code 0), uncertain (1), *in situ* (2) or invasive (3), to obtain some indication of the intensity of diagnostic activity. However, survival analyses included only primary, invasive melanomas. Quality control procedures have been described.[202]

We examined the differences in the distribution of relevant prognostic factors between men and women, i.e., age at diagnosis, anatomic location and stage at diagnosis. To evaluate the extent to which Erβ expression may play a role in explaining the survival advantage for women, we grouped patients into five age groups, based upon reproductive age bands for women: 15-29 (adolescent and young adults), 30-44 (pre-menopausal), 45-59 (menopausal), 60-74 (post-menopausal) and 75-99 (older adults) years. The working assumption was that sex differences

in survival would be smaller or disappear in older patients, when the Erβ expression decreases in women.

Patients were grouped into five broad anatomic locations according to the ICD-O-3 classification: head and neck (topography codes C440-C444), trunk (C445), limbs (C446, C447), genital organs (C519, C609, C632, C510) and locations that were not otherwise specified, or overlapping regions (C448, C449). Within the melanomas of the head and neck, we further defined two subgroups: melanomas on the face and ears (C440-C443) and on the scalp and neck (C444). We sub-categorised melanomas located on the limbs as arising on the upper limbs and shoulder (C446) or on the lower limbs and hips (C447).

Cancer registries were invited to provide data on stage at diagnosis, using one or more classifications: the UICC Tumour-Node-Metastasis staging system, 7th edition,[36] Condensed TNM,[167] or SEER Summary Stage 2000.[107] We categorised stage into two broad groups, because of different treatment strategies: non-metastatic (TNM Stage: I, II and III; SEER Summary Stage 2000: Localised and regional) *vs.* metastatic melanoma (TNM Stage: IV; SEER Summary Stage 2000: Distant).

We examined the distribution of age at diagnosis, anatomic location and stage at diagnosis in men and women and in each country.

We estimated trends in 5-year net survival by sex, country, calendar period and age group. We also estimated survival by anatomic location for men and women in each calendar period.

We estimated net survival with the non-parametric Pohar Perme estimator,[72] using the STATA command *stns*.[164] We examined survival for patients diagnosed in each of three calendar periods: 2000-2004, 2005-2009, 2010-2014. The cohort approach was used for patients diagnosed during 2000-2004 and 2005-2009, because they had all been followed up for at least five years. We used the period approach[78] to estimate survival for patients diagnosed during 2010-2014, because five years of follow-up for vital status were not available for all patients by 31 December 2014.

Stage at diagnosis was an optional variable for CONCORD-3. Therefore, the distributions of stage at diagnosis and survival by stage were only produced for registries from which data were available for at least 70% of patients diagnosed in each calendar period. The CONCORD protocol required data on stage of disease at the time of diagnosis for patients diagnosed from 2001 onward, because the completeness of data on stage in many countries was known to be much lower before 2001.

The method of data collection for stage changed in the United States.[107] During 2001-2003, most cancer registries coded the Surveillance, Epidemiology, and End Results (SEER)

Summary Stage 2000 directly from the medical records; from 2004 onwards, all registries derived stage from 15 pathological and clinical data items, using the Collaborative Staging System.[203]

Stage-specific survival was estimated with the cohort approach for patients diagnosed during 2001–03 and 2004-2008, while the complete approach was used for 2009–2014.

To control for wide differences in background mortality between countries or geographical areas, between men and women, and over time, we constructed life tables of all-cause mortality in the general population for each country or registry by single year of age, sex, single calendar year and, where possible, by race/ethnicity (Israel, Singapore, United States, the Northern Territory in Australia, and New Zealand).

Age-standardised estimates were obtained using the International Cancer Survival Standard weights designed for cancers with broadly constant incidence by age (type 2 weights: 0.28, 0.17, 0.21, 0.20 and 0.14).[77] We did not estimate survival if fewer than ten patients were available for analysis in a given combination of anatomic location (or stage at diagnosis), sex and calendar period. If 10-49 patients were available for analysis in a given calendar period, we only estimated unstandardised survival for all ages combined. If 50 or more patients were available, we attempted to estimate survival for each age group. If a single age-specific estimate could not be obtained, we merged the data for adjacent age groups and assigned the combined estimate to both age groups before standardisation for age. If two or more age-specific estimates could not be obtained, we present only the unstandardised estimate for all ages combined. The pooled estimates for countries with more than one registry do not include data from registries for which the estimates were considered less reliable (see Table 3), unless such estimates were the only ones available for a given country.

We only comment on survival by anatomic site for countries where at least 70% of the tumours were recorded with a specific ICD-O-3 topography code (i.e., C440-447, C510, C519, C609 C632), rather than the non-specific codes C448 or C449. Comments are also restricted to reliable, age-standardised survival estimates.

4.3 Results

We obtained data on 2,303,095 adults who were diagnosed with melanoma during 2000-2014 from 284 registries in 59 countries (Table 1).

Overall, 28% of patients were diagnosed with an *in situ* melanoma. The proportion was 20% or higher in Australia, Austria, Belgium, Ireland, Israel, the Netherlands, Puerto Rico, Sweden, the UK and the US (Table 1), indicating a highly effective approach to early diagnosis. The

proportion of melanomas of benign or uncertain behaviour was particularly high in Norway (22%), highlighting intensive activity of monitoring atypical naevi and pre-malignant lesions.

Exclusion of the 716,554 melanomas with a non-invasive behaviour left 1,586,551 patients eligible for inclusion in survival analyses. We further excluded 7,139 patients (0.5%) whose melanoma was diagnosed only from a death certificate or discovered at autopsy and 908 patients (less than 0.1%) for whom the information on the vital status or the sex was unknown. Finally, 1,578,482 patients diagnosed with a primary, invasive melanoma of the skin were available for survival analysis, 99.5% of those eligible. More than 99% of these tumours were microscopically confirmed, either cytologically or histologically.

The proportion of women with melanoma ranged between 25% in China and 64% in Switzerland and the UK (proportions not shown). Women were generally younger than men in most countries (Table 2). Men diagnosed with melanoma were slightly younger than women only in Korea (61 *vs.* 64 years), Türkiye (58 *vs.* 59 years), Latvia (63 *vs.* 65 years), Lithuania (61 *vs.* 62 years) and Russia (57 *vs.* 59 years).

The anatomic distribution by sex, continent and country is presented in Figure 1. The anatomic site distribution was rather stable during 2000-2014. The trunk was the most common primary location for melanomas in men in Europe, North America, and Oceania, with proportions ranging between 31% (Ireland) and 58% (Estonia), while the lower limbs and hips were the most common primary location in women, ranging between 26% (Austria and Finland) and 40% (Ireland). In South-East Asia, the lower limbs and hips were the most common primary site for both men (range 41%-58%) and women (37%-60%).

Melanoma arising on the head and neck accounted for 22% of the lesions in men and 13% in women. Of those lesions, most were located on the face and ears (62% and 75% in men and women, respectively); the remaining tumours were located on the scalp and neck. Patients with melanomas on the face and ears were considerably older than other patients (median age at diagnosis: 71 years for face and ears; 66 for scalp and neck; 58 for truncal locations; 62 for upper limbs and shoulders; 57 lower limbs and hips). In Central and South America, we observed a slightly higher proportion of melanomas on the face and ears in men (10%-23%) and women (5-19%) than in other regions of the world.

Only 6% of all cases were recorded with lesions on overlapping regions or not otherwise specified (NOS) location. Melanoma of the skin of the genital organs in men was extremely rare, with a total of 480 cases (less than 0.01%) worldwide. Melanoma of the skin of the labia majora and vulva accounted for less than 1% of all registrations in women worldwide (5,039 patients), but the proportion was higher in China, Japan and Thailand (4%), Singapore (6%)

and Kuwait (10%). Over 60% of women with melanoma of the skin of genital organs were aged 65 years or older.

In all countries, metastatic melanoma was more frequent in men than women (Supplementary table 1). During 2009-2014, the proportion of metastatic melanoma in men ranged from 1% in the Netherlands to 23% in Thailand, while in women the proportion ranged from less than 1% in Northern Ireland, Switzerland, Norway and the Netherlands to 21% in Thailand. Overall, the proportion of metastatic disease was 5-8% higher in men than in women in Puerto Rico (12% *vs.* 6%), Türkiye (17% *vs.* 9%) and Russia (11% *vs.* 6%). No difference in stage at diagnosis between women and men was observed in Japan, Germany, Italy, the Netherlands and Norway.

Survival by sex

For patients diagnosed during 2010-2014, age-standardised 5-year net survival in men was 85% or higher in North America and Oceania, in the range 48-73% in Central and South America, 43-86% in Asia and 54-92% in Europe (Table 3). Survival in women was 92% or higher in North America and Oceania, in the range 67-81% in Central and South America, 54-89% in Asia and 69-95% in Europe.

The gap In five-year survival between men and women was from 10% to 30% in Argentina (63% *vs.* 74%), Brazil (59% *vs.*81%), Ecuador (48% *vs.* 77%), Taiwan (43% *vs.* 61%), Türkiye (53% *vs.* 70%), Latvia (65% *vs.* 77%), Lithuania (63% *vs.* 83%), Spain (81% *vs.* 92%) and all eastern European countries, with the sole exception of Czech Republic. The gap was 3% or lower in Singapore, Austria, Germany, Iceland and Switzerland.

Survival was generally higher in women than in men throughout the 15-year period 2000-2014 (Supplementary Figure 1).

Survival improved for both men and women in most countries over time. Age-standardised 5-year net survival in men increased by 10% or more in Bulgaria (from 43% in 2000-2004 to 54% in 2010-2014), Croatia (from 62% to 75%), and Estonia (from 59% to 78%). For women, substantial increases were also seen in Taiwan (from 51% to 61%), Türkiye (from 56% to 71%) and Lithuania (from 72% to 82%) (Supplementary Figure 2).

Survival by age group

In most countries, 5-year survival during 2010-2014 was higher in women than in men in all age groups, and it was progressively lower at older ages for both sexes (Table 3).

Results for the impact of age on the sex gap in survival showed striking contrasts. The gap in survival was progressively lower with increasing age in Bulgaria, Croatia, Czech Republic,

Ecuador, the Netherlands, Poland, Russia and the United States (Supplementary Figure 3). In these countries, the differences in 5-year net survival between men and women were more pronounced in younger patients (15-29 years) than older patients (75-99 years).

However, the sex gap in five-year survival did not change substantially with increasing age in Brazil, Canada, Finland, Germany, Israel, Italy or Switzerland. Further, in Australia, Belgium, Denmark, France, New Zealand, Slovakia, Spain, Sweden and the UK, the gap in survival actually widened with increasing age.

Survival by anatomic location

Head and neck

Survival for melanomas located on the scalp and neck was lower than for those located on the face and ears, for both sexes and in most countries (Figure 2). During 2010-2014, age-standardised 5-year net survival for melanomas on the face and ears was in the range 44-99% in men and 60-97% in women. For the scalp and neck, however, survival was in the range 31-90% in men and 28-94% in women.

Survival was higher in women than in men for both anatomic sites in most countries (Figure 2). In Korea, the survival advantage for women was 20% or more for melanomas located on the face and ears (44% *vs.* 67%) and on the scalp and neck (31% *vs.* 62%). In Slovakia, by contrast, five-year net survival was as low as 28% for women diagnosed during 2010-2014, the lowest in Europe. Survival was much higher in men (55%).

Trunk

For men diagnosed with a melanoma of the trunk during 2010-2014, age-standardised five-year net survival was in the range 88-93% in North America and Oceania, 66-76% in Central and South America, 42-91% in Asia and 54-95% in Europe (Figure 2). For women, it was in the range 91-95% in North America and Oceania, 75-88% in Central and South America, 52-89% in Asia and 65-95% in Europe. For most countries in Europe, and in North America and Oceania, the absolute difference between 5-year net survival between men and women was less than 5%. The survival gap was higher than 15% in Brazil (68% *vs.* 84%). Five-year net survival was lower than 55% for both men and women in Korea and Taiwan.

Upper and lower limbs

In most countries, survival from melanomas of the upper limbs and shoulders was slightly higher than for the lower limbs and hips, and it was generally higher for women than men in both anatomic locations, but the global range was very wide. During 2010-2014, age-standardised 5-year net survival for melanomas of the upper limbs and shoulders was in the

range 52-98% in men and 66-98% in women. For the lower limbs and hips, five-year survival was in the range 21-94% in men and 20-97% in women.

During 2010-2014, the survival advantage for women diagnosed with melanoma on the upper limbs and shoulders was 20% or more in Bulgaria (56% in men *vs.* 77% in women), Lithuania (66% *vs.* 92%) and Türkiye (57% *vs.* 92%); for the lower limbs and hips, it was 20% or more in Brazil (58% *vs.* 87%), Lithuania (45% *vs.* 80%), Russia (52% *vs.* 76%), Slovakia (63% *vs.* 84%), Slovenia (63% *vs.* 85%) and Taiwan (46% *vs.* 69%).

Skin of the labia majora and vulva in women; skin of the penis and scrotum in men

In 5 out of 6 countries for which it was possible to obtain age-standardised estimates, 5-year net survival for women diagnosed with melanoma of the vulva or labia majora during 2010-2014 was in the range 35-66% in women (data not shown). For men, most estimates of 5-year net survival were not age-standardised because of the small number of patients available for analysis.

Survival by stage

During 2009-2014, age-standardised 5-year net survival for non-metastatic melanoma was higher in women than in men in all countries, except in Puerto Rico (Figure 3). Five-year survival ranged between 59% (Russia) and 96% (Germany and Australia) in men and between 69% (Puerto Rico) and 98% (Germany, Northern Ireland and Australia) in women. The gap in survival between men and women diagnosed with localised disease was 10% or more in Estonia (78% *vs.* 91%), Northern Ireland (78% *vs.* 98%), Russia (59% *vs.* 78%) and Türkiye (64% *vs.* 76%). The gap was 3% or lower in the US (93% *vs.* 96%), Canada (92% *vs.* 95%), Germany (96% *vs.* 98%), Denmark (94% *vs.* 95%), Italy (90% *vs.* 93%), Spain (89% *vs.* 91%) and Australia (96% *vs.* 98%). For localised disease, it was not possible to stratify the analysis by detailed clinical stage, because this information was scant at population level.

For melanoma diagnosed at metastatic stage, however, we were only able to produce age-standardised net survival separately for men and women in 7 countries, because the incidence of metastatic melanoma is much lower than that of localised disease. Age-standardised 5-year net survival for metastatic melanoma ranged from 15% (the Netherlands) to 38% (Australia) in men, and from 16% (Canada and the Netherlands) to 46% (Germany) in women. The gap in survival between men and women was higher than 10% in Germany (30% *vs.* 46%). We observed no gap between men and women in survival from metastatic melanoma in Canada or the Netherlands.

4.4 Discussion

This study of over 1.5 million adults diagnosed with cutaneous melanoma world-wide during 2000–2014 highlights wide global differences in survival between men and women. To our knowledge, this is the largest study to date on survival trends for cutaneous melanoma by sex and other prognostic factors. Our database includes data collected with the same protocol, harmonised through complex data quality control procedures, and analysed centrally with the same statistical methods.

Consistent with previous studies in Europe[117,160] and the United States,[80] we have shown persistently higher survival in women than men in most countries, throughout the period 2000-2014. The reasons for the poorer prognosis in men are not fully understood.

Several studies have shown that men diagnosed with cutaneous melanoma are generally older than women.[83,117,174,198] This has been confirmed by our findings. In most countries, the median age at diagnosis was 7 year higher in men than in women. Older age at diagnosis is a predictor of poor survival for most tumours, including cutaneous melanoma.[103,117,160]

When examining the influence of age at diagnosis on sex differences in melanoma survival, studies have reported conflicting findings.[159,174,197] Some studies have found that survival differences between men and women were more pronounced in younger than older patients.[122] We observed similar patterns in the United States, the Netherlands, Ecuador, Croatia and most eastern European countries. These findings seem compatible with a protective role of ERβ expression in the prognosis of cutaneous melanoma, since ERβ expression is higher in younger women and declines after the menopause.

In Australia, New Zealand, Canada and most European countries, however, the sex gap in melanoma survival remained stable or even higher with increasing age at diagnosis, as shown by previous studies.[204] This result seems to contradict the hypothesis of melanoma survival as hormone-dependent. Moreover, studies on the influence of pregnancy in melanoma prognosis and clinical trials of anti-oestrogens, found no increasing risk of cutaneous melanoma among pregnant women, nor poorer survival for women diagnosed during pregnancy.[205,206] These results show insufficient evidence to support the hypothesis of melanoma as a hormone-dependent disease.

We observed differences in the anatomic distribution of the lesions between sexes. Women presented with a higher proportion of primary melanomas located on the lower limbs and hips, while men showed a higher percentage of truncal locations. Our findings confirm on a world-wide scale the results from previous studies in Europe,[20,83,117] Australia[207] and the US.[83] These

differences in the anatomic location of melanomas of the skin depends on a diverse behaviour towards sunlight exposure, in dressing and clothing style in fair-skinned men and women, particularly in Europe, North America and Oceania.[208-210] It also depends on the different distribution of melanocytic nevi by sex, with women having higher density on the legs, and males on the head and neck and trunk.[211-215] By contrast, in East and South-East Asia, the lower limbs and hips are the most common anatomic site for melanomas in both sexes. This finding reflects the higher proportion of acral lentiginous melanoma in those populations.[193]

A previous analysis of the CONCORD-3 data on melanoma has shown that the proportion of acral lentiginous melanomas was higher in in East and South-East Asia than in Europe or North America.[202] The annual report of the Japanese Skin Cancer Society estimated the proportion of acral lentiginous melanoma to be 40% of 4,239 cases diagnosed in 26 institutes in 2016.[216] This subtype usually develops in areas with little to no sun exposure, such as the palms, soles of the feet, and nail-beds, and it is generally associated with a poorer prognosis than the more common superficial spreading melanoma. This may help to explain why 5-year net survival for all histological types of melanoma combined, as is usually reported, in South-East Asia is lower in both men (range 43%-66% in 2010-2014) and women (range 54%-72%) than in other world regions.

The proportion of melanomas on the scalp and neck was higher in men than women in all countries. This anatomic location is also associated with a poor prognosis. Five-year observed survival for 51,714 patients diagnosed with cutaneous melanoma during 1992-2003 in the United States was 83% for melanoma located on the scalp and neck, and 91% for melanomas located in other sites, including the extremities, trunk, face and ears. Melanomas of the scalp and neck were also thicker than melanomas at other sites, and more often ulcerated and with positive lymph nodes.[217] We found that 5-year survival for melanomas of the scalp and neck was poorer than those at other anatomic sites, and lower than 70% for both men and women in Croatia, Spain, Bulgaria and Russia. Unfortunately, population-based cancer registries do not routinely collect data on tumour thickness, so this information was not requested in the CONCORD-3 protocol. Therefore, we were not able to estimate survival for thin and thick melanomas, separately.

Older age at diagnosis and a higher proportion of melanomas arising in unfavourable anatomic locations are to be deemed as main reasons for poorer survival in men. However, differences in health-seeking behaviour may also play a role in the survival benefit for women. Traditionally, women tend to visit their healthcare provider more often and perform skin checks more frequently than men. This can translate to a higher percentage of disease diagnosed at an early stage in women, which may explain part of the survival gap between the sexes. [218,219]

In this study, metastatic disease represented less than 10% of melanomas in both men and women in most European countries, North America and Oceania, throughout the 15 years 2000-2014. The proportion of men diagnosed with metastatic disease was higher than women in all countries, particularly in Puerto Rico, Türkiye and Russia. The higher proportion of more advanced disease could contribute to the lower survival in men than women when melanoma survival is reported for all stages of disease combined.

We found that men with melanomas of the skin were generally older than women, tend to be diagnosed with a higher proportion of lesions located on unfavourable anatomic sites, such as the scalp and neck, and with metastatic disease. Overall, women diagnosed with melanoma not only presented with a more favourable distribution of main prognostic factors, but also showed higher survival when we took into account anatomic location, age and stage.

Public health efforts to reduce the number of deaths from melanoma of the skin should focus on raising awareness of early signs of melanoma, especially among elderly in South and East Europe. The poorer prognosis for both men and women with melanoma in South-East Asia than in other world regions is seen for all ages at diagnosis. Despite the low incidence of cutaneous melanoma in Asian populations, public health policies should aim to increase awareness of melanoma among the general public, and to promote specific training in diagnosis of melanoma for clinicians. This could reduce the time between first consultation and a definitive diagnosis, which would be expected to lead to a better prognosis.

Table 4.1: Data quality indicators, patients diagnosed with melanoma of the skin during 2000-2014, by continent and country

			Ineligible (%)				Exclusions (%)			Data quality indicators (%)			
	Calendar period	Patients submitted	Incomplete dates	In situ	Other †	Eligible patients	DCO	Other ¶	Available for analysis	MV	Non-specific morphology	Lost to follow-up	Censored
AFRICA		**498**	**9.6**	**0.0**	**9.2**	**404**	**0.0**	**8.9**	**368**	**91.3**	**45.9**	**3.0**	**54.1**
Algerian registries	2000-2014	**331**	13.3	0.0	0.9	**284**	0.0	12.7	**248**	99.2	25.0	0.0	47.6
Mauritius *	2010-2012	**5**	0.0	0.0	20.0	**4**	0.0	0.0	**4**	100.0	100.0	0.0	0.0
Nigeria (Ibadan)	2005-2014	**87**	4.6	0.0	16.1	**69**	0.0	0.0	**69**	72.4	92.8	0.0	87.0
South Africa (Eastern Ca	2000-2014	**75**	0.0	0.0	37.3	**47**	0.0	0.0	**47**	76.6	83.0	23.4	44.7
AMERICA (Central and South)		**10,610**	**3.2**	**10.7**	**5.1**	**8,599**	**1.4**	**0.3**	**8,452**	**99.0**	**62.4**	**0.5**	**6.8**
Argentinian registries	2000-2013	**1,196**	4.7	0.8	3.3	**1,092**	0.7	0.0	**1,084**	99.6	67.7	0.0	0.0
Brazilian registries	2000-2014	**2,169**	0.7	12.7	5.6	**1,758**	4.8	0.0	**1,674**	99.2	73.1	0.0	2.0
Chilean registries	2000-2012	**569**	0.0	0.0	2.5	**555**	0.2	0.0	**554**	99.5	60.1	0.0	19.3
Colombian registries	2000-2014	**1,698**	3.8	5.2	10.0	**1,376**	0.2	0.0	**1,373**	98.8	49.4	0.0	25.0
Costa Rica *	2002-2014	**1,448**	0.0	0.0	0.8	**1,436**	0.0	0.3	**1,432**	98.3	44.7	0.0	0.0
Ecuadorian registries	2000-2013	**1,483**	11.2	8.4	6.5	**1,096**	0.4	1.1	**1,080**	98.8	78.0	0.2	5.3
Guadeloupe (France)	2008-2013	**60**	0.0	13.3	0.0	**52**	0.0	0.0	**52**	100.0	0.0	0.0	71.2
Martinique (France)	2000-2012	**177**	0.0	0.0	2.8	**172**	0.0	4.7	**164**	100.0	23.2	25.0	0.0
Puerto Rico *	2000-2011	**1,810**	2.2	34.6	4.5	**1,062**	2.2	0.0	**1,039**	99.3	75.6	0.0	0.0
AMERICA (North)		**1,134,825**	**0.6**	**35.2**	**2.7**	**706,357**	**0.5**	**0.0**	**703,094**	**99.2**	**51.1**	**3.8**	**0.1**
Canadian registries	2000-2014	**94,011**	0.1	17.2	4.5	**73,496**	0.3	0.0	**73,278**	95.6	41.8	0.0	0.0
US registries	2000-2014	**1,040,814**	0.6	36.0	2.6	**632,861**	0.5	0.0	**629,816**	100.0	0.0	2.6	0.1
ASIA		**41,718**	**0.5**	**14.9**	**8.4**	**31,768**	**1.1**	**0.3**	**31,337**	**98.2**	**76.4**	**0.4**	**2.0**
Chinese registries	2003-2013	**1,733**	0.2	0.0	16.1	**1,450**	0.1	0.0	**1,449**	99.0	95.4	4.8	0.2
Cyprus *	2004-2014	**687**	3.6	3.1	6.1	**599**	1.7	0.0	**589**	99.7	32.8	0.0	53.7
Indian registries	2000-2014	**61**	0.0	0.0	8.2	**56**	0.0	7.1	**52**	98.1	94.2	3.8	5.8
Israel *	2000-2013	**18,303**	0.0	28.3	4.2	**12,348**	0.7	0.0	**12,265**	98.0	78.1	0.0	0.0
Japanese registries	2000-2014	**6,462**	1.3	10.4	22.3	**4,263**	5.7	0.0	**4,018**	95.3	88.1	0.0	2.4
Jordan *	2000-2014	**306**	0.3	1.0	27.8	**217**	0.0	1.4	**214**	99.5	84.1	14.0	0.0
Korea *	2000-2014	**5,824**	0.9	0.0	0.0	**5,771**	0.0	0.0	**5,771**	98.6	74.9	0.0	0.0
Kuwait *	2000-2013	**21**	0.0	0.0	14.3	**18**	0.0	0.0	**18**	100.0	72.2	0.0	0.0
Qatar *	2000-2014	**61**	0.0	1.6	8.2	**55**	0.0	0.0	**55**	98.2	87.3	0.0	70.9
Singapore *	2000-2014	**521**	0.0	9.0	20.3	**368**	0.3	0.0	**367**	100.0	56.1	0.0	0.0
Taiwan *	2000-2014	**3,123**	0.3	3.4	0.6	**2,988**	0.0	0.0	**2,988**	100.0	64.0	0.0	0.0
Thai registries	2000-2014	**817**	0.0	0.0	5.9	**769**	0.0	9.6	**695**	99.7	95.0	0.3	3.9
Turkish registries	2000-2013	**3,799**	1.4	4.8	18.4	**2,866**	0.3	0.0	**2,856**	99.3	64.8	0.2	4.8
EUROPE		**842,368**	**0.1**	**16.8**	**5.3**	**651,577**	**0.5**	**0.1**	**647,719**	**99.3**	**34.1**	**1.7**	**3.9**
Austria *	2000-2014	**28,233**	0.0	24.2	5.9	**19,742**	2.9	0.1	**19,150**	97.5	65.4	0.0	0.0
Belgium *	2004-2014	**29,278**	0.0	22.8	2.4	**21,905**	0.0	0.0	**21,905**	99.9	36.3	1.9	0.0
Bulgaria *	2000-2014	**6,057**	0.0	0.0	0.0	**6,056**	3.0	0.0	**5,875**	100.0	73.7	0.0	0.0
Croatia *	2000-2014	**8,602**	0.0	2.0	3.5	**8,126**	3.4	0.0	**7,848**	99.9	90.4	0.0	0.0
Czech Republic *	2000-2014	**33,285**	0.0	16.0	0.5	**27,802**	0.0	0.0	**27,800**	100.0	31.8	0.0	0.0
Denmark *	2000-2014	**24,683**	0.0	0.0	0.2	**24,630**	0.0	0.0	**24,630**	99.7	21.6	0.6	0.0
Estonia *	2000-2012	**2,556**	0.0	11.8	9.9	**2,002**	0.9	0.0	**1,983**	98.4	31.1	1.2	0.0
Finland *	2000-2014	**15,873**	0.4	0.0	5.3	**14,968**	0.1	0.0	**14,949**	100.0	90.8	0.3	0.0
French registries	2000-2010	**14,962**	0.3	0.0	6.0	**14,017**	0.0	2.4	**13,677**	100.0	11.4	3.4	0.0
German registries	2000-2014	**99,363**	0.3	16.2	2.6	**80,338**	2.0	0.0	**78,713**	99.4	28.4	0.6	28.7
Gibraltar *	2000-2010	**39**	0.0	12.8	7.7	**31**	0.0	0.0	**31**	100.0	19.4	0.0	51.6
Iceland *	2000-2014	**715**	0.0	0.0	0.3	**713**	0.0	0.0	**713**	99.9	29.3	0.0	0.0
Ireland *	2000-2013	**14,683**	0.0	35.3	0.1	**9,475**	0.1	0.0	**9,470**	99.8	36.9	0.0	0.0
Italian registries	2000-2014	**53,776**	0.0	7.8	5.4	**46,634**	0.1	0.0	**46,607**	98.2	26.5	1.2	1.5
Latvia *	2000-2014	**2,507**	0.0	0.0	0.2	**2,503**	0.1	0.0	**2,501**	99.8	47.5	0.0	0.0
Lithuania *	2000-2012	**4,129**	0.0	6.3	13.4	**3,317**	0.0	0.0	**3,317**	100.0	55.8	0.0	0.9
Malta *	2000-2013	**725**	0.0	14.2	10.9	**543**	0.4	0.0	**541**	99.6	36.4	0.0	0.0
Netherlands *	2000-2014	**80,641**	0.0	20.0	6.6	**59,141**	0.0	0.1	**59,088**	100.0	13.2	1.1	0.0
Norway *	2000-2014	**31,469**	0.0	8.6	27.9	**19,997**	0.0	0.0	**19,994**	99.9	21.0	0.3	0.0
Poland *	2000-2014	**38,834**	0.0	0.2	7.3	**35,932**	0.0	0.3	**35,834**	100.0	77.1	0.0	0.0
Portugal *	2000-2014	**10,897**	0.3	11.3	2.5	**9,358**	0.0	0.0	**9,358**	99.3	54.6	2.1	0.1
Romania (Cluj)	2006-2012	**515**	0.0	3.9	11.5	**436**	0.0	0.0	**436**	98.9	50.9	0.0	0.0
Russian registries	2000-2014	**5,081**	0.0	0.1	2.9	**4,927**	0.1	0.2	**4,914**	99.5	79.0	2.5	0.7
Slovakia *	2000-2010	**7,933**	0.0	11.1	7.3	**6,478**	1.4	0.0	**6,389**	100.0	21.9	0.0	0.0
Slovenia *	2000-2013	**7,442**	0.0	18.8	5.9	**5,605**	0.0	0.0	**5,603**	100.0	36.3	0.1	0.0
Spanish registries	2000-2013	**14,567**	0.5	18.8	3.2	**11,292**	0.3	0.1	**11,242**	99.7	25.8	0.6	0.1
Sweden *	2000-2014	**58,528**	0.0	30.2	6.7	**36,925**	0.0	0.0	**36,921**	100.0	20.8	0.3	0.1
Swiss registries	2000-2014	**19,030**	0.0	19.4	2.1	**14,923**	0.1	0.1	**14,893**	99.9	20.0	7.2	7.9
United Kingdom *	2000-2014	**227,965**	0.1	22.9	4.8	**163,761**	0.2	0.0	**163,337**	98.5	30.8	4.3	0.0
OCEANIA		**273,076**	**0.2**	**29.6**	**1.5**	**187,846**	**0.2**	**0.0**	**187,512**	**99.0**	**32.8**	**0.0**	**0.0**
Australia *	2000-2014	**241,133**	0.2	33.5	1.4	**156,531**	0.1	0.0	**156,302**	98.9	32.3	0.0	0.0
New Zealand *	2000-2014	**31,943**	0.0	0.0	2.0	**31,315**	0.3	0.0	**31,210**	99.7	35.3	0.0	0.0
Total		**2,303,095**	**0.4**	**27.7**	**3.5**	**1,586,551**	**0.5**	**0.0**	**1,578,482**	**99.2**	**43.2**	**2.5**	**1.6**

Other †: records with incomplete data or for tumours that are benign (behaviour code 0), of uncertain behaviour (behavior code 1), metastatic from another organ (behavior code 6), or unknown if primary or metastatic (behavior code 9); or for patients with age outside the range 15–99 years (adults); or with a topography code that is not in the range for skin (VAR20=C440-C449), or the skin of the labia majora (C510), vulva (C519), penis (C609) or scrotum (C632).
Other ¶: tumour coded with unknown vital status; or for patients for which the sex is unknown.
MV: Microscopically verified
* Data with 100% coverage of the national population

Table 4.2: Median age at diagnosis and age distribution for men and women (15-99 years) diagnosed with melanoma of the skin during 2000-2014

		Median age	15-29		30-44		45-59		60-74		75-99	
			No.	%	No.	%	No.	%	No.	%	No.	%
AFRICA												
Algeria	**Men**	**66**	6	**3.7**	18	**11.0**	31	**19.0**	62	**38.0**	46	**28.2**
	Women	**66**	3	**3.5**	12	**14.1**	13	**15.3**	35	**41.2**	22	**25.9**
Mauritius *	**Men**	**74**					1	**25.0**	1	**25.0**	2	**50.0**
	Women											
Nigeria	**Men**	**58**			7	**21.9**	11	**34.4**	12	**37.5**	2	**6.3**
(Ibadan)	**Women**	**59**	2	**5.4**	4	**10.8**	14	**37.8**	10	**27.0**	7	**18.9**
South Africa	**Men**	**68**	1	**5.9**			3	**17.6**	7	**41.2**	6	**35.3**
(Eastern Cape)	**Women**	**62**			3	**10.0**	10	**33.3**	8	**26.7**	9	**30.0**
AMERICA (CENTRAL AND SOUTH)												
Argentina	**Men**	**62**	16	**3.2**	69	**13.6**	132	**26.0**	191	**37.7**	99	**19.5**
	Women	**59**	41	**7.1**	95	**16.5**	154	**26.7**	197	**34.1**	90	**15.6**
Brazil	**Men**	**57**	35	**4.5**	153	**19.6**	239	**30.7**	239	**30.7**	113	**14.5**
	Women	**55**	49	**5.5**	192	**21.5**	282	**31.5**	221	**24.7**	151	**16.9**
Chile	**Men**	**61**	10	**4.2**	32	**13.3**	67	**27.9**	81	**33.8**	50	**20.8**
	Women	**61**	20	**6.4**	47	**15.0**	84	**26.8**	94	**29.9**	69	**22.0**
Colombia	**Men**	**62**	13	**2.1**	75	**12.2**	183	**29.7**	200	**32.5**	145	**23.5**
	Women	**60**	34	**4.5**	116	**15.3**	210	**27.7**	256	**33.8**	141	**18.6**
Costa Rica *	**Men**	**63**	27	**3.8**	81	**11.4**	194	**27.3**	232	**32.7**	176	**24.8**
	Women	**58**	55	**7.6**	130	**18.0**	195	**27.0**	187	**25.9**	155	**21.5**
Ecuador	**Men**	**65**	17	**3.3**	49	**9.6**	132	**25.8**	175	**34.2**	138	**27.0**
	Women	**64**	23	**4.0**	67	**11.8**	148	**26.0**	162	**28.5**	169	**29.7**
Guadeloupe*	**Men**	**63**			5	**15.6**	6	**18.8**	13	**40.6**	8	**25.0**
	Women	**48**	1	**5.0**	6	**30.0**	5	**25.0**	4	**20.0**	4	**20.0**
Martinique*	**Men**	**64**	2	**2.4**	11	**13.1**	15	**17.9**	33	**39.3**	23	**27.4**
	Women	**62**	1	**1.3**	12	**15.0**	22	**27.5**	25	**31.3**	20	**25.0**
Puerto Rico*	**Men**	**66**	16	**2.9**	53	**9.7**	122	**22.3**	208	**38.0**	148	**27.1**
	Women	**63**	19	**3.9**	79	**16.1**	126	**25.6**	132	**26.8**	136	**27.6**
AMERICA (NORTH)												
Canada	**Men**	**64**	958	**2.5**	4,121	**10.6**	10,644	**27.3**	13,724	**35.2**	9,496	**24.4**
	Women	**58**	1,797	**5.2**	5,927	**17.3**	10,409	**30.3**	9,114	**26.5**	7,088	**20.6**
United States	**Men**	**64**	9,027	**2.5**	37,381	**10.4**	96,996	**27.1**	125,316	**35.0**	89,157	**24.9**
	Women	**56**	18,862	**6.9**	52,781	**19.4**	80,579	**29.6**	67,973	**25.0**	51,744	**19.0**
ASIA												
China	**Men**	**66**	24	**3.3**	67	**9.3**	186	**25.8**	265	**36.8**	178	**24.7**
	Women	**64**	22	**3.0**	76	**10.4**	201	**27.6**	263	**36.1**	167	**22.9**
Cyprus*	**Men**	**63**	14	**4.7**	33	**11.1**	68	**23.0**	112	**37.8**	69	**23.3**
	Women	**56**	11	**3.8**	57	**19.5**	96	**32.8**	83	**28.3**	46	**15.7**
India	**Men**	**64**					7	**36.8**	8	**42.1**	4	**21.1**
	Women	**60**	2	**6.1**	5	**15.2**	8	**24.2**	11	**33.3**	7	**21.2**
Israel*	**Men**	**63**	231	**3.6**	769	**12.1**	1,706	**26.8**	2,203	**34.6**	1,452	**22.8**
	Women	**60**	327	**5.5**	938	**15.9**	1,591	**26.9**	1,734	**29.4**	1,314	**22.3**
Japan	**Men**	**67**	50	**2.6**	170	**8.7**	409	**20.9**	748	**38.3**	576	**29.5**
	Women	**68**	72	**3.5**	232	**11.2**	374	**18.1**	621	**30.1**	766	**37.1**
Korea*	**Men**	**61**	75	**2.7**	330	**11.9**	849	**30.6**	1,074	**38.7**	446	**16.1**
	Women	**64**	76	**2.5**	364	**12.1**	776	**25.9**	1,096	**36.6**	685	**22.9**
Kuwait *	**Men**	**66**			1	**12.5**	2	**25.0**	2	**25.0**	3	**37.5**
	Women	**51**	2	**20.0**	2	**20.0**	2	**20.0**	2	**20.0**	2	**20.0**

Table 4.2: Median age at diagnosis and age distribution for men and women (15-99 years) diagnosed with melanoma of the skin during 2000-2014

		Median age	15-29		30-44		45-59		60-74		75-99	
			No.	%	No.	%	No.	%	No.	%	No.	%
Qatar *	**Men**	**53**	2	**4.9**	10	**24.4**	18	**43.9**	11	**26.8**		
	Women	**43**			7	**50.0**	5	**35.7**	2	**14.3**		
Singapore*	**Men**	**60**	6	**3.2**	22	**11.8**	61	**32.6**	60	**32.1**	38	**20.3**
	Women	**60**	6	**3.3**	34	**18.9**	50	**27.8**	43	**23.9**	47	**26.1**
Taiwan*	**Men**	**68**	46	**2.8**	129	**7.9**	339	**20.7**	548	**33.5**	572	**35.0**
	Women	**64**	58	**4.3**	158	**11.7**	347	**25.6**	451	**33.3**	340	**25.1**
Thailand	**Men**	**64**	10	**3.2**	31	**10.1**	80	**26.0**	123	**39.9**	64	**20.8**
	Women	**60**	15	**3.9**	50	**12.9**	127	**32.8**	135	**34.9**	60	**15.5**
Turkey	**Men**	**58**	96	**6.3**	263	**17.3**	459	**30.2**	499	**32.9**	201	**13.2**
	Women	**59**	82	**6.1**	219	**16.4**	382	**28.6**	400	**29.9**	255	**19.1**
EUROPE												
Austria*	**Men**	**63**	451	**4.6**	1,457	**15.0**	2,343	**24.1**	3,408	**35.0**	2,074	**21.3**
	Women	**59**	655	**7.0**	1,847	**19.6**	2,291	**24.3**	2,397	**25.5**	2,227	**23.6**
Belgium*	**Men**	**60**	353	**4.0**	1,445	**16.3**	2,491	**28.1**	2,763	**31.1**	1,827	**20.6**
	Women	**55**	910	**7.0**	2,981	**22.9**	3,670	**28.2**	3,010	**23.1**	2,455	**18.8**
Bulgaria*	**Men**	**63**	85	**2.8**	374	**12.4**	803	**26.6**	1,131	**37.5**	622	**20.6**
	Women	**62**	99	**3.5**	446	**15.6**	754	**26.4**	972	**34.0**	589	**20.6**
Croatia*	**Men**	**62**	124	**3.1**	501	**12.6**	1,121	**28.2**	1,531	**38.6**	694	**17.5**
	Women	**61**	137	**3.5**	549	**14.2**	1,100	**28.4**	1,275	**32.9**	816	**21.0**
Czech Republic*	**Men**	**64**	391	**2.8**	1,505	**10.6**	3,667	**25.9**	5,484	**38.8**	3,094	**21.9**
	Women	**60**	700	**5.1**	2,127	**15.6**	3,781	**27.7**	4,248	**31.1**	2,803	**20.5**
Denmark*	**Men**	**62**	428	**3.8**	1,555	**13.9**	2,807	**25.0**	4,210	**37.6**	2,211	**19.7**
	Women	**56**	1,050	**7.8**	3,039	**22.6**	3,519	**26.2**	3,509	**26.1**	2,302	**17.2**
Estonia*	**Men**	**63**	25	**3.4**	113	**15.5**	172	**23.5**	266	**36.4**	155	**21.2**
	Women	**63**	75	**6.0**	188	**15.0**	285	**22.8**	430	**34.3**	274	**21.9**
Finland*	**Men**	**64**	160	**2.1**	695	**9.1**	1,945	**25.5**	3,024	**39.6**	1,810	**23.7**
	Women	**63**	322	**4.4**	985	**13.5**	1,815	**24.8**	2,288	**31.3**	1,905	**26.0**
France	**Men**	**61**	245	**3.9**	964	**15.2**	1,711	**26.9**	2,104	**33.1**	1,336	**21.0**
	Women	**58**	423	**5.8**	1,469	**20.1**	2,057	**28.1**	1,807	**24.7**	1,561	**21.3**
Germany	**Men**	**65**	1,094	**2.8**	4,349	**11.2**	8,859	**22.9**	16,692	**43.1**	7,754	**20.0**
	Women	**60**	2,448	**6.1**	7,516	**18.8**	9,851	**24.6**	11,998	**30.0**	8,152	**20.4**
Gibraltar *	**Men**	**63**			2	**11.8**	4	**23.5**	8	**47.1**	3	**17.6**
	Women	**64**			2	**14.3**	4	**28.6**	3	**21.4**	5	**35.7**
Iceland*	**Men**	**59**	25	**8.7**	45	**15.7**	75	**26.1**	83	**28.9**	59	**20.6**
	Women	**47**	74	**17.4**	121	**28.4**	128	**30.0**	54	**12.7**	49	**11.5**
Ireland*	**Men**	**63**	193	**4.8**	577	**14.3**	971	**24.1**	1,360	**33.8**	924	**23.0**
	Women	**59**	372	**6.8**	1,078	**19.8**	1,275	**23.4**	1,472	**27.0**	1,248	**22.9**
Italy	**Men**	**61**	872	**3.7**	4,055	**17.3**	5,992	**25.6**	8,074	**34.4**	4,449	**19.0**
	Women	**56**	1,462	**6.3**	5,593	**24.1**	5,819	**25.1**	5,901	**25.5**	4,390	**19.0**
Latvia*	**Men**	**63**	22	**2.4**	112	**12.4**	235	**26.0**	342	**37.8**	193	**21.3**
	Women	**65**	68	**4.3**	170	**10.6**	356	**22.3**	590	**36.9**	413	**25.9**
Lithuania*	**Men**	**61**	54	**4.5**	171	**14.3**	344	**28.7**	417	**34.8**	213	**17.8**
	Women	**62**	65	**3.1**	289	**13.6**	584	**27.6**	707	**33.4**	473	**22.3**
Malta*	**Men**	**61**	16	**6.6**	35	**14.3**	65	**26.6**	82	**33.6**	46	**18.9**
	Women	**54**	22	**7.4**	67	**22.6**	92	**31.0**	77	**25.9**	39	**13.1**
Netherlands*	**Men**	**60**	864	**3.3**	4,147	**15.8**	7,944	**30.2**	9,221	**35.0**	4,153	**15.8**
	Women	**55**	1,929	**5.9**	7,371	**22.5**	9,985	**30.5**	8,361	**25.5**	5,113	**15.6**

Table 4.2: Median age at diagnosis and age distribution for men and women (15-99 years) diagnosed with melanoma of the skin during 2000-2014

		Median age	15-29		30-44		45-59		60-74		75-99	
			No.	%	No.	%	No.	%	No.	%	No.	%
Norway*	**Men**	**64**	161	**1.7**	1,033	**10.8**	2,405	**25.1**	3,545	**37.0**	2,439	**25.5**
	Women	**61**	401	**3.9**	1,741	**16.7**	2,707	**26.0**	3,020	**29.0**	2,542	**24.4**
Poland*	**Men**	**61**	596	**3.6**	2,173	**13.1**	5,023	**30.4**	5,920	**35.8**	2,820	**17.1**
	Women	**59**	1,077	**5.6**	3,005	**15.6**	5,599	**29.0**	5,943	**30.8**	3,678	**19.1**
Portugal*	**Men**	**63**	166	**4.1**	567	**14.0**	1,016	**25.1**	1,440	**35.6**	861	**21.3**
	Women	**61**	254	**4.8**	926	**17.4**	1,344	**25.3**	1,548	**29.2**	1,236	**23.3**
Romania (Cluj)	**Men**	**61**	7	**3.4**	36	**17.3**	57	**27.4**	76	**36.5**	32	**15.4**
	Women	**57**	15	**6.6**	40	**17.5**	72	**31.6**	74	**32.5**	27	**11.8**
Russia	**Men**	**57**	109	**6.1**	299	**16.6**	588	**32.7**	594	**33.0**	210	**11.7**
	Women	**59**	131	**4.2**	485	**15.6**	966	**31.0**	1,015	**32.6**	517	**16.6**
Slovakia*	**Men**	**61**	131	**4.3**	358	**11.8**	950	**31.2**	1,097	**36.1**	506	**16.6**
	Women	**59**	126	**3.8**	562	**16.8**	1,033	**30.9**	1,017	**30.4**	609	**18.2**
Slovenia*	**Men**	**60**	92	**3.4**	399	**14.8**	800	**29.7**	973	**36.1**	432	**16.0**
	Women	**58**	157	**5.4**	545	**18.7**	799	**27.5**	823	**28.3**	583	**20.1**
Spain	**Men**	**61**	258	**5.1**	853	**16.8**	1,271	**25.0**	1,552	**30.5**	1,154	**22.7**
	Women	**57**	414	**6.7**	1,304	**21.2**	1,628	**26.5**	1,573	**25.6**	1,235	**20.1**
Sweden*	**Men**	**66**	380	**2.1**	1,934	**10.5**	4,055	**22.1**	6,963	**37.9**	5,033	**27.4**
	Women	**61**	763	**4.1**	3,099	**16.7**	4,676	**25.2**	5,391	**29.1**	4,627	**24.9**
Switzerland	**Men**	**65**	214	**2.8**	964	**12.8**	1,718	**22.9**	2,698	**35.9**	1,915	**25.5**
	Women	**59**	452	**6.1**	1,457	**19.7**	1,847	**25.0**	1,981	**26.8**	1,647	**22.3**
United Kingdom*	**Men**	**64**	2,499	**3.3**	9,693	**12.6**	18,101	**23.6**	27,276	**35.6**	19,076	**24.9**
	Women	**59**	5,146	**5.9**	16,037	**18.5**	22,269	**25.7**	23,606	**27.2**	19,634	**22.6**
OCEANIA												
Australia*	**Men**	**64**	2,719	**3.0**	9,967	**11.0**	23,020	**25.4**	31,971	**35.3**	22,879	**25.3**
	Women	**59**	3,501	**5.3**	11,425	**17.4**	18,466	**28.1**	18,087	**27.5**	14,267	**21.7**
New Zealand*	**Men**	**65**	342	**2.1**	1,560	**9.5**	4,174	**25.5**	6,080	**37.2**	4,189	**25.6**
	Women	**60**	586	**3.9**	2,390	**16.1**	4,170	**28.1**	4,346	**29.2**	3,373	**22.7**

* Data with 100% coverage of the national population

Table 4.3: Age-specific and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI) for adults (15-99 years) diagnosed with melanoma of the skin during 2010-2014 by continent, country and sex

		All ages		15-29		30-44		45-59		60-74		75-99	
		NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
AFRICA													
§ Algeria	**Men**	*19.6*	*3.1 - 36.2*										
	Women	*0.3*	*0.0 - 1.1*										
§ South Africa (Eastern Cape)	**Men**												
	Women	*34.3*	*0.0 - 71.3*										
AMERICA (CENTRAL AND SOUTH)													
Argentina	**Men**	**63.4**	54.4 - 72.4	**53.5**	12.8 - 94.3	**70.8**	51.1 - 90.6	**59.7**	45.9 - 73.5	**53.0**	39.6 - 66.4	**88.2**	55.1 - 100.0
	Women	**73.9**	67.6 - 80.2	**94.4**	83.5 - 100.0	**85.2**	72.9 - 97.6	**83.8**	73.3 - 94.4	**67.4**	55.2 - 79.7	**42.0**	17.2 - 66.8
Brazil	**Men**	**58.5**	51.5 - 65.6	**70.0**	37.7 - 100.0	**61.6**	46.1 - 77.1	**61.8**	50.2 - 73.5	**60.9**	47.7 - 74.2	**38.1**	20.1 - 56.1
	Women	**80.5**	74.6 - 86.3	**87.7**	66.2 - 100.0	**87.3**	78.9 - 95.8	**79.4**	69.4 - 89.4	**83.8**	72.6 - 95.0	**61.9**	40.5 - 83.3
§ Chile	**Men**	**50.1**	36.8 - 63.3		-		-		-		-		-
	Women	**64.7**	52.2 - 77.3	**61.3**	29.9 - 92.8	**48.3**	12.6 - 84.1	**67.3**	40.4 - 94.2	**63.5**	41.6 - 85.5	**86.4**	52.3 - 100.0
§ Colombia	**Men**	**63.8**	55.2 - 72.4		-		-		-		-		-
	Women	**65.9**	57.8 - 74.0	**66.8**	38.0 - 95.7	**60.3**	38.6 - 82.0	**66.2**	53.3 - 79.1	**70.7**	58.3 - 83.2	**66.0**	41.3 - 90.7
Costa Rica *	**Men**	**73.0**	66.4 - 79.5	**80.5**	56.9 - 100.0	**89.3**	78.6 - 100.0	**63.2**	51.2 - 75.2	**71.2**	59.9 - 82.5	**65.6**	39.9 - 91.4
	Women	**80.6**	74.4 - 86.9	**95.9**	87.7 - 100.0	**84.6**	73.9 - 95.3	**82.9**	74.2 - 91.6	**74.2**	61.8 - 86.5	**79.4**	53.4 - 100.0
Ecuador	**Men**	**47.6**	38.1 - 57.0	**30.2**	0.8 - 59.6	**45.9**	17.2 - 74.5	**54.9**	40.2 - 69.5	**48.3**	33.8 - 62.9	**41.6**	18.3 - 64.9
	Women	**66.5**	59.1 - 74.0	**100.0**	100.0 - 100.0	**75.8**	58.4 - 93.2	**75.3**	63.1 - 87.6	**52.7**	36.5 - 68.8	**44.5**	26.6 - 62.4
§ Guadeloupe*	**Men**		-		-		-		-		-		-
	Women	*58.8*	*0.0 - 100.0*		-		-		-		-		-
§ Martinique*	**Men**	**41.1**	28.7 - 53.6		-		-		-		-		-
	Women	**100.0**	100.0 - 100.0		-		-		-		-		-
Puerto Rico*	**Men**	**70.1**	60.0 - 80.3	**67.4**	23.3 - 100.0	**72.8**	46.6 - 99.1	**75.9**	57.1 - 94.8	**69.1**	52.8 - 85.4	**50.9**	22.7 - 79.1
	Women	**77.4**	68.0 - 86.7	**100.0**	100.0 - 100.0	**86.5**	68.8 - 100.0	**97.0**	88.0 - 100.0	**53.7**	32.0 - 75.4	**69.5**	40.0 - 99.0
AMERICA (NORTH)													
Canada	**Men**	**85.4**	84.6 - 86.2	**89.0**	85.5 - 92.6	**88.7**	86.9 - 90.4	**86.7**	85.6 - 87.9	**84.5**	83.2 - 85.8	**78.3**	75.7 - 81.0
	Women	**92.0**	91.4 - 92.7	**96.4**	94.9 - 97.9	**95.3**	94.4 - 96.3	**93.9**	93.1 - 94.8	**90.6**	89.4 - 91.9	**84.2**	81.3 - 87.1
United States	**Men**	**88.8**	88.5 - 89.1	**91.7**	90.6 - 92.8	**90.1**	89.5 - 90.7	**88.7**	88.3 - 89.1	**89.2**	88.7 - 89.6	**85.0**	84.0 - 86.0
	Women	**93.0**	92.7 - 93.2	**97.0**	96.6 - 97.5	**95.8**	95.5 - 96.1	**94.0**	93.6 - 94.3	**91.8**	91.3 - 92.3	**87.3**	86.0 - 88.5
ASIA													
China	**Men**	**46.7**	39.7 - 53.6	**75.2**	47.2 - 100.0	**54.6**	35.7 - 73.5	**47.0**	35.4 - 58.5	**48.2**	36.4 - 59.9	**20.0**	6.7 - 33.2
	Women	**54.0**	47.0 - 61.1	**49.3**	21.4 - 77.2	**52.4**	35.6 - 69.3	**57.7**	45.1 - 70.4	**47.5**	36.3 - 58.7	**66.4**	45.5 - 87.4
§ Cyprus*	**Men**	**69.2**	59.9 - 78.5	**47.0**	14.2 - 79.7	**69.1**	48.2 - 90.0	**77.7**	63.0 - 92.4	**70.1**	56.0 - 84.3	**72.2**	39.4 - 100.0
	Women	**86.5**	79.3 - 93.6	**85.8**	61.8 - 100.0	**93.2**	83.9 - 100.0	**88.9**	79.8 - 97.9	**88.0**	76.1 - 99.9	**71.6**	36.7 - 100.0
Israel*	**Men**	**85.5**	83.5 - 87.6	**93.3**	86.8 - 99.8	**87.9**	83.6 - 92.3	**88.5**	85.4 - 91.6	**85.3**	81.9 - 88.7	**74.3**	66.2 - 82.4
	Women	**89.2**	87.4 - 91.0	**95.5**	91.0 - 99.9	**95.5**	92.9 - 98.0	**90.5**	87.6 - 93.3	**88.4**	85.1 - 91.8	**77.0**	69.6 - 84.3
Japan	**Men**	**66.2**	61.7 - 70.8	**72.3**	49.4 - 95.2	**75.1**	63.9 - 86.3	**63.0**	54.4 - 71.6	**66.5**	59.6 - 73.4	**55.0**	44.5 - 65.5
	Women	**71.9**	67.9 - 76.0	**85.1**	71.7 - 98.4	**72.8**	62.9 - 82.7	**72.9**	64.2 - 81.5	**74.1**	67.8 - 80.5	**57.4**	47.8 - 67.0
Korea*	**Men**	**53.2**	49.7 - 56.8	**73.1**	54.9 - 91.3	**60.3**	51.3 - 69.4	**51.0**	45.4 - 56.6	**48.6**	43.2 - 54.0	**50.0**	39.3 - 60.6
	Women	**66.4**	63.4 - 69.5	**69.5**	52.2 - 86.8	**78.9**	71.7 - 86.1	**66.6**	61.1 - 72.1	**62.2**	57.2 - 67.3	**51.8**	43.5 - 60.2
Singapore*	**Men**	**59.1**	48.7 - 69.4		-		-		-		-		-
	Women	**61.7**	50.0 - 73.4		-		-		-		-		-
Taiwan*	**Men**	**43.3**	38.5 - 48.2	**69.1**	47.2 - 91.0	**39.4**	26.8 - 52.0	**49.5**	40.9 - 58.2	**37.8**	29.8 - 45.8	**38.4**	29.6 - 47.1
	Women	**61.2**	56.3 - 66.1	**65.7**	42.2 - 89.1	**69.7**	56.9 - 82.4	**61.9**	53.5 - 70.3	**62.5**	54.1 - 70.9	**41.0**	30.2 - 51.7
§ Thailand	**Men**	**30.7**	20.6 - 40.8		-		-		-		-		-
	Women	**30.0**	22.2 - 37.7		-		-		-		-		-
Turkey	**Men**	**53.4**	49.2 - 57.6	**67.7**	55.0 - 80.4	**55.5**	46.8 - 64.3	**54.7**	47.6 - 61.8	**49.4**	41.8 - 56.9	**50.4**	35.7 - 65.0
	Women	**69.7**	65.5 - 73.9	**73.6**	59.2 - 88.0	**70.9**	61.9 - 79.9	**71.3**	64.5 - 78.0	**71.6**	63.8 - 79.5	**58.6**	44.2 - 73.0
EUROPE													
Austria*	**Men**	**86.7**	85.1 - 88.2	**97.3**	94.6 - 99.9	**92.7**	90.3 - 95.1	**86.8**	84.3 - 89.4	**83.4**	80.6 - 86.2	**79.1**	72.5 - 85.6
	Women	**89.0**	87.6 - 90.4	**98.4**	96.7 - 100.0	**95.2**	93.5 - 96.9	**90.5**	88.4 - 92.7	**88.1**	85.4 - 90.8	**74.6**	68.3 - 80.9
Belgium*	**Men**	**88.4**	87.0 - 89.8	**94.4**	90.9 - 98.0	**91.3**	89.0 - 93.6	**92.1**	90.2 - 94.1	**86.0**	83.3 - 88.7	**79.6**	73.4 - 85.8
	Women	**92.7**	91.7 - 93.7	**97.1**	95.5 - 98.7	**96.5**	95.4 - 97.5	**94.4**	93.1 - 95.8	**91.0**	88.9 - 93.0	**85.6**	80.8 - 90.5
Bulgaria*	**Men**	**53.6**	50.0 - 57.2	**64.7**	47.8 - 81.6	**60.6**	52.4 - 68.8	**56.3**	49.8 - 62.8	**48.1**	42.1 - 54.2	**45.9**	35.5 - 56.3
	Women	**68.5**	65.2 - 71.7	**91.0**	82.5 - 99.5	**72.2**	65.4 - 79.1	**70.5**	64.9 - 76.1	**65.0**	59.4 - 70.7	**57.6**	46.6 - 68.6
Croatia*	**Men**	**74.7**	71.8 - 77.6	**82.3**	71.1 - 93.5	**80.6**	74.5 - 86.7	**79.1**	74.6 - 83.7	**66.6**	61.6 - 71.5	**71.1**	60.4 - 81.9
	Women	**80.0**	77.5 - 82.4	**94.8**	87.6 - 100.0	**88.5**	83.9 - 93.2	**81.4**	77.3 - 85.4	**76.0**	71.3 - 80.7	**66.2**	57.0 - 75.5
Czech Republic*	**Men**	**83.6**	82.2 - 84.9	**89.4**	83.8 - 95.0	**90.6**	88.1 - 93.1	**85.8**	83.6 - 88.1	**81.2**	78.8 - 83.6	**70.9**	65.8 - 76.0
	Women	**87.7**	86.5 - 88.9	**96.5**	94.2 - 98.8	**94.8**	93.1 - 96.5	**92.5**	90.9 - 94.2	**85.4**	83.1 - 87.6	**68.7**	63.3 - 74.0
Denmark*	**Men**	**89.1**	87.8 - 90.4	**97.2**	94.6 - 99.9	**94.7**	92.8 - 96.6	**91.9**	89.9 - 93.9	**87.4**	85.2 - 89.6	**74.8**	68.8 - 80.7
	Women	**92.9**	91.8 - 94.0	**99.4**	98.6 - 100.0	**97.2**	96.2 - 98.2	**95.8**	94.5 - 97.1	**92.2**	90.2 - 94.1	**79.6**	73.7 - 85.4
Estonia*	**Men**	**78.2**	70.9 - 85.5	**100.0**	100.0 - 100.0	**97.9**	90.5 - 100.0	**70.8**	55.7 - 86.0	**66.8**	52.7 - 80.8	**73.5**	44.5 - 100.0
	Women	**84.1**	79.3 - 88.8	**96.6**	89.8 - 100.0	**87.5**	77.7 - 97.3	**83.7**	74.7 - 92.6	**88.1**	80.0 - 96.3	**66.4**	49.5 - 83.3
Finland*	**Men**	**86.4**	84.7 - 88.1	**95.1**	89.2 - 100.0	**92.6**	89.2 - 96.1	**87.1**	84.3 - 89.9	**83.4**	80.6 - 86.2	**79.0**	72.2 - 85.8
	Women	**91.0**	89.6 - 92.4	**97.5**	94.5 - 100.0	**96.0**	93.8 - 98.1	**93.7**	91.6 - 95.7	**89.1**	86.5 - 91.7	**79.7**	73.5 - 86.0
France	**Men**	**87.9**	84.6 - 91.3	**84.2**	69.9 - 98.4	**100.0**	98.6 - 100.0	**87.4**	81.9 - 92.9	**85.7**	79.6 - 91.7	**76.9**	61.7 - 92.0
	Women	**93.4**	90.9 - 96.0	**92.7**	84.6 - 100.0	**97.6**	95.0 - 100.0	**95.5**	92.3 - 98.7	**89.2**	83.7 - 94.6	**92.0**	81.4 - 100.0
Germany	**Men**	**91.4**	90.6 - 92.2	**96.7**	94.7 - 98.7	**93.2**	91.8 - 94.7	**90.0**	88.7 - 91.3	**92.3**	91.1 - 93.5	**87.4**	84.1 - 90.8
	Women	**94.4**	93.8 - 95.0	**98.4**	97.5 - 99.4	**96.9**	96.1 - 97.7	**95.1**	94.2 - 96.0	**93.5**	92.4 - 94.6	**89.0**	85.8 - 92.2

Table 4.3: Age-specific and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI) for adults (15-99 years) diagnosed with melanoma of the skin during 2010-2014 by continent, country and sex

		All ages		15-29		30-44		45-59		60-74		75-99	
		NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
Iceland*	**Men**	**86.9**	79.4 - 94.4	**100.0**	100.0 - 100.0	**91.3**	75.0 - 100.0	**89.9**	77.3 - 100.0	**82.9**	66.3 - 99.5	**70.1**	41.9 - 98.3
	Women	**88.0**	80.4 - 95.7	**100.0**	100.0 - 100.0	**97.6**	92.4 - 100.0	**84.6**	73.4 - 95.8	**88.3**	69.9 - 100.0	**70.4**	36.6 - 100.0
Ireland*	**Men**	**84.6**	82.1 - 87.1	**81.0**	70.3 - 91.6	**92.2**	88.1 - 96.3	**88.8**	84.7 - 92.8	**85.7**	81.4 - 90.1	**64.5**	54.4 - 74.5
	Women	**92.6**	90.7 - 94.4	**95.5**	91.6 - 99.4	**94.8**	92.4 - 97.3	**92.3**	89.3 - 95.3	**92.7**	89.5 - 96.0	**87.4**	78.6 - 96.2
Italy	**Men**	**83.8**	82.7 - 84.9	**91.8**	87.8 - 95.7	**90.5**	88.7 - 92.3	**86.8**	85.0 - 88.6	**81.6**	79.6 - 83.5	**69.0**	64.4 - 73.6
	Women	**87.7**	86.6 - 88.7	**94.9**	92.6 - 97.3	**94.4**	93.2 - 95.6	**92.1**	90.7 - 93.5	**84.9**	82.9 - 86.9	**71.6**	67.2 - 76.1
Latvia*	**Men**	**65.1**	58.7 - 71.5	**63.9**	33.1 - 94.7	**79.4**	65.3 - 93.5	**60.2**	49.4 - 71.0	**61.9**	50.1 - 73.6	**59.6**	41.1 - 78.2
	Women	**76.5**	72.1 - 80.9	**90.4**	80.1 - 100.0	**76.1**	63.9 - 88.3	**78.4**	70.5 - 86.2	**73.3**	65.8 - 80.9	**70.7**	57.5 - 83.9
Lithuania*	**Men**	**62.6**	56.1 - 69.0	**93.9**	80.7 - 100.0	**77.2**	63.4 - 91.0	**58.5**	46.6 - 70.5	**57.9**	46.1 - 69.8	**43.2**	22.5 - 63.9
	Women	**82.5**	78.5 - 86.4	**85.8**	67.8 - 100.0	**85.6**	76.2 - 94.9	**86.2**	79.7 - 92.6	**84.0**	77.1 - 90.9	**64.4**	51.7 - 77.1
Malta*	**Men**	**79.4**	68.5 - 90.3	**100.0**	100.0 - 100.0	**100.0**	100.0 - 100.0	**88.5**	70.9 - 100.0	**62.2**	39.8 - 84.5	**62.2**	16.8 - 100.0
	Women	**83.9**	77.6 - 90.2	**100.0**	100.0 - 100.0	**96.6**	89.6 - 100.0	**91.7**	81.4 - 100.0	**95.8**	84.0 - 100.0	**24.6**	2.0 - 47.1
Netherlands*	**Men**	**88.3**	87.4 - 89.2	**93.8**	91.0 - 96.6	**91.9**	90.4 - 93.4	**89.0**	87.7 - 90.3	**86.5**	85.0 - 88.1	**83.2**	78.7 - 87.7
	Women	**93.2**	92.5 - 93.9	**97.7**	96.5 - 98.9	**97.2**	96.5 - 97.9	**95.1**	94.3 - 95.9	**93.3**	92.1 - 94.6	**81.6**	77.8 - 85.3
Norway*	**Men**	**86.5**	84.9 - 88.0	**100.0**	100.0 - 100.0	**91.1**	88.2 - 94.1	**88.7**	86.3 - 91.2	**85.4**	82.9 - 87.9	**72.7**	66.4 - 79.0
	Women	**92.0**	90.7 - 93.2	**94.2**	90.1 - 98.2	**95.8**	94.1 - 97.5	**94.4**	92.7 - 96.0	**90.9**	88.7 - 93.1	**82.3**	76.1 - 88.5
Poland*	**Men**	**63.5**	62.0 - 64.9	**69.8**	63.6 - 76.0	**73.3**	70.0 - 76.6	**62.9**	60.4 - 65.3	**59.6**	57.1 - 62.1	**54.9**	50.3 - 59.6
	Women	**75.1**	73.9 - 76.2	**92.3**	89.7 - 94.9	**85.4**	83.2 - 87.6	**77.3**	75.3 - 79.3	**70.2**	68.0 - 72.4	**57.0**	53.0 - 60.9
Portugal*	**Men**	**81.4**	76.0 - 86.9	**100.0**	100.0 - 100.0	**87.3**	77.0 - 97.6	**82.7**	73.8 - 91.6	**73.1**	62.2 - 84.0	**79.8**	60.2 - 99.3
	Women	**86.0**	82.0 - 89.9	**100.0**	100.0 - 100.0	**93.8**	88.1 - 99.5	**89.2**	82.8 - 95.6	**85.3**	77.0 - 93.5	**62.5**	47.4 - 77.7
Romania (Cluj)	**Men**	**61.8**	50.1 - 73.6		-		-		-		-		-
	Women	**79.3**	69.2 - 89.5	**80.2**	56.7 - 100.0	**79.1**	62.6 - 95.6	**91.2**	80.7 - 100.0	**65.9**	37.2 - 94.6	**73.2**	37.3 - 100.0
Russia	**Men**	**56.4**	51.2 - 61.5	**66.7**	46.8 - 86.5	**52.3**	42.3 - 62.4	**51.7**	44.3 - 59.1	**56.5**	47.4 - 65.7	**67.9**	48.3 - 87.6
	Women	**72.6**	69.3 - 75.9	**80.0**	68.6 - 91.4	**78.1**	71.3 - 84.9	**72.6**	67.4 - 77.8	**67.1**	61.3 - 73.0	**73.1**	61.1 - 85.0
Slovakia*	**Men**	**72.3**	66.3 - 78.3	**75.3**	47.3 - 100.0	**86.9**	76.2 - 97.6	**71.5**	61.4 - 81.5	**70.5**	59.4 - 81.6	**52.3**	30.4 - 74.2
	Women	**83.9**	78.0 - 89.8	**83.4**	56.2 - 100.0	**85.8**	76.3 - 95.2	**84.9**	77.0 - 92.7	**79.3**	69.5 - 89.1	**85.3**	56.7 - 100.0
Slovenia*	**Men**	**82.7**	79.3 - 86.0	**97.1**	90.9 - 100.0	**88.1**	82.0 - 94.2	**82.5**	77.3 - 87.7	**78.7**	72.8 - 84.6	**77.2**	62.8 - 91.6
	Women	**87.2**	84.6 - 89.8	**98.2**	94.6 - 100.0	**91.7**	87.6 - 95.8	**95.0**	91.9 - 98.0	**83.5**	78.2 - 88.8	**69.0**	58.0 - 80.0
Spain	**Men**	**81.1**	78.0 - 84.2	**91.6**	83.4 - 99.7	**87.2**	81.8 - 92.6	**80.6**	74.9 - 86.2	**79.9**	73.9 - 85.9	**70.0**	58.6 - 81.3
	Women	**91.9**	89.6 - 94.2	**96.7**	92.0 - 100.0	**97.2**	95.0 - 99.5	**92.0**	88.5 - 95.4	**91.0**	86.7 - 95.4	**83.1**	72.7 - 93.5
Sweden*	**Men**	**89.1**	88.1 - 90.1	**93.9**	90.0 - 97.9	**93.7**	91.8 - 95.6	**91.6**	89.9 - 93.3	**89.3**	87.6 - 90.9	**75.1**	71.0 - 79.1
	Women	**93.8**	93.0 - 94.7	**97.2**	95.1 - 99.3	**96.1**	94.9 - 97.3	**95.7**	94.5 - 96.8	**93.8**	92.4 - 95.3	**85.2**	81.0 - 89.3
Switzerland	**Men**	**92.2**	90.4 - 93.9	**98.2**	94.2 - 100.0	**94.6**	91.7 - 97.5	**93.8**	91.2 - 96.5	**90.9**	87.9 - 93.9	**86.5**	79.1 - 94.0
	Women	**95.0**	93.4 - 96.5	**98.3**	95.9 - 100.0	**98.2**	96.7 - 99.7	**95.2**	93.1 - 97.4	**95.7**	93.2 - 98.3	**86.9**	79.0 - 94.8
United Kingdom*	**Men**	**87.8**	87.3 - 88.4	**92.9**	91.1 - 94.6	**90.7**	89.6 - 91.7	**88.8**	87.9 - 89.7	**87.3**	86.4 - 88.2	**80.6**	78.4 - 82.8
	Women	**93.7**	93.2 - 94.1	**97.0**	96.2 - 97.8	**96.1**	95.5 - 96.6	**94.1**	93.5 - 94.7	**93.4**	92.6 - 94.2	**88.3**	86.2 - 90.3
OCEANIA													
Australia*	**Men**	**91.3**	90.9 - 91.8	**94.9**	93.3 - 96.6	**94.6**	93.7 - 95.5	**92.4**	91.7 - 93.2	**91.2**	90.4 - 92.0	**82.5**	80.6 - 84.4
	Women	**95.1**	94.6 - 95.5	**97.2**	96.2 - 98.3	**96.7**	96.1 - 97.4	**95.7**	95.1 - 96.3	**95.8**	94.9 - 96.6	**88.8**	86.4 - 91.1
New Zealand*	**Men**	**89.6**	88.5 - 90.7	**93.7**	88.7 - 98.8	**93.6**	91.3 - 95.9	**90.5**	88.8 - 92.2	**88.4**	86.6 - 90.2	**82.7**	78.2 - 87.2
	Women	**94.2**	93.3 - 95.2	**95.1**	91.9 - 98.3	**96.0**	94.5 - 97.5	**95.1**	93.8 - 96.3	**93.9**	92.3 - 95.6	**90.3**	85.6 - 95.0

* Data with 100% coverage of the national population

§ Survival estimate considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), ***or*** (b) registered only from a death certificate or at autopsy, ***or*** (c) registered with incomplete dates, i.e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status

Italics denote survival estimates that are not age-standardised

Figure 4.1: Anatomic distribution by sex, continent and country, all periods combined.

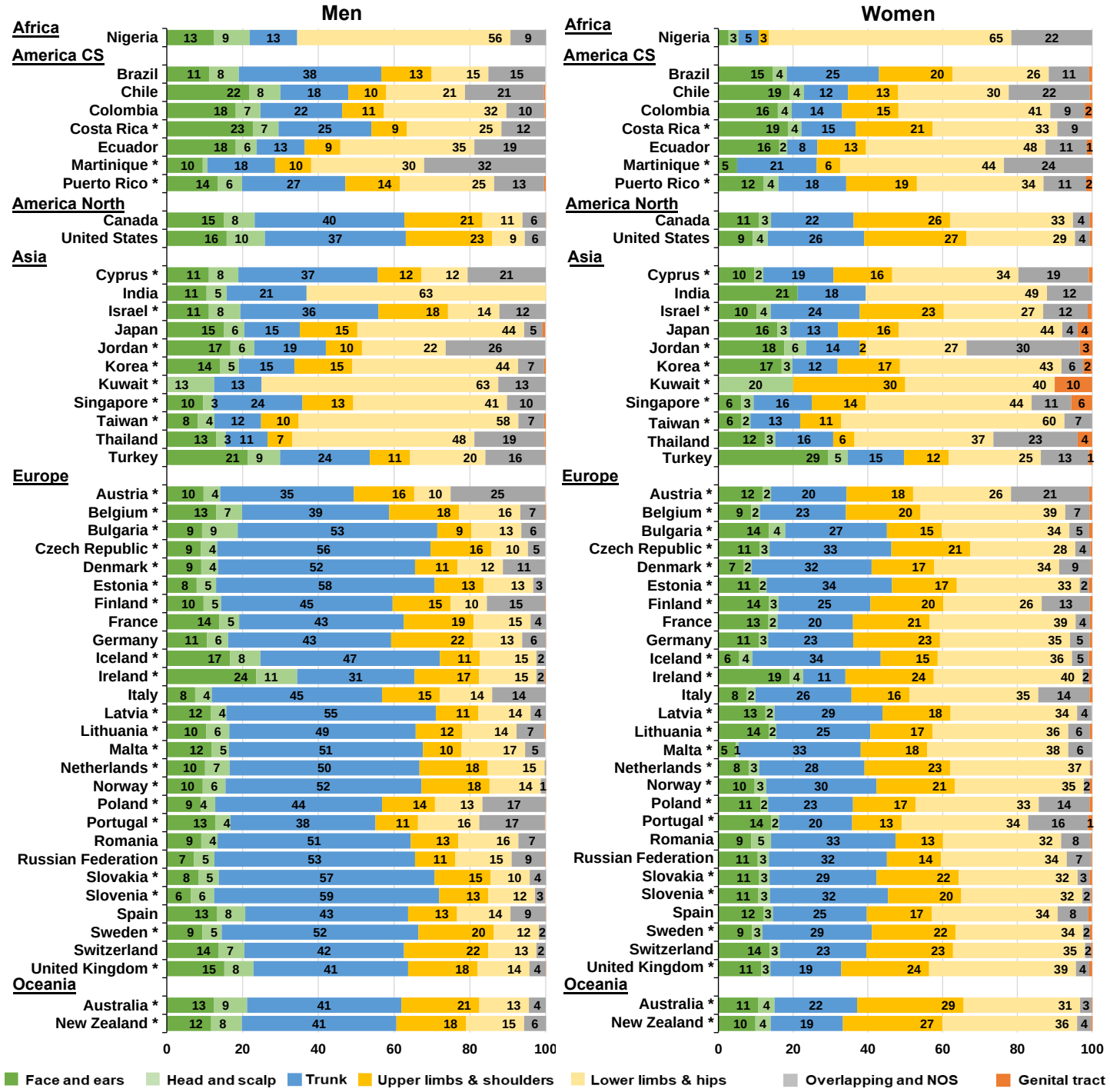
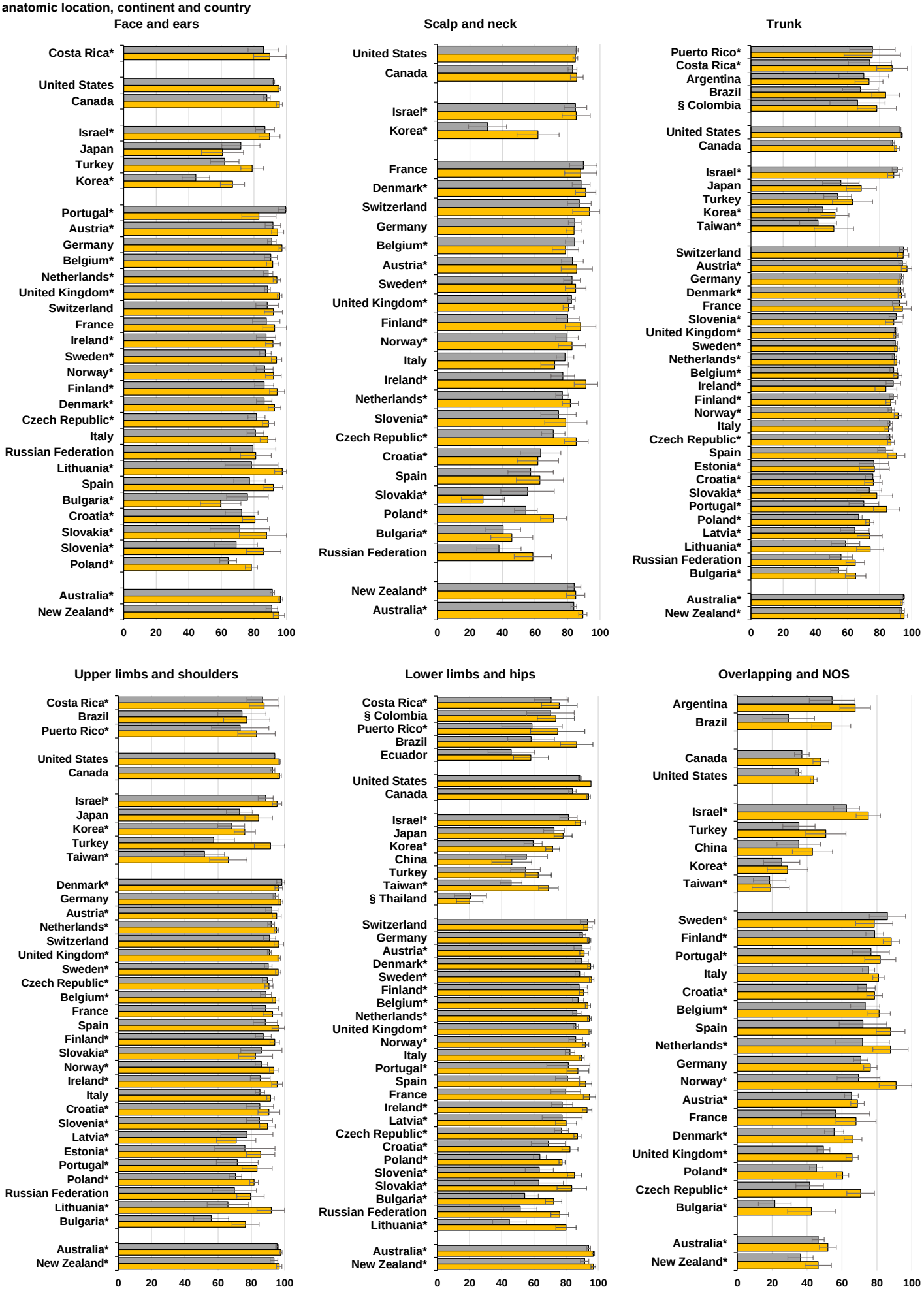
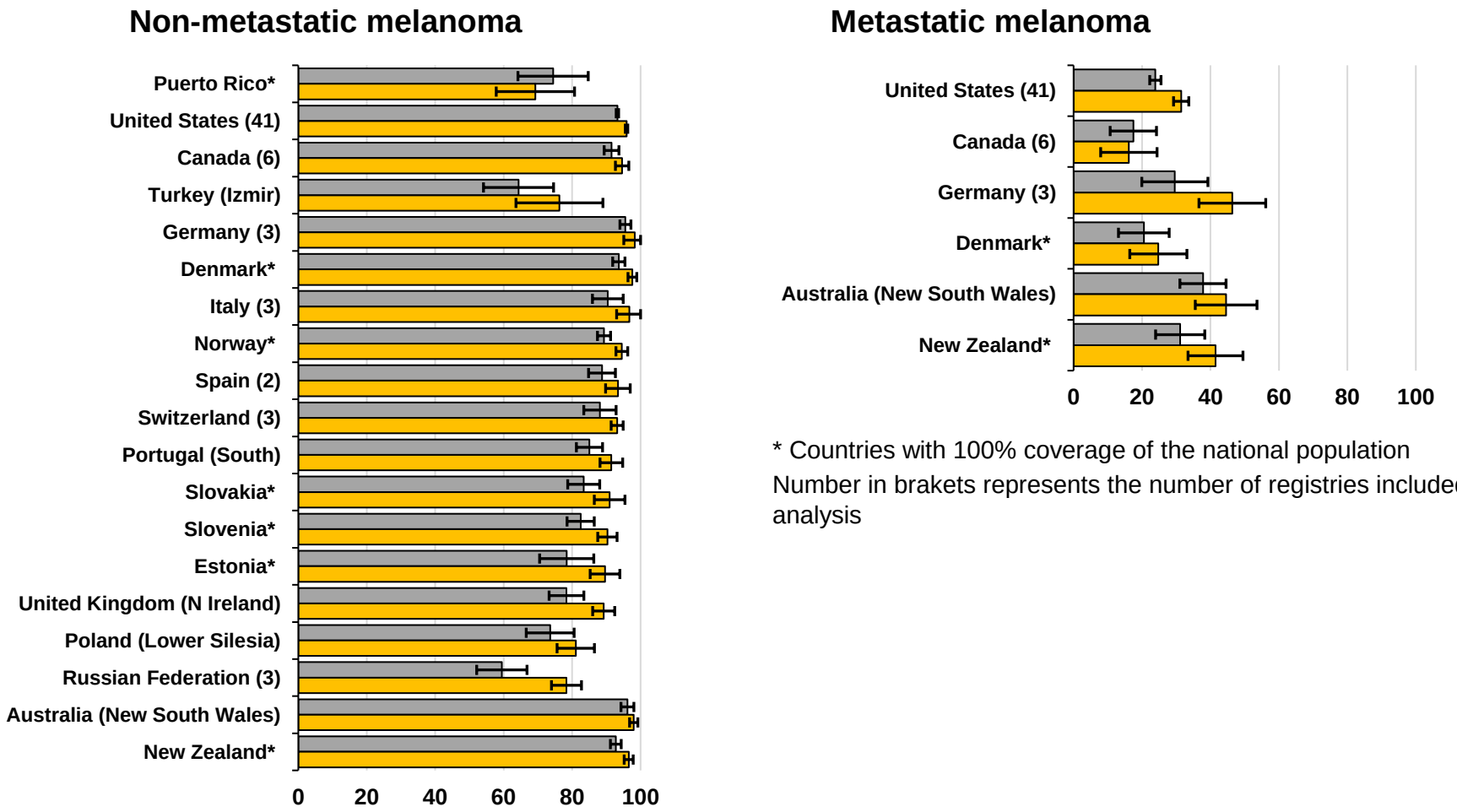


Figure 4.2: Age-standardised 5-year net survival for men (grey) and women (yellow) diagnosed with cutaneous melanoma during 2010–2014 by anatomic location, continent and country



* Countries with 100% coverage of the national population
§ Survival estimates considered less reliable

Figure 4.3: Age-standardised 5-year net survival for men (gray) and women (yellow) diagnosed with non metastatic and metastatic melanoma of the skin during 2009-2014



* Countries with 100% coverage of the national population

Number in brakets represents the number of registries included in analysis

Supplementary table 4.1: Stage distribution for men and women (15-99 years) diagnosed with melanoma of the skin during 2001-2003, 2004-2008 and 2009-2014, by continent and country

		Men						Women					
		Non metastatic		Metastatic		Unknown		Non metastatic		Metastatic		Unknown	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
AMERICA (CENTRAL AND SOUTH)													
Brazil	**2001-2003**	16	**61.5**	8	**30.8**	2	**7.7**	11	**50.0**	6	**27.3**	5	**22.7**
(Barretos)	**2004-2008**	24	**72.7**	5	**15.2**	4	**12.1**	34	**75.6**	6	**13.3**	5	**11.1**
	2009-2014	37	**69.8**	6	**11.3**	10	**18.9**	46	**78.0**	4	**6.8**	9	**15.3**
Puerto Rico*	**2001-2003**	80	**66.1**	13	**10.7**	28	**23.1**	88	**73.9**	4	**3.4**	27	**22.7**
	2004-2008	172	**75.1**	23	**10.0**	34	**14.8**	135	**71.1**	6	**3.2**	49	**25.8**
	2009-2014	114	**69.1**	19	**11.5**	32	**19.4**	100	**71.9**	8	**5.8**	31	**22.3**
AMERICA (NORTH)													
Canada	**2001-2003**												
(6 registries)	**2004-2008**	358	**93.0**	25	**6.5**	2	**0.5**	327	**95.9**	13	**3.8**	1	**0.3**
	2009-2014	3,714	**92.7**	228	**5.7**	65	**1.6**	3,547	**95.7**	108	**2.9**	53	**1.4**
United States	**2001-2003**	65,255	**86.8**	3,502	**4.7**	6,422	**8.5**	52,149	**89.0**	1,651	**2.8**	4,793	**8.2**
(40 registries)	**2004-2008**	135,145	**89.0**	7,252	**4.8**	9,505	**6.3**	105,693	**90.8**	3,608	**3.1**	7,087	**6.1**
	2009-2014	156,546	**87.6**	9,901	**5.5**	12,358	**6.9**	118,057	**89.6**	4,767	**3.6**	8,944	**6.8**
ASIA													
Cyprus*	**2001-2003**												
	2004-2008	84	**85.7**	12	**12.2**	2	**2.0**	99	**84.6**	9	**7.7**	9	**7.7**
	2009-2014	156	**78.8**	23	**11.6**	19	**9.6**	151	**85.8**	12	**6.8**	13	**7.4**
Japan	**2001-2003**	42	**79.2**	6	**11.3**	5	**9.4**	62	**89.9**	3	**4.3**	4	**5.8**
(2 registries)	**2004-2008**	94	**83.9**	8	**7.1**	10	**8.9**	127	**83.0**	10	**6.5**	16	**10.5**
	2009-2014	68	**82.9**	4	**4.9**	10	**12.2**	76	**80.9**	5	**5.3**	13	**13.8**
Thailand	**2001-2003**	6	**37.5**	9	**56.3**	1	**6.3**	9	**47.4**	5	**26.3**	5	**26.3**
(3 registries)	**2004-2008**	10	**66.7**	4	**26.7**	1	**6.7**	16	**55.2**	5	**17.2**	8	**27.6**
	2009-2014	6	**46.2**	3	**23.1**	4	**30.8**	10	**52.6**	4	**21.1**	5	**26.3**
Turkey	**2001-2003**												
(Izmir)	**2004-2008**	132	**64.1**	34	**16.5**	40	**19.4**	114	**63.7**	19	**10.6**	46	**25.7**
	2009-2014	183	**71.2**	43	**16.7**	31	**12.1**	165	**80.5**	18	**8.8**	22	**10.7**
EUROPE													
Denmark*	**2001-2003**												
	2004-2008	2,408	**72.6**	168	**5.1**	743	**22.4**	3,198	**77.0**	121	**2.9**	834	**20.1**
	2009-2014	4,701	**79.0**	235	**3.9**	1,016	**17.1**	5,522	**80.5**	158	**2.3**	1,183	**17.2**
Estonia*	**2001-2003**	113	**90.4**	5	**4.0**	7	**5.6**	209	**92.9**	10	**4.4**	6	**2.7**
	2004-2008	226	**91.5**	16	**6.5**	5	**2.0**	435	**90.6**	24	**5.0**	21	**4.4**
	2009-2014	268	**83.2**	24	**7.5**	30	**9.3**	410	**86.9**	19	**4.0**	43	**9.1**
Germany	**2001-2003**	130	**59.9**	31	**14.3**	56	**25.8**	143	**65.6**	25	**11.5**	50	**22.9**
(3 registries)	**2004-2008**	3,168	**70.2**	115	**2.5**	1,230	**27.3**	3,592	**71.8**	91	**1.8**	1,319	**26.4**
	2009-2014	6,297	**72.6**	219	**2.5**	2,160	**24.9**	6,360	**74.7**	153	**1.8**	2,001	**23.5**
Italy	**2001-2003**	110	**82.1**	9	**6.7**	15	**11.2**	95	**79.2**	10	**8.3**	15	**12.5**
(3 registries)	**2004-2008**	431	**78.4**	45	**8.2**	74	**13.5**	469	**77.5**	31	**5.1**	105	**17.4**
	2009-2014	587	**82.8**	32	**4.5**	90	**12.7**	536	**84.1**	25	**3.9**	76	**11.9**
Netherlands*	**2001-2003**												
	2004-2008	5,540	**70.5**	110	**1.4**	2,204	**28.1**	7,010	**68.9**	97	**1.0**	3,070	**30.2**
	2009-2014	9,918	**71.2**	180	**1.3**	3,823	**27.5**	11,402	**70.5**	103	**0.6**	4,658	**28.8**
Norway*	**2001-2003**	927	**67.2**	72	**5.2**	381	**27.6**	1,115	**67.2**	46	**2.8**	498	**30**
	2004-2008												
	2009-2014	4,728	**96.0**	79	**1.6**	119	**2.4**	4,976	**96.5**	44	**0.9**	138	**2.7**
Poland	**2001-2003**												
(Lower Silesia)	**2004-2008**	235	**55.8**	86	**20.4**	100	**23.8**	266	**57.0**	88	**18.8**	113	**24.2**
	2009-2014	383	**65.0**	83	**14.1**	123	**20.9**	387	**63.1**	66	**10.8**	160	**26.1**
Portugal South	**2001-2003**	314	**72.0**	58	**13.3**	64	**14.7**	488	**79.7**	47	**7.7**	77	**12.6**
	2004-2008	689	**75.8**	99	**10.9**	121	**13.3**	906	**78.2**	63	**5.4**	189	**16.3**
	2009-2014	1,264	**88.8**	97	**6.8**	63	**4.4**	1,485	**90.3**	67	**4.1**	93	**5.7**
Russia	**2001-2003**	33	**66.0**	8	**16.0**	9	**18.0**	79	**79.8**	4	**4.0**	16	**16.2**
(3 registries)	**2004-2008**	329	**74.3**	25	**5.6**	89	**20.1**	568	**76.1**	22	**2.9**	156	**20.9**
	2009-2014	654	**76.6**	94	**11.0**	106	**12.4**	1,254	**84.7**	82	**5.5**	144	**9.7**

Supplementary table 4.1: Stage distribution for men and women (15-99 years) diagnosed with melanoma of the skin during 2001-2003, 2004-2008 and 2009-2014, by continent and country

		Men						Women					
		Non metastatic		Metastatic		Unknown		Non metastatic		Metastatic		Unknown	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Slovakia*	**2001-2003**	556	**84.0**	62	**9.4**	44	**6.6**	698	**85.3**	46	**5.6**	74	**9**
	2004-2008	1,214	**83.2**	112	**7.7**	133	**9.1**	1,360	**86.0**	89	**5.6**	132	**8.3**
	2009-2014	623	**84.9**	67	**9.1**	44	**6.0**	618	**86.6**	48	**6.7**	48	**6.7**
Slovenia*	**2001-2003**	392	**93.6**	23	**5.5**	4	**1.0**	454	**96.6**	13	**2.8**	3	**0.6**
	2004-2008	896	**97.0**	19	**2.1**	9	**1.0**	1,042	**97.0**	26	**2.4**	6	**0.6**
	2009-2014	1,188	**96.7**	34	**2.8**	7	**0.6**	1,226	**98.4**	16	**1.3**	4	**0.3**
Spain	**2001-2003**	251	**90.3**	2	**0.7**	25	**9.0**	308	**85.8**	7	**1.9**	44	**12.3**
(2 registries)	**2004-2008**	676	**86.6**	28	**3.6**	77	**9.9**	900	**89.4**	15	**1.5**	92	**9.1**
	2009-2014	723	**91.3**	34	**4.3**	35	**4.4**	861	**91.8**	26	**2.8**	51	**5.4**
Switzerland	**2001-2003**	354	**86.6**	9	**2.2**	46	**11.2**	361	**87.4**	4	**1.0**	48	**11.6**
(3 registries)	**2004-2008**	526	**94.3**	9	**1.6**	23	**4.1**	503	**93.1**	6	**1.1**	31	**5.7**
	2009-2014	648	**92.3**	13	**1.9**	41	**5.8**	600	**95.7**	4	**0.6**	23	**3.7**
United Kingdom*	**2001-2003**												
(Northern Ireland)	**2004-2008**												
	2009-2014	568	**68.7**	23	**2.8**	236	**28.5**	775	**70.3**	5	**0.5**	323	**29.3**
OCEANIA													
Australia*	**2001-2003**	4,847	**86.3**	339	**6.0**	430	**7.7**	3,505	**88.9**	160	**4.1**	278	**7.1**
(New South Wale	**2004-2008**	9,442	**90.3**	556	**5.3**	464	**4.4**	6,708	**92.4**	263	**3.6**	292	**4**
	2009-2014	8,586	**90.9**	525	**5.6**	337	**3.6**	5,999	**93.2**	236	**3.7**	205	**3.2**
New Zealand*	**2001-2003**	2,508	**91.3**	185	**6.7**	54	**2.0**	2,503	**93.6**	106	**4.0**	66	**2.5**
	2004-2008	4,871	**89.7**	364	**6.7**	193	**3.6**	4,552	**92.3**	206	**4.2**	173	**3.5**
	2009-2014	6,524	**89.1**	453	**6.2**	344	**4.7**	5,821	**90.9**	263	**4.1**	317	**5**

* Data with 100% coverage of the national population

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): men (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

MEN

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AFRICA																
Algeria	2000-2004										**12**	*0.2*	*0.0 - 0.9*			
	2005-2009										**69**	*15.4*	*0.0 - 31.0*			
	2010-2014										**64**	**45.1**	**45.0 - 45.2**			
Nigeria (Ibadan)	2000-2004															
	2005-2009															
	2010-2014															
South Africa (Eastern Cape)	2000-2004															
	2005-2009															
	2010-2014															
AMERICA (CENTRAL AND SOUTH)																
Argentina	2000-2004	**13**	*64.5*	*38.0 - 91.0*	**13**	*87.8*	*59.2 - 100.0*	**13**	*83.5*	*60.1 - 100.0*	**46**	*66.0*	*47.8 - 84.3*			
	2005-2009	**32**	*59.3*	*36.3 - 82.3*	**44**	*64.9*	*48.6 - 81.3*	**61**	**62.4**	50.1 - 74.7	**100**	**58.8**	47.6 - 70.0			
	2010-2014	**20**	*100.0*	*89.9 - 100.0*	**40**	**70.1**	54.7 - 85.6	**31**	**65.0**	48.5 - 81.6	**83**	**54.3**	41.3 - 67.4			
Brazil	2000-2004	**40**	*56.6*	*35.7 - 77.5*	**81**	**75.4**	64.7 - 86.0	**74**	**72.9**	62.7 - 83.1	**37**	*39.6*	*23.2 - 56.0*			
	2005-2009	**58**	*71.3*	*56.0 - 86.6*	**111**	**75.3**	65.5 - 85.2	**66**	**71.0**	60.1 - 81.8	**49**	*41.4*	*26.8 - 56.1*			
	2010-2014	**24**	**53.5**	36.2 - 70.8	**57**	**68.0**	57.0 - 79.1	**57**	**65.4**	53.1 - 77.7	**26**	**29.5**	14.7 - 44.3			
Chile	2000-2004	**12**	*60.7*	*30.0 - 91.5*	**8**	*46.1*	*10.7 - 81.5*	**11**	*45.0*	*13.3 - 76.6*	**10**	*41.8*	*12.8 - 70.8*			
	2005-2009	**19**	*72.7*	*45.7 - 99.7*	**15**	*47.5*	*21.1 - 73.9*	**24**	*47.7*	*25.3 - 70.1*	**3**	*52.0*	*0.4 - 100.0*			
	2010-2014	**18**	*49.4*	*18.2 - 80.6*	**9**	*68.3*	*36.6 - 100.0*	**18**	*47.7*	*25.3 - 70.1*	**9**	*45.9*	*0.9 - 90.9*			
Colombia §	2000-2004	**33**	*57.7*	*34.4 - 81.1*	**41**	*78.5*	*61.2 - 95.7*	**64**	**47.1**	33.5 - 60.6	**19**	*12.6*	*0.0 - 27.4*			
	2005-2009	**59**	*75.6*	*56.6 - 94.6*	**49**	*93.1*	*79.3 - 100.0*	**98**	**67.1**	55.9 - 78.3	**18**	*34.5*	*12.7 - 56.4*			
	2010-2014	**38**	**68.3**	52.6 - 83.9	**35**	**66.3**	49.1 - 83.4	**85**	**67.8**	55.5 - 80.1	**18**	*13.5*	*0.0 - 31.7*			
Costa Rica *	2000-2004	**34**	*100.0*	*85.1 - 100.0*	**36**	*60.8*	*43.1 - 78.5*	**54**	*74.0*	*56.6 - 91.5*	**14**	*75.6*	*47.0 - 100.0*			
	2005-2009	**58**	**73.0**	59.5 - 86.4	**58**	*72.9*	*58.4 - 87.3*	**90**	**77.3**	66.9 - 87.7	**26**	*41.3*	*19.3 - 63.3*			
	2010-2014	**117**	**81.1**	68.5 - 93.7	**80**	**73.9**	60.5 - 87.3	**100**	**72.6**	63.2 - 81.9	**43**	*75.6*	*47.0 - 100.0*			
Ecuador	2000-2004	**23**	*72.1*	*45.8 - 98.4*	**9**	*68.6*	*39.1 - 98.1*	**39**	*47.2*	*29.9 - 64.4*	**5**	*80.1*	*48.6 - 100.0*			
	2005-2009	**37**	*62.1*	*42.9 - 81.4*	**19**	*47.8*	*20.2 - 75.5*	**83**	**52.7**	41.9 - 63.5	**53**	*29.3*	*14.7 - 44.0*			
	2010-2014	**53**	**57.9**	38.1 - 77.6	**30**	*0.5*	*0.0 - 1.5*	**93**	**52.1**	39.0 - 65.2	**36**	**37.4**	24.1 - 50.6			
Guadeloupe *	2000-2004															
	2005-2009															
	2010-2014							**15**	*2.2*	*0.0 - 7.3*						
Martinique *	2000-2004	**3**	*100.0*	-	**5**	*82.4*	*44.2 - 100.0*	**8**	*56.0*	*19.6 - 92.3*	**20**	*88.9*	*68.3 - 100.0*			
	2005-2009	**6**	*55.4*	*13.8 - 96.9*	**4**	*87.0*	*39.7 - 100.0*	**14**	*86.5*	*59.6 - 100.0*	**5**	*57.1*	*6.5 - 100.0*			
	2010-2014	**6**	*55.4*	*13.8 - 96.9*	**6**	*59.8*	*16.9 - 100.0*	**11**	*89.0*	*47.1 - 100.0*	**2**	*56.8*	*1.3 - 100.0*			
Puerto Rico *	2000-2004	**47**	*65.1*	*45.9 - 84.3*	**37**	*67.5*	*46.6 - 88.3*	**84**	**70.9**	60.6 - 81.2	**28**	*35.1*	*16.4 - 53.8*			
	2005-2009	**38**	*70.9*	*52.2 - 89.6*	**80**	**81.0**	70.8 - 91.3	**88**	**61.7**	50.9 - 72.5	**25**	*61.7*	*42.5 - 80.9*			
	2010-2014	**24**	**34.9**	20.8 - 49.0	**32**	**75.5**	61.5 - 89.6	**43**	**67.5**	53.5 - 81.5	**19**	*35.1*	*16.4 - 53.8*			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): men (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

MEN

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AMERICA (NORTH)																
Canada	2000-2004	**2,375**	**84.4**	82.4 - 86.3	**4,195**	**86.3**	84.8 - 87.7	**3,211**	**87.7**	86.2 - 89.2	**681**	**50.5**	46.0 - 55.0	**9**	*48.3*	*15.3 - 81.2*
	2005-2009	**2,967**	**83.1**	81.3 - 85.0	**5,236**	**86.5**	85.2 - 87.8	**4,004**	**89.1**	87.8 - 90.4	**886**	**42.5**	38.6 - 46.4	**11**	*9.7*	*0.0 - 24.2*
	2010-2014	**3,655**	**86.1**	84.5 - 87.8	**5,965**	**88.1**	86.9 - 89.3	**4,942**	**89.8**	88.5 - 91.0	**797**	**37.0**	32.8 - 41.2	**9**	*76.7*	*27.7 - 100.0*
United States	2000-2004	**26,775**	**87.0**	86.4 - 87.6	**39,479**	**90.8**	90.3 - 91.2	**31,839**	**91.2**	90.7 - 91.7	**6,374**	**39.3**	37.9 - 40.8	**53**	*63.9*	*47.5 - 80.3*
	2005-2009	**33,085**	**88.6**	88.1 - 89.2	**46,924**	**92.4**	92.0 - 92.8	**40,220**	**92.4**	92.0 - 92.9	**6,901**	**37.8**	36.4 - 39.2	**58**	**60.1**	48.2 - 72.0
	2010-2014	**29,777**	**89.3**	88.7 - 89.8	**40,439**	**92.8**	92.4 - 93.2	**35,153**	**92.7**	92.2 - 93.1	**5,723**	**35.1**	33.6 - 36.6	**48**	**67.6**	56.3 - 78.8
ASIA																
China	2000-2004	**9**	*0.1*	*0.0 - 0.2*	**7**	*30.6*	*0.2 - 61.0*	**16**	*20.8*	*0.6 - 41.1*	**14**	*17.6*	*0.0 - 38.4*			
	2005-2009	**52**	*38.6*	*23.7 - 53.4*	**26**	*25.0*	*8.1 - 42.0*	**125**	**48.1**	37.3 - 59.0	**83**	**30.9**	21.1 - 40.7			
	2010-2014	**56**	**45.6**	32.1 - 59.1	**32**	*62.7*	*40.4 - 85.0*	**133**	**51.1**	39.5 - 62.6	**108**	**35.2**	22.7 - 47.7			
Cyprus *	2000-2004	**4**	*75.2*	*38.4 - 100.0*				**4**	*77.7*	*36.0 - 100.0*	**4**	*51.9*	*8.9 - 95.0*			
	2005-2009	**25**	*83.8*	*57.9 - 100.0*	**44**	*75.3*	*60.6 - 90.1*	**19**	*87.4*	*66.6 - 100.0*	**23**	*74.0*	*39.7 - 100.0*			
	2010-2014	**27**	*83.8*	*57.9 - 100.0*	**64**	**64.5**	53.5 - 75.5	**47**	**75.5**	60.7 - 90.2	**34**	*40.2*	*16.6 - 63.7*			
India	2000-2004															
	2005-2009															
	2010-2014															
Israel *	2000-2004	**365**	**81.8**	76.8 - 86.8	**629**	**87.9**	84.3 - 91.5	**550**	**82.8**	79.1 - 86.4	**331**	**80.2**	75.0 - 85.5			
	2005-2009	**435**	**83.7**	79.4 - 87.9	**879**	**91.6**	88.6 - 94.5	**775**	**89.4**	86.3 - 92.4	**223**	**68.0**	61.0 - 75.1			
	2010-2014	**433**	**86.1**	81.6 - 90.6	**807**	**91.0**	87.8 - 94.1	**705**	**86.0**	82.6 - 89.5	**226**	**62.6**	55.2 - 70.0			
Japan	2000-2004	**69**	*55.8*	*41.7 - 69.9*	**46**	*46.8*	*31.6 - 62.1*	**207**	**66.4**	58.7 - 74.1	**37**	*49.9*	*31.2 - 68.6*			
	2005-2009	**173**	**58.9**	50.1 - 67.8	**126**	**55.1**	44.6 - 65.6	**526**	**70.1**	65.0 - 75.2	**40**	*25.4*	*10.8 - 40.0*			
	2010-2014	**131**	**63.5**	52.9 - 74.1	**95**	**55.9**	44.6 - 67.2	**362**	**72.4**	67.1 - 77.7	**13**	*25.4*	*10.8 - 40.0*			
Korea *	2000-2004	**98**	**35.8**	25.8 - 45.7	**98**	**30.8**	21.7 - 39.9	**350**	**53.0**	46.9 - 59.1	**55**	*22.1*	*10.5 - 33.7*			
	2005-2009	**217**	**42.9**	35.8 - 50.1	**142**	**37.0**	28.9 - 45.0	**575**	**56.9**	52.1 - 61.8	**68**	**28.1**	17.9 - 38.2			
	2010-2014	**211**	**41.2**	33.9 - 48.4	**168**	**44.7**	35.9 - 53.5	**712**	**62.5**	57.8 - 67.1	**68**	**25.5**	15.1 - 35.8			
Kuwait *	2000-2004															
	2005-2009															
	2010-2014															
Qatar *	2000-2004										**4**	*100.0*	*100.0 - 100.0*			
	2005-2009										**8**	*50.7*	*1.1 - 100.0*			
	2010-2014							**11**	*100.0*	*100.0 - 100.0*	**8**	*100.0*	*100.0 - 100.0*			
Singapore *	2000-2004	**4**	*90.0*	*50.7 - 100.0*	**11**	*73.6*	*48.5 - 98.7*	**19**	*58.3*	*17.2 - 99.3*	**5**	*40.6*	*3.8 - 77.3*			
	2005-2009	**8**	*63.9*	*31.7 - 96.1*	**13**	*79.1*	*56.0 - 100.0*	**32**	*52.0*	*32.4 - 71.6*	**7**	*73.4*	*39.0 - 100.0*			
	2010-2014	**11**	*63.9*	*31.7 - 96.1*	**20**	*83.8*	*60.1 - 100.0*	**50**	**53.9**	43.9 - 63.8	**7**	*73.4*	*39.0 - 100.0*			
Taiwan *	2000-2004	**60**	*48.0*	*33.6 - 62.5*	**50**	*46.9*	*31.8 - 61.9*	**285**	**44.7**	37.2 - 52.2	**27**	*24.2*	*7.1 - 41.3*			
	2005-2009	**61**	*41.9*	*26.8 - 57.1*	**60**	**33.5**	21.8 - 45.2	**382**	**53.2**	47.3 - 59.1	**34**	*19.3*	*4.8 - 33.9*			
	2010-2014	**85**	**43.5**	30.3 - 56.7	**91**	**41.7**	30.2 - 53.2	**442**	**47.6**	41.5 - 53.7	**50**	**18.5**	9.2 - 27.9			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): men (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

MEN

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Thailand §	2000-2004	**6**	*77.6*	*40.7 - 100.0*	**8**	*13.4*	*0.0 - 32.7*	**20**	*39.2*	*16.0 - 62.5*	**9**	*14.4*	*0.0 - 33.8*			
	2005-2009	**20**	*57.8*	*35.9 - 79.7*	**8**	*18.9*	*0.0 - 51.7*	**65**	**31.2**	20.9 - 41.5	**32**	*31.5*	*14.7 - 48.4*			
	2010-2014	**12**	*47.7*	*17.5 - 77.9*	**13**	*18.9*	*0.0 - 51.7*	**62**	**55.2**	44.8 - 65.5	**10**	*21.0*	*0.0 - 46.7*			
Turkey	2000-2004	**35**	*70.3*	*50.4 - 90.1*	**45**	*63.9*	*46.6 - 81.2*	**50**	*60.4*	*43.0 - 77.9*	**26**	*59.8*	*35.3 - 84.3*			
	2005-2009	**194**	**61.6**	53.6 - 69.6	**161**	**48.3**	39.0 - 57.5	**200**	**55.4**	47.9 - 62.9	**103**	**24.6**	16.6 - 32.6			
	2010-2014	**225**	**59.6**	52.2 - 67.0	**154**	**53.9**	45.3 - 62.5	**213**	**55.1**	47.4 - 62.8	**111**	**35.3**	26.1 - 44.6			
EUROPE																
Austria *	2000-2004	**360**	**84.1**	79.2 - 89.0	**953**	**92.0**	*89.0 - 95.0*	**677**	**87.0**	*83.5 - 90.5*	**797**	**61.1**	57.3 - 65.0			
	2005-2009	**431**	**88.1**	83.6 - 92.5	**1,089**	**92.1**	*89.5 - 94.8*	**757**	**88.5**	*85.1 - 91.9*	**797**	**60.6**	56.7 - 64.6			
	2010-2014	**585**	**89.0**	85.1 - 92.9	**1,398**	**94.2**	*91.9 - 96.5*	**1,048**	**91.7**	*88.7 - 94.8*	**834**	**65.4**	61.5 - 69.4			
Belgium *	2000-2004	**112**	*78.6*	*65.4 - 91.9*	**191**	**83.3**	76.1 - 90.4	**170**	**86.6**	79.1 - 94.0	**130**	**82.6**	74.7 - 90.5			
	2005-2009	**678**	**83.2**	79.2 - 87.3	**1,220**	**83.6**	80.8 - 86.5	**1,108**	**87.0**	84.2 - 89.7	**340**	**85.5**	80.1 - 90.9			
	2010-2014	**972**	**87.9**	84.6 - 91.2	**2,035**	**88.7**	86.4 - 91.1	**1,790**	**88.7**	86.3 - 91.0	**119**	**73.3**	64.9 - 81.6			
Bulgaria *	2000-2004	**159**	**34.4**	25.3 - 43.5	**421**	**45.5**	*39.6 - 51.4*	**191**	**47.5**	*38.9 - 56.2*	**62**	**26.7**	16.5 - 36.8			
	2005-2009	**200**	**47.8**	38.8 - 56.8	**521**	**48.1**	*42.9 - 53.3*	**213**	**47.7**	*40.3 - 55.1*	**58**	**12.1**	5.0 - 19.2			
	2010-2014	**205**	**57.2**	48.1 - 66.3	**647**	**54.5**	*49.6 - 59.3*	**267**	**55.6**	*48.9 - 62.3*	**70**	**21.5**	12.1 - 30.9			
Croatia *	2000-2004	**130**	**68.8**	58.1 - 79.5	**223**	**62.1**	54.0 - 70.2	**100**	**56.3**	46.8 - 65.7	**616**	**59.9**	55.1 - 64.8			
	2005-2009	**221**	**71.5**	64.0 - 79.0	**461**	**73.3**	68.1 - 78.4	**167**	**72.6**	64.6 - 80.6	**556**	**67.7**	62.8 - 72.7			
	2010-2014	**188**	**69.9**	61.9 - 77.9	**528**	**75.8**	71.1 - 80.5	**242**	**77.8**	70.8 - 84.9	**538**	**74.1**	69.1 - 79.0			
Czech Republic *	2000-2004	**477**	**71.2**	65.6 - 76.7	**2,139**	**80.1**	*77.8 - 82.5*	**989**	**80.1**	*77.0 - 83.3*	**244**	**51.9**	44.2 - 59.6			
	2005-2009	**652**	**78.9**	74.5 - 83.2	**2,708**	**84.9**	*83.0 - 86.8*	**1,225**	**82.0**	*79.3 - 84.8*	**207**	**50.2**	42.2 - 58.1			
	2010-2014	**761**	**78.1**	73.8 - 82.4	**3,112**	**86.3**	*84.6 - 88.1*	**1,418**	**85.4**	*82.9 - 88.0*	**203**	**41.5**	33.6 - 49.4			
Denmark *	2000-2004	**323**	**85.4**	80.2 - 90.6	**1,156**	**85.3**	*82.4 - 88.1*	**583**	**84.5**	*80.2 - 88.7*	**388**	**71.4**	65.5 - 77.3			
	2005-2009	**481**	**83.5**	79.1 - 87.8	**1,869**	**90.6**	*88.7 - 92.6*	**815**	**93.4**	*90.5 - 96.3*	**573**	**59.9**	55.1 - 64.6			
	2010-2014	**704**	**87.1**	83.5 - 90.8	**2,806**	**93.1**	*91.5 - 94.8*	**1,209**	**94.8**	*92.2 - 97.4*	**300**	**55.5**	50.0 - 61.0			
Estonia *	2000-2004	**30**	*59.9*	*37.2 - 82.7*	**112**	**57.5**	47.6 - 67.5	**57**	*54.0*	*37.3 - 70.7*	**6**	*37.1*	*0.0 - 74.7*			
	2005-2009	**38**	*60.9*	*40.9 - 80.9*	**162**	**64.8**	55.7 - 73.8	**73**	*77.6*	*65.2 - 89.9*	**9**	*23.7*	*0.0 - 48.8*			
	2010-2014	**27**	**92.1**	78.9 - 100.0	**148**	**76.4**	67.3 - 85.6	**60**	**83.8**	72.5 - 95.1	**9**	*37.1*	*0.0 - 74.7*			
Finland *	2000-2004	**252**	**71.8**	64.8 - 78.8	**886**	**82.3**	*78.9 - 85.7*	**415**	**85.7**	*80.9 - 90.5*	**248**	**75.1**	68.3 - 81.9			
	2005-2009	**362**	**84.0**	79.5 - 88.6	**1,176**	**85.7**	*82.9 - 88.4*	**644**	**88.7**	*85.2 - 92.2*	**325**	**75.7**	70.1 - 81.3			
	2010-2014	**479**	**84.4**	80.0 - 88.9	**1,394**	**88.5**	*86.0 - 91.0*	**843**	**88.7**	*85.6 - 91.9*	**605**	**78.7**	73.7 - 83.8			
France	2000-2004	**360**	**83.6**	78.3 - 88.8	**841**	**87.4**	84.0 - 90.7	**657**	**85.8**	82.5 - 89.1	**129**	**91.2**	84.4 - 97.9			
	2005-2009	**695**	**87.0**	83.2 - 90.9	**1,503**	**89.7**	87.4 - 92.0	**1,134**	**88.2**	85.0 - 91.4	**106**	**85.7**	77.2 - 94.1			
	2010-2014	**136**	**88.9**	81.6 - 96.1	**353**	**92.4**	87.9 - 96.8	**293**	**85.6**	79.4 - 91.9	**20**	**56.3**	36.8 - 75.9			
Germany	2000-2004	**1,510**	**88.9**	86.4 - 91.3	**3,911**	**92.4**	90.9 - 93.9	**3,184**	**88.8**	87.2 - 90.4	**772**	**70.8**	66.8 - 74.9	**7**	*34.5*	*1.2 - 67.8*
	2005-2009	**2,013**	**86.7**	84.3 - 89.1	**5,280**	**92.5**	91.3 - 93.7	**4,249**	**92.9**	91.6 - 94.2	**729**	**67.6**	63.3 - 71.9	**6**	*39.6*	*1.5 - 77.8*
	2010-2014	**1,926**	**88.2**	85.8 - 90.5	**5,320**	**93.7**	92.6 - 94.9	**4,335**	**93.2**	92.0 - 94.5	**677**	**70.8**	66.7 - 74.9	**9**	*66.5*	*30.6 - 100.0*

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		MEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Gibraltar *	2000-2004				**5**	*62.9*	*23.9 - 100.0*	**3**	*34.9*	*0.0 - 76.4*						
	2005-2009				**3**	*100.0*	*100.0 - 100.0*	**2**	*100.0*	*100.0 - 100.0*						
	2010-2014				**5**	*100.0*	*100.0 - 100.0*	**3**	*100.0*	*100.0 - 100.0*						
Iceland *	2000-2004	**24**	*72.2*	*50.8 - 93.6*	**41**	*97.8*	*87.9 - 100.0*	**28**	*75.0*	*54.1 - 96.0*						
	2005-2009	**31**	*81.1*	*59.4 - 100.0*	**54**	*82.4*	*69.1 - 95.7*	**17**	*71.9*	*47.5 - 96.2*						
	2010-2014	**16**	*81.1*	*59.4 - 100.0*	**41**	**86.7**	76.4 - 96.9	**28**	**87.9**	77.8 - 98.0						
Ireland *	2000-2004	**311**	**82.2**	76.1 - 88.3	**295**	**79.3**	72.9 - 85.7	**347**	**75.5**	69.8 - 81.2	**28**	*43.2*	*22.4 - 64.0*			
	2005-2009	**537**	**82.5**	78.1 - 86.8	**423**	**81.0**	76.3 - 85.6	**459**	**77.7**	73.3 - 82.2	**28**	*28.5*	*11.3 - 45.7*			
	2010-2014	**539**	**84.5**	80.0 - 89.0	**528**	**88.5**	84.0 - 93.0	**490**	**82.3**	77.8 - 86.8	**33**	*43.2*	*22.4 - 64.0*			
Italy	2000-2004	**869**	**76.6**	72.9 - 80.3	**3,082**	**82.9**	81.2 - 84.6	**1,989**	**82.3**	80.3 - 84.4	**1,065**	**71.6**	68.5 - 74.6			
	2005-2009	**1,317**	**80.4**	77.5 - 83.3	**5,147**	**86.4**	85.1 - 87.6	**3,322**	**84.7**	83.2 - 86.3	**1,714**	**76.5**	74.1 - 78.8			
	2010-2014	**587**	**80.2**	76.6 - 83.9	**2,231**	**86.4**	84.9 - 88.0	**1,434**	**84.2**	82.2 - 86.2	**511**	**75.2**	71.7 - 78.7			
Latvia *	2000-2004	**44**	*63.0*	*42.6 - 83.3*	**128**	**63.5**	53.5 - 73.6	**51**	*53.0*	*35.7 - 70.3*	**9**	*48.3*	*16.7 - 79.8*			
	2005-2009	**48**	*42.3*	*24.1 - 60.6*	**160**	**65.7**	56.4 - 74.9	**87**	**57.8**	47.0 - 68.6	**13**	*24.5*	*2.3 - 46.7*			
	2010-2014	**50**	**48.9**	33.7 - 64.0	**212**	**64.6**	55.7 - 73.4	**88**	**76.8**	66.8 - 86.9	**14**	*35.8*	*9.5 - 62.0*			
Lithuania *	2000-2004	**60**	**61.9**	50.8 - 72.9	**193**	**57.7**	48.8 - 66.7	**110**	**63.3**	52.5 - 74.0	**38**	*42.9*	*25.1 - 60.6*			
	2005-2009	**77**	**63.6**	50.9 - 76.4	**224**	**60.2**	52.7 - 67.7	**108**	**46.1**	36.9 - 55.3	**35**	*56.9*	*35.8 - 78.0*			
	2010-2014	**61**	**74.5**	59.4 - 89.6	**173**	**58.8**	49.9 - 67.7	**101**	**53.8**	44.4 - 63.2	**16**	*56.9*	*35.8 - 78.0*			
Malta *	2000-2004	**13**	*91.7*	*70.5 - 100.0*	**42**	*98.3*	*84.1 - 100.0*	**22**	*70.5*	*47.9 - 93.2*						
	2005-2009	**11**	*36.7*	*3.1 - 70.3*	**34**	*80.1*	*60.4 - 99.7*	**16**	*72.6*	*49.1 - 96.1*						
	2010-2014	**16**	*36.7*	*3.1 - 70.3*	**49**	**79.9**	72.2 - 87.6	**28**	*93.3*	*72.3 - 100.0*						
Netherlands *	2000-2004	**1,018**	**81.9**	78.6 - 85.1	**2,858**	**85.4**	*83.2 - 87.6*	**2,024**	**85.5**	*83.1 - 88.0*	**23**	*72.9*	*49.0 - 96.8*			
	2005-2009	**1,341**	**84.1**	81.5 - 86.8	**4,199**	**87.0**	*85.4 - 88.6*	**2,766**	**87.8**	*86.0 - 89.6*	**27**	*76.5*	*56.7 - 96.3*			
	2010-2014	**2,001**	**83.4**	80.9 - 85.9	**6,134**	**89.2**	*87.8 - 90.5*	**3,898**	**89.7**	*88.1 - 91.3*	**23**	**71.8**	56.5 - 87.1			
Norway *	2000-2004	**386**	**76.1**	70.2 - 82.0	**1,206**	**82.3**	*79.5 - 85.1*	**706**	**83.0**	*79.4 - 86.6*	**33**	*49.1*	*29.8 - 68.4*			
	2005-2009	**477**	**82.8**	78.2 - 87.4	**1,523**	**82.8**	*80.5 - 85.1*	**942**	**84.2**	*81.2 - 87.3*	**48**	*51.7*	*36.0 - 67.4*			
	2010-2014	**623**	**84.7**	80.6 - 88.9	**2,224**	**87.3**	*85.2 - 89.4*	**1,365**	**86.3**	*83.6 - 89.0*	**45**	**69.5**	57.2 - 81.7			
Poland *	2000-2004	**522**	**57.3**	52.1 - 62.4	**1,780**	**64.6**	*61.7 - 67.6*	**1,083**	**61.6**	*58.0 - 65.1*	**867**	**34.1**	30.4 - 37.8			
	2005-2009	**753**	**55.9**	51.6 - 60.2	**2,396**	**64.5**	*62.1 - 66.8*	**1,442**	**65.3**	*62.3 - 68.2*	**921**	**41.6**	37.9 - 45.4			
	2010-2014	**834**	**61.2**	57.0 - 65.3	**3,093**	**66.9**	*64.7 - 69.1*	**1,847**	**67.6**	*64.9 - 70.4*	**981**	**45.3**	41.5 - 49.1			
Portugal	2000-2004	**190**	**77.9**	70.0 - 85.8	**346**	**71.7**	66.1 - 77.3	**245**	**71.1**	64.9 - 77.3	**235**	**67.4**	60.5 - 74.2			
	2005-2009	**253**	**84.8**	78.2 - 91.4	**597**	**76.3**	72.4 - 80.3	**445**	**73.5**	68.5 - 78.4	**285**	**71.1**	65.2 - 77.1			
	2010-2014	**238**	**92.4**	82.0 - 100.0	**607**	**70.2**	61.0 - 79.4	**422**	**75.3**	63.9 - 86.8	**182**	**76.6**	66.1 - 87.1			
Romania (Cluj)	2000-2004															
	2005-2009	**17**	*59.1*	*28.2 - 90.1*	**52**	**70.1**	*59.4 - 80.8*	**29**	*64.9*	*45.8 - 84.0*	**6**	*18.5*	*0.0 - 43.6*			
	2010-2014	**11**	*68.0*	*30.1 - 100.0*	**54**	*66.7*	*48.0 - 85.5*	**30**	*59.8*	*38.6 - 80.9*	**9**	*23.4*	*0.0 - 48.1*			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): men (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

MEN

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Russia	2000-2004	**56**	**50.6**	37.9 - 63.4	**245**	**64.1**	56.0 - 72.3	**119**	**64.4**	53.7 - 75.2	**82**	**30.9**	19.7 - 42.1			
	2005-2009	**87**	**40.9**	30.0 - 51.8	**307**	**57.3**	49.9 - 64.7	**145**	**55.2**	45.3 - 65.0	**45**	*41.3*	*22.9 - 59.6*			
	2010-2014	**85**	**54.8**	41.6 - 68.0	**400**	**56.0**	48.9 - 63.1	**195**	**59.7**	50.6 - 68.8	**33**	*34.0*	*14.4 - 53.5*			
Slovakia *	2000-2004	**158**	**61.8**	52.9 - 70.6	**649**	**69.8**	*65.0 - 74.5*	**283**	**68.3**	*61.7 - 74.9*	**39**	*40.6*	*23.6 - 57.6*			
	2005-2009	**209**	**69.0**	60.5 - 77.5	**889**	**79.5**	*75.8 - 83.2*	**393**	**77.4**	*72.1 - 82.6*	**79**	**36.4**	25.0 - 47.9			
	2010-2014	**49**	**63.5**	47.8 - 79.1	**195**	**73.6**	*65.9 - 81.3*	**86**	**79.6**	*68.4 - 90.9*	**12**	**16.9**	4.3 - 29.5			
Slovenia *	2000-2004	**97**	**62.9**	51.9 - 73.8	**410**	**74.2**	*68.8 - 79.6*	**180**	**76.7**	*68.7 - 84.6*	**24**	*50.4*	*27.0 - 73.9*			
	2005-2009	**115**	**79.4**	70.8 - 88.1	**573**	**86.1**	*81.8 - 90.4*	**247**	**80.8**	*74.3 - 87.2*	**28**	*20.9*	*5.3 - 36.6*			
	2010-2014	**126**	**72.8**	63.6 - 81.9	**619**	**90.3**	*85.9 - 94.7*	**255**	**75.5**	*68.9 - 82.1*	**19**	*58.0*	*27.4 - 88.6*			
Spain	2000-2004	**321**	**78.5**	72.1 - 84.9	**645**	**80.5**	76.4 - 84.7	**438**	**78.4**	73.8 - 82.9	**237**	**76.4**	69.9 - 82.9			
	2005-2009	**456**	**77.0**	71.7 - 82.4	**921**	**84.3**	81.3 - 87.4	**608**	**82.9**	79.3 - 86.5	**189**	**82.9**	76.6 - 89.3			
	2010-2014	**275**	**69.8**	61.4 - 78.3	**621**	**83.6**	78.8 - 88.3	**328**	**84.2**	78.8 - 89.6	**45**	**72.0**	58.4 - 85.6			
Sweden *	2000-2004	**656**	**80.8**	76.5 - 85.1	**2,390**	**87.7**	85.9 - 89.4	**1,327**	**86.3**	83.9 - 88.8	**167**	**82.0**	75.6 - 88.4			
	2005-2009	**893**	**84.2**	80.9 - 87.5	**3,036**	**88.1**	86.5 - 89.6	**1,834**	**87.2**	85.2 - 89.3	**138**	**87.4**	80.2 - 94.6			
	2010-2014	**1,109**	**85.7**	82.8 - 88.6	**4,103**	**89.7**	88.3 - 91.1	**2,668**	**89.8**	88.0 - 91.5	**40**	**86.0**	75.6 - 96.4			
Switzerland	2000-2004	**163**	**93.6**	87.2 - 100.0	**364**	**88.4**	84.0 - 92.8	**274**	**85.1**	80.1 - 90.1	**16**	*38.2*	*15.3 - 61.2*			
	2005-2009	**451**	**86.1**	81.2 - 91.0	**992**	**93.5**	91.0 - 96.0	**888**	**91.2**	88.6 - 93.9	**54**	*59.2*	*41.9 - 76.4*			
	2010-2014	**301**	**88.7**	83.9 - 93.6	**712**	**94.8**	92.3 - 97.3	**510**	**92.3**	89.5 - 95.1	**38**	**56.0**	40.2 - 71.8			
United Kingdom *	2000-2004	**3,940**	**81.0**	79.1 - 82.8	**6,849**	**83.6**	82.3 - 84.9	**5,655**	**85.1**	83.7 - 86.4	**1,254**	**53.5**	50.4 - 56.6	**17**	*24.2*	*2.1 - 46.4*
	2005-2009	**5,657**	**84.7**	83.2 - 86.1	**10,515**	**87.3**	86.4 - 88.3	**8,024**	**87.6**	86.6 - 88.7	**1,206**	**58.2**	54.9 - 61.4	**32**	*57.0*	*34.7 - 79.3*
	2010-2014	**7,944**	**86.4**	85.0 - 87.7	**13,881**	**90.0**	89.1 - 90.8	**10,789**	**88.9**	88.0 - 89.9	**853**	**49.4**	45.7 - 53.1	**29**	*56.5*	*30.0 - 83.1*
OCEANIA																
Australia *	2000-2004	**5,678**	**88.2**	87.1 - 89.4	**11,429**	**93.3**	92.6 - 94.0	**9,325**	**93.6**	92.8 - 94.4	**1,312**	**50.1**	47.0 - 53.3			
	2005-2009	**6,855**	**88.1**	87.0 - 89.2	**13,019**	**94.0**	93.3 - 94.7	**10,824**	**94.2**	93.5 - 95.0	**1,361**	**45.0**	41.7 - 48.3			
	2010-2014	**6,627**	**88.2**	87.1 - 89.3	**12,391**	**94.8**	94.1 - 95.5	**10,428**	**94.8**	94.1 - 95.6	**1,294**	**46.3**	42.8 - 49.8			
New Zealand *	2000-2004	**908**	**85.7**	82.7 - 88.8	**1,895**	**92.0**	90.1 - 94.0	**1,441**	**90.7**	88.4 - 93.1	**299**	**41.5**	35.0 - 47.9			
	2005-2009	**1,100**	**85.9**	83.0 - 88.8	**2,267**	**92.2**	90.5 - 93.9	**1,970**	**93.1**	91.3 - 94.8	**329**	**35.7**	29.5 - 41.8			
	2010-2014	**1,225**	**88.4**	85.7 - 91.0	**2,506**	**93.8**	92.2 - 95.4	**2,089**	**92.7**	91.0 - 94.5	**313**	**36.2**	29.0 - 43.4			

* Data with 100% coverage of the national population

[§] Survival estimate considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), ***or*** (b) registered only from a death certificate or at autopsy, ***or*** (c) registered with incomplete dates, i.e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status

Italics denote survival estimates that are not age-standardised

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): women (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		WOMEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AFRICA																
Algeria	2000-2004										**7**	*9.0*	*0.0 - 29.5*			
	2005-2009										**37**	*0.3*	*0.0 - 1.1*			
	2010-2014										**28**	*0.3*	*0.0 - 1.1*			
Nigeria (Ibadan)	2000-2004															
	2005-2009							**12**	*100.0*	*100.0 - 100.0*						
	2010-2014							**13**	*100.0*	*100.0 - 100.0*						
South Africa (Eastern Cape)	2000-2004															
	2005-2009															
	2010-2014															
AMERICA (CENTRAL AND SOUTH)																
Argentina	2000-2004	**14**	*62.0*	*34.9 - 89.0*	**15**	*67.6*	*44.0 - 91.2*	**26**	*70.8*	*51.5 - 90.0*	**40**	*54.1*	*36.9 - 71.2*			
	2005-2009	**29**	*88.1*	*65.7 - 100.0*	**35**	*72.9*	*57.8 - 88.0*	**81**	**71.3**	61.4 - 81.1	**110**	**69.5**	61.1 - 77.8			
	2010-2014	**20**	*49.9*	*15.8 - 83.9*	**21**	**73.4**	64.7 - 82.1	**65**	**78.0**	67.8 - 88.1	**97**	**67.6**	58.8 - 76.3			
Brazil	2000-2004	**43**	*93.0*	*79.3 - 100.0*	**61**	*80.4*	*69.2 - 91.6*	**123**	**86.2**	78.0 - 94.3	**18**	*45.9*	*22.4 - 69.3*			
	2005-2009	**56**	*87.2*	*71.3 - 100.0*	**77**	**88.2**	80.7 - 95.7	**139**	**88.7**	82.3 - 95.2	**41**	*49.4*	*33.3 - 65.5*			
	2010-2014	**34**	**85.8**	74.9 - 96.6	**45**	**83.8**	75.1 - 92.4	**87**	**84.6**	76.1 - 93.0	**34**	**53.9**	42.8 - 65.0			
Chile	2000-2004	**15**	*64.1*	*38.3 - 89.8*	**2**	*50.3*	*0.7 - 99.8*	**26**	*65.8*	*44.3 - 87.4*	**9**	*70.7*	*40.7 - 100.0*			
	2005-2009	**18**	*75.4*	*34.3 - 100.0*	**7**	*57.8*	*23.9 - 91.7*	**35**	*78.4*	*56.3 - 100.0*	**8**	*38.5*	*7.2 - 69.9*			
	2010-2014	**16**	*75.4*	*34.3 - 100.0*	**7**	*82.0*	*47.0 - 100.0*	**32**	**85.3**	74.5 - 96.0	**14**	*69.3*	*43.3 - 95.3*			
Colombia §	2000-2004	**27**	*77.1*	*51.9 - 100.0*	**28**	*79.7*	*62.2 - 97.2*	**111**	**68.6**	59.4 - 77.8	**18**	*0.6*	*0.0 - 2.0*			
	2005-2009	**50**	*77.0*	*58.7 - 95.4*	**38**	*83.1*	*68.7 - 97.5*	**154**	**72.5**	63.8 - 81.2	**22**	*38.2*	*16.1 - 60.3*			
	2010-2014	**39**	**58.4**	42.1 - 74.6	**32**	**78.2**	66.1 - 90.4	**121**	**72.0**	61.6 - 82.5	**22**	*30.9*	*5.1 - 56.7*			
Costa Rica *	2000-2004	**29**	*100.0*	*91.0 - 100.0*	**20**	*84.8*	*67.9 - 100.0*	**95**	**85.6**	78.0 - 93.2	**17**	*64.7*	*39.1 - 90.3*			
	2005-2009	**45**	*85.2*	*68.2 - 100.0*	**34**	*82.8*	*68.8 - 96.8*	**151**	**79.5**	71.6 - 87.5	**20**	*33.9*	*12.3 - 55.5*			
	2010-2014	**86**	**87.1**	76.9 - 97.3	**51**	**87.8**	78.2 - 97.4	**144**	**80.7**	72.5 - 89.0	**30**	*33.9*	*12.3 - 55.5*			
Ecuador	2000-2004	**25**	*71.3*	*41.7 - 100.0*	**11**	*40.0*	*11.7 - 68.3*	**70**	**57.8**	46.9 - 68.7	**5**	*25.0*	*0.0 - 62.8*			
	2005-2009	**33**	*75.1*	*52.3 - 98.0*	**18**	*73.3*	*46.6 - 100.0*	**115**	**69.7**	60.5 - 78.9	**32**	*51.8*	*33.8 - 69.8*			
	2010-2014	**36**	*93.5*	*68.7 - 100.0*	**11**	*60.4*	*19.2 - 100.0*	**135**	**62.0**	52.5 - 71.4	**22**	*56.4*	*31.9 - 80.9*			
Guadeloupe *	2000-2004															
	2005-2009							**5**	*83.3*	*27.9 - 100.0*						
	2010-2014				**6**	*100.0*	*100.0 - 100.0*	**6**	*27.8*	*0.0 - 82.2*						
Martinique *	2000-2004				**3**	*68.4*	*21.4 - 100.0*	**10**	*31.9*	*3.0 - 60.9*	**14**	*100.0*	*100.0 - 100.0*			
	2005-2009				**10**	*93.4*	*74.0 - 100.0*	**17**	*90.1*	*70.3 - 100.0*	**5**	*100.0*	*100.0 - 100.0*			
	2010-2014				**4**	*93.4*	*74.0 - 100.0*	**13**	*31.9*	*3.0 - 60.9*	**14**	*100.0*	*100.0 - 100.0*			
Puerto Rico *	2000-2004	**31**	*82.8*	*56.7 - 100.0*	**31**	*82.2*	*66.6 - 97.8*	**109**	**80.7**	72.1 - 89.3	**29**	*66.8*	*44.9 - 88.7*			
	2005-2009	**27**	*69.2*	*48.1 - 90.4*	**41**	*93.5*	*82.2 - 100.0*	**113**	**78.9**	71.0 - 86.8	**13**	*63.5*	*33.2 - 93.8*			
	2010-2014	**21**	**74.8**	59.8 - 89.8	**17**	**75.4**	57.9 - 93.0	**38**	**84.8**	73.9 - 95.7	**14**	*67.7*	*41.2 - 94.3*			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): women (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		WOMEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AMERICA (NORTH)																
Canada	2000-2004	**1,313**	**90.8**	88.6 - 93.0	**2,116**	**87.0**	85.0 - 89.1	**5,482**	**93.6**	92.6 - 94.6	**383**	**59.1**	53.9 - 64.3	**76**	*62.0*	*49.2 - 74.9*
	2005-2009	**1,664**	**92.0**	90.1 - 93.8	**2,537**	**88.3**	86.5 - 90.0	**6,713**	**94.6**	93.8 - 95.4	**610**	**55.9**	51.7 - 60.1	**94**	**57.3**	47.1 - 67.6
	2010-2014	**1,848**	**93.1**	91.4 - 94.8	**2,918**	**90.7**	89.2 - 92.3	**7,977**	**95.4**	94.6 - 96.2	**510**	**47.9**	43.4 - 52.5	**94**	**48.5**	36.0 - 61.0
United States	2000-2004	**10,959**	**90.5**	89.7 - 91.3	**20,668**	**91.7**	91.0 - 92.3	**45,714**	**95.0**	94.6 - 95.3	**3,511**	**49.3**	47.5 - 51.1	**643**	**59.1**	54.8 - 63.5
	2005-2009	**12,976**	**91.2**	90.5 - 91.9	**24,965**	**92.9**	92.4 - 93.5	**54,543**	**96.0**	95.7 - 96.3	**3,724**	**45.5**	43.7 - 47.3	**664**	**57.1**	52.4 - 61.8
	2010-2014	**10,620**	**92.1**	91.4 - 92.8	**21,307**	**93.6**	93.1 - 94.2	**46,203**	**96.3**	96.0 - 96.6	**2,971**	**43.8**	41.9 - 45.7	**590**	**59.5**	54.8 - 64.2
ASIA																
China	2000-2004	**17**	*68.2*	*45.2 - 91.2*	**9**	*25.5*	*0.0 - 51.7*	**17**	*54.0*	*30.5 - 77.5*	**21**	*34.5*	*11.7 - 57.4*			
	2005-2009	**38**	*87.3*	*66.2 - 100.0*	**37**	*51.5*	*34.8 - 68.2*	**98**	**55.2**	45.4 - 65.0	**91**	**33.4**	23.2 - 43.7	**8**	*28.5*	*0.0 - 58.9*
	2010-2014	**64**	**56.9**	40.1 - 73.7	**25**	*66.6*	*47.4 - 85.9*	**144**	**52.1**	41.1 - 63.1	**84**	**43.1**	31.6 - 54.6	**13**	*60.7*	*32.8 - 88.6*
Cyprus *	2000-2004	**5**	*80.6*	*47.6 - 100.0*												
	2005-2009	**16**	*96.9*	*66.3 - 100.0*	**25**	*81.7*	*64.6 - 98.9*	**65**	**86.1**	79.2 - 93.0	**22**	*80.1*	*62.4 - 97.7*			
	2010-2014	**14**	*100.0*	*100.0 - 100.0*	**29**	**87.0**	76.4 - 97.6	**77**	**89.8**	83.6 - 96.0	**27**	*56.1*	*25.0 - 87.2*			
India	2000-2004															
	2005-2009															
	2010-2014															
Israel *	2000-2004	**245**	**88.9**	84.5 - 93.3	**442**	**87.9**	83.9 - 91.9	**823**	**89.6**	86.9 - 92.3	**307**	**78.0**	72.7 - 83.2	**19**	*21.8*	*3.2 - 40.4*
	2005-2009	**319**	**88.0**	83.3 - 92.7	**533**	**86.6**	83.1 - 90.2	**1,120**	**93.3**	91.2 - 95.3	**220**	**78.0**	72.3 - 83.8	**17**	*31.6*	*8.6 - 54.7*
	2010-2014	**265**	**89.1**	83.9 - 94.2	**432**	**88.8**	85.0 - 92.6	**960**	**92.1**	89.9 - 94.3	**174**	**75.0**	68.1 - 82.0	**28**	*55.1*	*32.7 - 77.6*
Japan	2000-2004	**55**	*74.0*	*56.6 - 91.5*	**44**	*61.8*	*46.5 - 77.2*	**231**	**79.0**	73.3 - 84.7	**28**	*76.2*	*60.1 - 92.2*	**16**	*38.8*	*15.5 - 62.1*
	2005-2009	**194**	**58.1**	48.1 - 68.0	**117**	**60.5**	51.1 - 69.8	**560**	**83.5**	79.9 - 87.2	**38**	*58.6*	*38.1 - 79.0*	**39**	*22.8*	*7.7 - 37.8*
	2010-2014	**120**	**57.1**	45.7 - 68.5	**89**	**68.6**	59.3 - 77.9	**362**	**80.2**	75.5 - 84.9	**12**	*58.6*	*38.1 - 79.0*	**25**	*22.8*	*7.7 - 37.8*
Korea *	2000-2004	**126**	**57.5**	48.6 - 66.4	**94**	**48.1**	37.8 - 58.5	**387**	**67.6**	62.5 - 72.7	**55**	**27.2**	17.6 - 36.7	**11**	*37.1*	*7.8 - 66.4*
	2005-2009	**203**	**55.8**	47.9 - 63.6	**128**	**50.7**	41.8 - 59.6	**586**	**68.7**	64.7 - 72.7	**55**	**31.7**	20.1 - 43.3	**20**	*67.6*	*46.1 - 89.2*
	2010-2014	**265**	**66.2**	59.3 - 73.0	**141**	**52.2**	43.6 - 60.9	**822**	**72.8**	69.1 - 76.5	**64**	**28.8**	17.2 - 40.5	**40**	*0.1*	*0.0 - 0.2*
Kuwait *	2000-2004															
	2005-2009															
	2010-2014															
Qatar *	2000-2004															
	2005-2009															
	2010-2014															
Singapore *	2000-2004	**4**	*0.1*	*0.0 - 0.3*	**6**	*33.7*	*0.5 - 66.9*	**31**	*74.0*	*55.2 - 92.9*	**3**	*36.2*	*0.0 - 81.1*			
	2005-2009	**7**	*61.6*	*25.3 - 97.9*	**9**	*44.7*	*14.6 - 74.7*	**40**	*50.8*	*32.3 - 69.3*	**13**	*54.4*	*28.0 - 80.7*			
	2010-2014	**6**	*0.1*	*0.0 - 0.3*	**13**	*77.4*	*47.5 - 100.0*	**35**	**61.4**	51.2 - 71.6	**3**	*54.4*	*28.0 - 80.7*			
Taiwan *	2000-2004	**30**	*34.2*	*17.0 - 51.3*	**55**	*43.7*	*30.1 - 57.3*	**266**	**59.4**	52.7 - 66.1	**31**	*17.2*	*4.3 - 30.0*			
	2005-2009	**44**	*49.0*	*32.9 - 65.2*	**56**	*54.6*	*41.0 - 68.2*	**330**	**64.7**	58.9 - 70.6	**24**	*22.0*	*5.9 - 38.1*			
	2010-2014	**43**	**45.7**	30.4 - 60.9	**69**	**51.5**	39.3 - 63.8	**361**	**69.2**	63.8 - 74.6	**45**	**19.1**	8.5 - 29.8			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): women (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		WOMEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Thailand §	2000-2004	**11**	*88.2*	*47.3 - 100.0*	**13**	*52.3*	*24.4 - 80.2*	**24**	*36.3*	*15.8 - 56.8*	**11**	*73.7*	*48.5 - 98.9*			
	2005-2009	**22**	*64.0*	*40.8 - 87.2*	**15**	*34.9*	*11.6 - 58.2*	**57**	*35.9*	*22.3 - 49.5*	**35**	*44.4*	*12.4 - 76.4*			
	2010-2014	**19**	*64.0*	*40.8 - 87.2*	**21**	*34.9*	*11.6 - 58.2*	**62**	**27.2**	16.8 - 37.6	**23**	*44.4*	*12.4 - 76.4*			
Turkey	2000-2004	**44**	*80.5*	*64.5 - 96.5*	**21**	*45.9*	*23.1 - 68.6*	**42**	*59.4*	*42.3 - 76.6*	**18**	*15.4*	*0.0 - 32.4*			
	2005-2009	**203**	**70.8**	63.9 - 77.7	**94**	**56.5**	46.2 - 66.8	**196**	**68.7**	61.8 - 75.6	**74**	**50.2**	38.2 - 62.2			
	2010-2014	**216**	**76.1**	69.6 - 82.7	**87**	**63.1**	50.7 - 75.6	**251**	**71.0**	63.8 - 78.1	**79**	**50.8**	39.3 - 62.3			
EUROPE																
Austria *	2000-2004	**377**	**89.9**	85.0 - 94.9	**484**	**87.8**	*83.3 - 92.3*	**1,190**	**90.4**	*88.2 - 92.6*	**664**	**71.5**	67.6 - 75.4	**24**	*43.8*	*22.5 - 65.1*
	2005-2009	**411**	**94.7**	91.7 - 97.7	**632**	**89.0**	*85.3 - 92.8*	**1,302**	**92.8**	*90.8 - 94.8*	**658**	**63.6**	59.7 - 67.6	**25**	*33.7*	*13.0 - 54.4*
	2010-2014	**540**	**92.8**	89.1 - 96.6	**784**	**97.0**	*93.5 - 100.0*	**1,652**	**93.1**	*91.2 - 95.1*	**647**	**68.9**	65.0 - 72.7	**27**	*41.4*	*10.2 - 72.5*
Belgium *	2000-2004	**82**	**83.2**	74.9 - 91.5	**152**	**86.2**	80.2 - 92.2	**440**	**90.7**	87.0 - 94.4	**203**	**84.3**	78.3 - 90.3	**11**	*34.0*	*0.0 - 72.2*
	2005-2009	**597**	**84.6**	80.5 - 88.7	**1,118**	**87.9**	84.8 - 90.9	**2,938**	**93.3**	91.9 - 94.6	**492**	**87.3**	83.5 - 91.1	**48**	*45.4*	*27.6 - 63.1*
	2010-2014	**768**	**87.8**	84.2 - 91.5	**1,728**	**91.4**	88.8 - 93.9	**4,267**	**94.1**	92.9 - 95.4	**146**	**81.3**	74.9 - 87.7	**36**	*45.4*	*27.6 - 63.1*
Bulgaria *	2000-2004	**146**	**52.3**	42.2 - 62.4	**196**	**50.5**	*43.3 - 57.7*	**358**	**68.9**	*63.1 - 74.8*	**55**	**33.5**	21.6 - 45.5	**10**	*22.1*	*0.0 - 45.7*
	2005-2009	**153**	**61.5**	52.0 - 71.0	**250**	**55.9**	*49.3 - 62.5*	**469**	**74.6**	*69.8 - 79.4*	**47**	*19.9*	*8.4 - 31.4*	**7**	*67.5*	*29.0 - 100.0*
	2010-2014	**212**	**57.7**	48.2 - 67.1	**332**	**65.1**	*58.7 - 71.5*	**567**	**73.5**	*69.1 - 77.9*	**50**	**42.5**	28.8 - 56.2	**8**	*48.9*	*10.2 - 87.6*
Croatia *	2000-2004	**125**	**69.7**	59.5 - 80.0	**172**	**60.5**	52.2 - 68.7	**179**	**76.1**	69.4 - 82.8	**645**	**71.7**	67.6 - 75.9			
	2005-2009	**195**	**86.0**	80.0 - 92.1	**273**	**74.9**	68.9 - 81.0	**366**	**80.2**	75.8 - 84.6	**551**	**74.9**	70.8 - 79.1			
	2010-2014	**179**	**75.2**	67.7 - 82.7	**293**	**76.1**	70.7 - 81.6	**437**	**85.1**	81.0 - 89.2	**447**	**78.7**	74.2 - 83.1			
Czech Republic *	2000-2004	**548**	**85.5**	81.3 - 89.7	**1,237**	**80.5**	*77.6 - 83.5*	**1,887**	**85.8**	*83.8 - 87.8*	**201**	**63.4**	56.0 - 70.8	**20**	*33.3*	*9.4 - 57.1*
	2005-2009	**640**	**84.5**	80.6 - 88.3	**1,459**	**85.7**	*83.3 - 88.1*	**2,287**	**89.6**	*87.7 - 91.4*	**161**	**63.4**	55.3 - 71.4	**20**	*43.4*	*20.6 - 66.1*
	2010-2014	**682**	**88.0**	84.6 - 91.5	**1,751**	**87.1**	*85.0 - 89.2*	**2,552**	**88.7**	*87.0 - 90.3*	**183**	**70.7**	62.8 - 78.6	**31**	*44.7*	*15.0 - 74.4*
Denmark *	2000-2004	**279**	**88.4**	82.8 - 94.0	**823**	**88.7**	*85.4 - 92.0*	**1,610**	**92.3**	*90.3 - 94.4*	**375**	**83.2**	78.3 - 88.0	**8**	*44.6*	*7.6 - 81.6*
	2005-2009	**356**	**90.9**	87.0 - 94.9	**1,457**	**92.2**	*89.8 - 94.6*	**2,172**	**95.8**	*94.2 - 97.4*	**529**	**73.1**	68.9 - 77.4	**16**	*80.3*	*56.7 - 100.0*
	2010-2014	**554**	**92.8**	89.4 - 96.2	**2,028**	**93.6**	*91.5 - 95.8*	**2,951**	**96.0**	*94.5 - 97.4*	**247**	**66.3**	61.2 - 71.4	**14**	*45.6*	*17.0 - 74.2*
Estonia *	2000-2004	**66**	*78.7*	*63.0 - 94.4*	**128**	**69.2**	60.0 - 78.4	**195**	**80.8**	74.6 - 87.1	**10**	*62.2*	*31.4 - 93.0*			
	2005-2009	**58**	*70.1*	*54.7 - 85.5*	**150**	**73.5**	66.1 - 80.8	**273**	**82.7**	77.7 - 87.8	**8**	*25.6*	*0.0 - 52.4*			
	2010-2014	**37**	**95.7**	89.0 - 100.0	**142**	**76.7**	67.5 - 86.0	**162**	**88.4**	82.5 - 94.3	**12**	*34.4*	*9.6 - 59.2*			
Finland *	2000-2004	**301**	**89.3**	84.6 - 94.0	**426**	**85.6**	*81.2 - 90.1*	**798**	**91.4**	*88.9 - 94.0*	**237**	**81.0**	75.7 - 86.3	**14**	*32.9*	*6.3 - 59.4*
	2005-2009	**371**	**89.2**	84.3 - 94.0	**582**	**86.8**	*83.5 - 90.2*	**1,069**	**92.7**	*90.6 - 94.8*	**238**	**80.4**	74.6 - 86.2	**15**	*36.9*	*11.6 - 62.2*
	2010-2014	**504**	**93.7**	89.8 - 97.6	**789**	**86.9**	*83.9 - 89.9*	**1,481**	**92.3**	*90.4 - 94.3*	**468**	**88.2**	83.6 - 92.8	**22**	*59.5*	*25.2 - 93.7*
France	2000-2004	**401**	**88.9**	84.6 - 93.3	**472**	**88.8**	84.8 - 92.8	**1,452**	**92.2**	90.3 - 94.2	**166**	**93.4**	88.0 - 98.7	**14**	*54.2*	*27.2 - 81.1*
	2005-2009	**634**	**93.2**	90.5 - 96.0	**779**	**90.7**	87.3 - 94.0	**2,289**	**94.6**	93.1 - 96.1	**95**	**84.0**	75.8 - 92.2	**24**	*32.6*	*9.3 - 56.0*
	2010-2014	**104**	**92.6**	86.2 - 99.0	**193**	**94.2**	88.7 - 99.7	**535**	**94.2**	90.9 - 97.5	**16**	**68.0**	56.6 - 79.5	**5**	*32.6*	*9.3 - 56.0*
Germany	2000-2004	**1,440**	**89.7**	87.2 - 92.2	**2,226**	**91.9**	89.8 - 94.0	**6,031**	**94.4**	93.5 - 95.4	**735**	**78.8**	75.4 - 82.1	**81**	*62.0*	*48.8 - 75.3*
	2005-2009	**1,716**	**93.6**	91.5 - 95.7	**2,874**	**91.8**	90.1 - 93.4	**7,428**	**95.3**	94.4 - 96.1	**648**	**74.0**	70.1 - 77.9	**71**	*47.4*	*34.2 - 60.7*
	2010-2014	**1,505**	**94.4**	92.4 - 96.3	**2,783**	**93.0**	91.4 - 94.5	**6,923**	**96.1**	95.3 - 96.8	**552**	**76.2**	72.4 - 80.1	**72**	**66.1**	54.4 - 77.9

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): women (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		WOMEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Gibraltar *	2000-2004															
	2005-2009															
	2010-2014															
Iceland *	2000-2004	**11**	*81.3*	*46.1 - 100.0*	**51**	*90.8*	*82.3 - 99.3*	**81**	*97.4*	*88.9 - 100.0*						
	2005-2009	**17**	*99.4*	*69.4 - 100.0*	**53**	*92.2*	*83.9 - 100.0*	**72**	*88.1*	*78.4 - 97.8*						
	2010-2014	**11**	*99.4*	*69.4 - 100.0*	**42**	*86.9*	*74.0 - 99.7*	**65**	**88.0**	77.6 - 98.4						
Ireland *	2000-2004	**357**	**91.1**	86.8 - 95.4	**147**	*87.8*	*81.6 - 94.1*	**995**	**89.8**	87.1 - 92.4	**23**	*77.8*	*58.8 - 96.8*	**8**	*47.8*	*7.8 - 87.7*
	2005-2009	**482**	**91.9**	88.2 - 95.6	**228**	**84.1**	78.6 - 89.6	**1,168**	**92.1**	89.8 - 94.4	**29**	*76.0*	*58.9 - 93.0*	**20**	*56.7*	*20.1 - 93.2*
	2010-2014	**400**	**92.4**	88.6 - 96.1	**242**	**83.9**	77.1 - 90.7	**1,294**	**94.3**	92.1 - 96.6	**34**	**84.8**	76.6 - 93.0	**18**	*56.7*	*20.1 - 93.2*
Italy	2000-2004	**767**	**84.8**	81.3 - 88.3	**1,655**	**86.7**	84.3 - 89.0	**3,582**	**89.8**	88.5 - 91.0	**1,082**	**83.2**	80.7 - 85.8	**69**	*42.4*	*27.6 - 57.1*
	2005-2009	**1,086**	**86.0**	83.2 - 88.7	**3,008**	**87.3**	85.5 - 89.0	**5,601**	**90.1**	89.1 - 91.1	**1,633**	**84.1**	81.9 - 86.2	**83**	*47.5*	*34.9 - 60.0*
	2010-2014	**414**	**84.1**	80.1 - 88.2	**1,236**	**85.6**	83.3 - 87.8	**2,281**	**90.4**	89.1 - 91.6	**460**	**80.9**	77.6 - 84.2	**30**	**59.5**	47.8 - 71.2
Latvia *	2000-2004	**78**	*74.4*	*57.9 - 91.0*	**117**	**68.7**	59.4 - 78.1	**253**	**70.0**	63.6 - 76.4	**16**	*39.1*	*15.0 - 63.2*			
	2005-2009	**83**	*69.0*	*54.4 - 83.6*	**148**	**62.4**	53.8 - 71.0	**265**	**74.8**	68.6 - 81.0	**25**	*30.3*	*12.1 - 48.4*			
	2010-2014	**79**	**69.0**	53.5 - 84.5	**196**	**73.8**	66.0 - 81.6	**315**	**78.2**	72.3 - 84.1	**22**	*82.8*	*57.2 - 100.0*			
Lithuania *	2000-2004	**96**	**76.7**	66.7 - 86.6	**187**	**63.6**	55.9 - 71.2	**381**	**77.2**	72.2 - 82.3	**38**	*33.0*	*17.6 - 48.5*			
	2005-2009	**131**	**78.0**	69.4 - 86.6	**172**	**67.8**	60.1 - 75.4	**432**	**79.8**	75.4 - 84.2	**63**	**75.6**	65.1 - 86.0			
	2010-2014	**101**	**93.0**	86.4 - 99.6	**175**	**74.1**	65.7 - 82.5	**308**	**84.4**	79.3 - 89.5	**22**	**77.0**	68.2 - 85.8			
Malta *	2000-2004				**20**	*92.2*	*78.6 - 100.0*	**45**	*79.8*	*66.6 - 93.0*	**6**	*76.1*	*39.1 - 100.0*			
	2005-2009				**35**	*86.4*	*73.6 - 99.1*	**66**	*90.5*	*80.4 - 100.0*	**9**	*69.5*	*30.7 - 100.0*			
	2010-2014				**42**	*91.1*	*79.8 - 100.0*	**54**	**88.0**	83.0 - 93.0	**4**	*69.5*	*30.7 - 100.0*			
Netherlands *	2000-2004	**923**	**94.2**	91.8 - 96.6	**2,189**	**89.3**	*87.0 - 91.7*	**5,063**	**91.9**	*90.7 - 93.1*	**21**	*79.3*	*60.5 - 98.0*	**47**	*45.2*	*27.1 - 63.4*
	2005-2009	**1,149**	**89.5**	87.2 - 91.9	**3,036**	**89.1**	*87.2 - 91.0*	**6,522**	**94.3**	*93.3 - 95.2*	**33**	*73.4*	*57.2 - 89.6*	**48**	*35.0*	*19.8 - 50.1*
	2010-2014	**1,498**	**90.9**	88.7 - 93.1	**4,003**	**90.7**	*89.0 - 92.3*	**8,146**	**94.8**	*93.9 - 95.6*	**34**	**87.8**	77.7 - 97.9	**47**	*35.0*	*19.8 - 50.1*
Norway *	2000-2004	**393**	**86.9**	81.8 - 92.0	**749**	**88.3**	*85.1 - 91.5*	**1,576**	**92.1**	*90.2 - 94.0*	**42**	*67.0*	*52.0 - 82.0*	**18**	*64.3*	*34.4 - 94.2*
	2005-2009	**412**	**89.9**	85.4 - 94.5	**930**	**89.1**	*86.5 - 91.7*	**1,768**	**92.7**	*91.0 - 94.4*	**56**	**83.7**	72.6 - 94.7	**23**	*53.2*	*29.9 - 76.5*
	2010-2014	**531**	**89.9**	85.7 - 94.2	**1,389**	**91.5**	*89.0 - 93.9*	**2,439**	**92.8**	*91.3 - 94.4*	**58**	**91.0**	81.3 - 100.0	**27**	*53.2*	*29.9 - 76.5*
Poland *	2000-2004	**664**	**69.9**	65.4 - 74.5	**1,123**	**64.9**	*61.6 - 68.1*	**2,546**	**75.0**	*73.0 - 77.0*	**794**	**47.8**	44.0 - 51.5	**41**	*43.5*	*27.3 - 59.7*
	2005-2009	**834**	**73.5**	69.8 - 77.3	**1,438**	**71.6**	*68.8 - 74.3*	**3,190**	**78.1**	*76.5 - 79.7*	**928**	**56.5**	53.0 - 59.9	**44**	*37.8*	*21.5 - 54.0*
	2010-2014	**1,070**	**76.9**	73.5 - 80.3	**1,812**	**73.9**	*71.4 - 76.5*	**3,852**	**79.1**	*77.5 - 80.6*	**901**	**60.4**	57.0 - 63.8	**65**	**34.6**	*21.7 - 47.5*
Portugal	2000-2004	**270**	**80.4**	73.4 - 87.5	**244**	**82.4**	76.0 - 88.9	**656**	**82.5**	79.4 - 85.7	**326**	**77.7**	72.9 - 82.6	**20**	*24.6*	*5.2 - 44.0*
	2005-2009	**338**	**83.6**	77.8 - 89.5	**411**	**82.9**	78.4 - 87.4	**1,042**	**85.6**	82.9 - 88.3	**363**	**85.0**	80.6 - 89.4	**21**	*35.5*	*14.2 - 56.8*
	2010-2014	**255**	**82.9**	71.1 - 94.7	**383**	**84.3**	76.2 - 92.5	**800**	**85.8**	80.0 - 91.5	**164**	**81.9**	73.0 - 90.8	**15**	*0.0*	*0.0 - 0.1*
Romania (Cluj)	2000-2004															
	2005-2009	**14**	*79.9*	*55.1 - 100.0*	**45**	*66.5*	*51.0 - 82.0*	**46**	*79.0*	*65.5 - 92.5*	**6**	*16.8*	*0.0 - 39.8*			
	2010-2014	**18**	*71.5*	*42.9 - 100.0*	**31**	*91.1*	*78.3 - 100.0*	**55**	**82.7**	*71.0 - 94.3*	**12**	*56.8*	*26.4 - 87.2*			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): women (15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

		WOMEN														
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Russia	2000-2004	**99**	**63.2**	52.1 - 74.3	**242**	**63.0**	55.2 - 70.8	**401**	**75.5**	70.1 - 80.9	**102**	**43.5**	33.3 - 53.8			
	2005-2009	**139**	**68.5**	58.7 - 78.3	**323**	**64.6**	58.4 - 70.8	**469**	**72.4**	67.2 - 77.5	**74**	**46.2**	35.6 - 56.9			
	2010-2014	**183**	**75.1**	66.2 - 84.1	**418**	**64.8**	59.1 - 70.6	**629**	**77.2**	72.5 - 81.8	**28**	**42.3**	26.2 - 58.4			
Slovakia *	2000-2004	**172**	**82.1**	73.8 - 90.4	**419**	**80.9**	*75.8 - 86.0*	**752**	**82.4**	*78.7 - 86.1*	**44**	*44.3*	*28.0 - 60.7*	**7**	*45.3*	*11.2 - 79.3*
	2005-2009	**232**	**84.0**	76.2 - 91.8	**439**	**78.3**	*73.6 - 83.1*	**854**	**84.3**	*81.1 - 87.5*	**51**	*28.2*	*15.1 - 41.3*	**13**	*16.5*	*0.0 - 35.0*
	2010-2014	**56**	**77.9**	60.5 - 95.2	**100**	**78.2**	*68.4 - 88.1*	**193**	**85.1**	*78.1 - 92.0*	**13**	*28.2*	*15.1 - 41.3*	**2**	*16.5*	*0.0 - 35.0*
Slovenia *	2000-2004	**117**	**84.8**	75.6 - 93.9	**235**	**81.2**	*75.3 - 87.1*	**391**	**83.1**	*79.0 - 87.1*	**30**	*60.7*	*35.0 - 86.4*			
	2005-2009	**160**	**86.6**	79.0 - 94.2	**341**	**85.3**	*80.3 - 90.2*	**604**	**86.9**	*83.7 - 90.1*	**25**	*52.1*	*30.0 - 74.1*			
	2010-2014	**123**	**83.6**	74.6 - 92.6	**343**	**88.8**	*83.6 - 94.0*	**517**	**87.2**	*83.9 - 90.5*	**12**	*45.0*	*12.0 - 78.1*			
Spain	2000-2004	**289**	**81.6**	75.6 - 87.7	**486**	**82.8**	78.2 - 87.4	**1,087**	**89.4**	87.1 - 91.7	**261**	**93.8**	88.8 - 98.8	**20**	*41.2*	*19.0 - 63.4*
	2005-2009	**395**	**89.3**	85.1 - 93.6	**664**	**89.8**	86.1 - 93.5	**1,313**	**90.5**	88.5 - 92.5	**196**	**88.4**	82.9 - 93.9	**23**	*39.2*	*17.1 - 61.3*
	2010-2014	**214**	**88.9**	82.5 - 95.4	**396**	**90.4**	85.1 - 95.7	**753**	**93.9**	91.0 - 96.8	**50**	**87.9**	79.6 - 96.1	**14**	*39.2*	*17.1 - 61.3*
Sweden *	2000-2004	**595**	**88.7**	84.9 - 92.4	**1,305**	**92.1**	89.7 - 94.5	**2,573**	**92.6**	91.2 - 94.0	**159**	**86.5**	80.4 - 92.7	**38**	*47.4*	*25.2 - 69.7*
	2005-2009	**718**	**88.7**	85.0 - 92.3	**1,734**	**91.9**	90.0 - 93.8	**3,396**	**94.6**	93.4 - 95.7	**143**	**94.6**	88.8 - 100.0	**42**	*40.2*	*21.3 - 59.1*
	2010-2014	**872**	**91.3**	88.2 - 94.3	**2,392**	**90.9**	89.2 - 92.7	**4,515**	**96.0**	95.0 - 97.1	**39**	**78.5**	67.8 - 89.1	**35**	*47.4*	*25.2 - 69.7*
Switzerland	2000-2004	**168**	**86.3**	78.3 - 94.2	**204**	**90.0**	83.5 - 96.6	**533**	**93.6**	89.4 - 97.7	**17**	*59.8*	*34.8 - 84.9*	**4**	*30.8*	*0.0 - 69.3*
	2005-2009	**364**	**91.8**	87.8 - 95.9	**533**	**93.3**	89.7 - 97.0	**1,361**	**94.9**	93.1 - 96.7	**31**	*77.8*	*58.8 - 96.8*	**14**	*15.0*	*0.0 - 33.3*
	2010-2014	**232**	**92.7**	88.1 - 97.3	**389**	**94.6**	91.1 - 98.1	**796**	**95.3**	93.3 - 97.2	**17**	*70.8*	*8.2 - 100.0*	**7**	*87.5*	*45.4 - 100.0*
United Kingdom *	2000-2004	**3,213**	**89.8**	88.1 - 91.5	**3,815**	**85.4**	83.6 - 87.2	**14,145**	**92.7**	92.1 - 93.4	**1,231**	**66.4**	63.5 - 69.3	**206**	**57.0**	48.8 - 65.2
	2005-2009	**4,020**	**91.7**	90.3 - 93.2	**5,573**	**88.2**	86.8 - 89.6	**18,037**	**94.7**	94.1 - 95.2	**1,155**	**65.1**	62.0 - 68.1	**229**	**57.5**	49.4 - 65.5
	2010-2014	**4,810**	**93.2**	91.9 - 94.5	**7,116**	**90.1**	88.8 - 91.4	**22,241**	**95.6**	95.1 - 96.1	**665**	**65.8**	62.3 - 69.3	**236**	**45.3**	36.9 - 53.8
OCEANIA																
Australia *	2000-2004	**3,179**	**94.6**	93.4 - 95.7	**4,490**	**94.3**	93.0 - 95.5	**12,348**	**96.0**	95.4 - 96.6	**749**	**61.5**	57.6 - 65.3	**38**	*53.5*	*35.4 - 71.6*
	2005-2009	**3,554**	**94.6**	93.4 - 95.7	**5,081**	**93.5**	92.4 - 94.6	**13,792**	**97.1**	96.6 - 97.6	**683**	**57.5**	53.2 - 61.9	**55**	*35.5*	*20.3 - 50.7*
	2010-2014	**3,122**	**94.4**	93.2 - 95.7	**4,966**	**94.1**	93.0 - 95.2	**13,062**	**97.3**	96.7 - 97.9	**580**	**51.9**	47.1 - 56.7	**47**	*35.5*	*20.3 - 50.7*
New Zealand *	2000-2004	**642**	**91.5**	88.3 - 94.7	**839**	**92.6**	89.2 - 95.9	**2,808**	**95.9**	94.6 - 97.2	**174**	**51.5**	43.3 - 59.7	**15**	*33.5*	*3.9 - 63.1*
	2005-2009	**700**	**90.8**	87.7 - 93.9	**946**	**95.6**	93.4 - 97.9	**3,142**	**97.2**	96.0 - 98.4	**202**	**49.8**	42.2 - 57.3	**10**	*32.4*	*5.1 - 59.8*
	2010-2014	**732**	**93.5**	90.5 - 96.6	**1,080**	**95.2**	93.1 - 97.3	**3,368**	**96.9**	95.8 - 98.0	**188**	**46.3**	38.8 - 53.9	**19**	*32.4*	*5.1 - 59.8*

* Data with 100% coverage of the national population

[§] Survival estimate considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), ***or*** (b) registered only from a death certificate or at autopsy, ***or*** (c) registered with incomplete dates, i.e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status

Italics denote survival estimates that are not age-standardised

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (both sexes, 15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

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		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs, women			Genital organs, men		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
AFRICA																			
Algeria	2000-2004										**19**	*1.6*	**0.0 - 5.5**						
	2005-2009										**106**	*0.1*	**0.0 - 0.4**						
	2010-2014										**92**	**52.3**	**44.5 - 60.1**						
Nigeria (Ibadan)	2000-2004																		
	2005-2009							**20**	*100.0*	100.0 - 100.0									
	2010-2014							**23**	*100.0*	90.8 - 100.0									
South Africa (Eastern Cape)	2000-2004							**7**	*100.0*	100.0 - 100.0									
	2005-2009							**3**	*100.0*	100.0 - 100.0									
	2010-2014							**10**	*27.5*	0.0 - 64.4									
AMERICA (CENTRAL AND SOUTH)																			
Argentina	2000-2004	**27**	*64.0*	*44.3 - 83.7*	**28**	*77.1*	58.0 - 96.2	**39**	*74.9*	59.6 - 90.3	**86**	**62.0**	50.7 - 73.2						
	2005-2009	**61**	*73.3*	*56.4 - 90.1*	**79**	**67.8**	57.1 - 78.5	**142**	**68.8**	60.5 - 77.2	**210**	**66.1**	59.0 - 73.3						
	2010-2014	**40**	**73.7**	61.0 - 86.4	**61**	**79.2**	67.6 - 90.9	**96**	**75.8**	66.4 - 85.1	**180**	**64.3**	56.1 - 72.6						
Brazil	2000-2004	**83**	**74.2**	62.8 - 85.7	**142**	**76.7**	67.5 - 86.0	**197**	**81.5**	74.4 - 88.6	**55**	*43.6*	29.2 - 57.9						
	2005-2009	**114**	**73.2**	62.7 - 83.7	**188**	**81.1**	73.6 - 88.6	**205**	**83.2**	76.8 - 89.6	**90**	**46.9**	36.6 - 57.2						
	2010-2014	**58**	**68.8**	57.6 - 80.0	**102**	**74.7**	66.3 - 83.1	**144**	**77.4**	70.1 - 84.7	**60**	**43.1**	32.6 - 53.7						
Chile	2000-2004	**27**	*67.3*	*45.9 - 88.7*	**10**	*47.5*	15.7 - 79.3	**37**	*59.8*	41.3 - 78.3	**19**	*55.4*	32.9 - 78.0						
	2005-2009	**37**	*73.3*	*48.4 - 98.2*	**22**	*50.8*	29.2 - 72.5	**59**	*65.7*	49.3 - 82.1	**11**	*41.4*	12.1 - 70.7						
	2010-2014	**34**	**65.7**	50.2 - 81.3	**16**	*56.1*	30.1 - 82.1	**50**	**70.0**	55.1 - 85.0	**23**	*34.8*	7.1 - 62.5						
Colombia §	2000-2004	**60**	*66.7*	*48.9 - 84.5*	**69**	**77.7**	65.2 - 90.2	**175**	**64.5**	57.0 - 72.1	**37**	*8.2*	0.0 - 18.1						
	2005-2009	**109**	**75.4**	64.6 - 86.2	**87**	**82.6**	73.2 - 92.0	**252**	**70.4**	63.4 - 77.3	**40**	*38.3*	21.7 - 54.9						
	2010-2014	**77**	**65.6**	52.8 - 78.3	**67**	**63.1**	49.2 - 77.0	**206**	**71.1**	63.0 - 79.3	**40**	*23.5*	9.4 - 37.5						
Costa Rica *	2000-2004	**63**	**88.0**	79.7 - 96.4	**56**	*70.7*	57.2 - 84.3	**149**	**84.5**	77.1 - 91.9	**31**	*69.7*	50.2 - 89.1						
	2005-2009	**103**	**80.4**	71.4 - 89.4	**92**	**74.5**	65.4 - 83.5	**241**	**78.8**	72.5 - 85.2	**46**	*38.9*	22.5 - 55.2						
	2010-2014	**203**	**83.6**	75.3 - 91.9	**131**	**77.6**	67.5 - 87.8	**244**	**77.7**	71.3 - 84.0	**73**	**48.2**	35.9 - 60.6						
Ecuador	2000-2004	**48**	*73.0*	*52.2 - 93.7*	**20**	*52.8*	30.8 - 74.8	**109**	**54.0**	44.1 - 64.0	**10**	*61.4*	22.2 - 100.0						
	2005-2009	**70**	*69.1*	*53.9 - 84.3*	**37**	*59.9*	39.7 - 80.0	**198**	**65.7**	58.1 - 73.2	**85**	**43.7**	34.0 - 53.3						
	2010-2014	**89**	**61.5**	48.7 - 74.3	**41**	**71.9**	56.7 - 87.2	**228**	**58.4**	50.5 - 66.3	**58**	**47.2**	34.2 - 60.2						
Guadeloupe *	2000-2004																		
	2005-2009				**3**	*100.0*	100.0 - 100.0	**8**	*77.5*	36.7 - 100.0									
	2010-2014				**12**	*100.0*	100.0 - 100.0	**21**	*0.5*	0.0 - 1.6									
Martinique *	2000-2004	**4**	*75.3*	*38.4 - 100.0*	**8**	*78.1*	46.3 - 100.0	**18**	*42.6*	18.0 - 67.3	**34**	*100.0*	90.8 - 100.0						
	2005-2009	**8**	*67.1*	*31.4 - 100.0*	**14**	*91.2*	70.3 - 100.0	**31**	*90.4*	75.1 - 100.0	**10**	*82.1*	50.6 - 100.0						
	2010-2014	**1**	*82.7*	*42.1 - 100.0*	**10**	*87.8*	64.7 - 100.0	**24**	*98.4*	80.6 - 100.0	**2**	*55.2*	1.2 - 100.0						
Puerto Rico *	2000-2004	**78**	*72.5*	*56.4 - 88.6*	**68**	**74.9**	63.5 - 86.3	**193**	**76.5**	69.7 - 83.4	**57**	*53.1*	37.6 - 68.7						
	2005-2009	**65**	*72.6*	*58.0 - 87.3*	**121**	**83.9**	75.9 - 91.9	**201**	**71.1**	64.1 - 78.0	**38**	*66.1*	48.4 - 83.7						
	2010-2014	**45**	**59.4**	40.0 - 78.8	**49**	**78.0**	65.4 - 90.6	**81**	**76.4**	67.3 - 85.5	**33**	*73.3*	49.8 - 96.8						
AMERICA (NORTH)																			
Canada	2000-2004	**3,688**	**86.6**	85.0 - 88.1	**6,311**	**86.9**	85.7 - 88.0	**8,693**	**91.4**	90.5 - 92.2	**1,064**	**54.4**	51.0 - 57.9	**76**	*62.0*	49.2 - 74.9	**9**	*48.3*	15.3 - 81.2
	2005-2009	**4,631**	**86.5**	85.2 - 87.8	**7,773**	**87.5**	86.5 - 88.5	**10,717**	**92.6**	91.9 - 93.3	**1,496**	**48.8**	45.9 - 51.7	**94**	**57.3**	47.1 - 67.6	**11**	*9.7*	0.0 - 24.2
	2010-2014	**5,503**	**88.6**	87.4 - 89.8	**8,883**	**89.4**	88.5 - 90.3	**12,919**	**93.4**	92.7 - 94.0	**1,307**	**42.1**	39.0 - 45.2	**94**	**48.5**	36.0 - 61.0	**9**	**31.4**	0.7 - 62.2
United States	2000-2004	**37,734**	**88.1**	87.6 - 88.6	**60,147**	**91.4**	91.0 - 91.7	**77,553**	**93.5**	93.2 - 93.8	**9,885**	**43.1**	42.0 - 44.3	**643**	**59.1**	54.8 - 63.5	**53**	**63.9**	47.5 - 80.3
	2005-2009	**46,061**	**89.5**	89.0 - 89.9	**71,889**	**93.0**	92.7 - 93.3	**94,763**	**94.6**	94.4 - 94.9	**####**	**40.8**	39.7 - 42.0	**664**	**57.1**	52.4 - 61.8	**58**	**60.1**	48.2 - 72.0
	2010-2014	**40,397**	**90.1**	89.7 - 90.6	**61,746**	**93.4**	93.1 - 93.8	**81,356**	**94.9**	94.7 - 95.2	**8,694**	**38.5**	37.4 - 39.7	**590**	**59.5**	54.8 - 64.2	**48**	**67.6**	56.3 - 78.8

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (both sexes, 15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

BOTH SEXES

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs, women			Genital organs, men		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
ASIA																			
China	2000-2004	**26**	*46.2*	*26.2 - 66.3*	**16**	*27.8*	6.4 - 49.2	**33**	*39.3*	21.1 - 57.4	**35**	*27.3*	10.4 - 44.1						
	2005-2009	**90**	**55.2**	44.6 - 65.8	**63**	**41.5**	29.7 - 53.2	**223**	**52.2**	44.7 - 59.6	**174**	**32.0**	24.4 - 39.5	**8**	*28.5*	0.0 - 58.9			
	2010-2014	**120**	**54.4**	42.9 - 65.9	**57**	**49.0**	35.3 - 62.6	**277**	**52.5**	44.5 - 60.5	**192**	**38.8**	29.9 - 47.6	**13**	*38.1*	6.6 - 69.6			
Cyprus *	2000-2004	**9**	*78.2*	*51.9 - 100.0*	**2**	*100.0*	-	**7**	*89.1*	61.7 - 100.0	**10**	*93.6*	68.1 - 100.0						
	2005-2009	**41**	*89.0*	*68.7 - 100.0*	**69**	**72.9**	63.5 - 82.4	**84**	**82.9**	74.9 - 90.9	**45**	*76.4*	56.1 - 96.7						
	2010-2014	**41**	**93.6**	83.8 - 100.0	**93**	**72.5**	62.2 - 82.7	**124**	**85.8**	78.2 - 93.5	**61**	**55.3**	41.4 - 69.2						
India	2000-2004																		
	2005-2009							**3**	*89.7*	39.3 - 100.0									
	2010-2014							**10**	*55.9*	16.4 - 95.5									
Israel *	2000-2004	**610**	**84.6**	81.0 - 88.2	**1,071**	**88.5**	85.8 - 91.2	**1,373**	**86.9**	84.7 - 89.1	**638**	**79.7**	75.9 - 83.4	**19**	*21.8*	3.2 - 40.4			
	2005-2009	**754**	**85.9**	82.7 - 89.1	**1,412**	**90.4**	88.1 - 92.6	**1,895**	**91.7**	90.0 - 93.5	**443**	**73.7**	69.1 - 78.3	**17**	*31.6*	8.6 - 54.7			
	2010-2014	**698**	**87.6**	84.2 - 91.0	**1,239**	**90.6**	88.2 - 93.0	**1,665**	**89.5**	87.6 - 91.5	**400**	**68.6**	63.4 - 73.8	**28**	*41.4*	16.9 - 65.9			
Japan	2000-2004	**124**	**62.1**	51.1 - 73.1	**90**	**54.7**	45.3 - 64.0	**438**	**74.2**	69.4 - 79.0	**65**	**65.6**	55.2 - 75.9	**16**	*38.8*	15.5 - 62.1			
	2005-2009	**367**	**57.2**	49.8 - 64.6	**243**	**57.0**	50.0 - 63.9	**1,086**	**76.9**	73.8 - 80.0	**78**	*41.6*	28.5 - 54.8	**39**	*22.8*	7.7 - 37.8			
	2010-2014	**251**	**57.8**	49.4 - 66.3	**184**	**61.4**	53.8 - 69.0	**724**	**76.2**	72.6 - 79.8	**25**	*22.6*	8.3 - 37.0	**25**	*15.6*	2.9 - 28.3			
Korea *	2000-2004	**224**	**46.9**	39.8 - 54.0	**192**	**40.4**	32.7 - 48.1	**737**	**60.7**	56.7 - 64.8	**110**	**21.9**	14.3 - 29.5	**11**	*37.1*	7.8 - 66.4			
	2005-2009	**420**	**49.0**	43.7 - 54.4	**270**	**43.9**	37.6 - 50.1	**1,161**	**63.1**	59.9 - 66.2	**123**	**29.1**	21.1 - 37.1	**20**	*67.6*	46.1 - 89.2			
	2010-2014	**476**	**52.7**	47.4 - 58.1	**309**	**49.2**	42.9 - 55.5	**1,534**	**67.8**	64.9 - 70.8	**132**	**25.6**	17.4 - 33.8	**40**	*56.4*	37.7 - 75.2			
Kuwait *	2000-2004							**3**	*70.0*	24.4 - 100.0									
	2005-2009							**4**	*27.0*	0.0 - 65.1									
	2010-2014							**5**	*58.8*	2.8 - 100.0									
Qatar *	2000-2004	**3**	*66.8*	*23.1 - 100.0*				**1**	*100.0*	-	**6**	*75.2*	38.3 - 100.0						
	2005-2009	**2**	*100.0*	*100.0 - 100.0*				**2**	*0.3*	0.0 - 0.9	**10**	*33.8*	0.0 - 73.5						
	2010-2014	**2**	*100.0*	*100.0 - 100.0*	**2**	*100.0*	100.0 - 100.0	**16**	*100.0*	100.0 - 100.0	**11**	*91.8*	66.1 - 100.0						
Singapore *	2000-2004	**8**	*60.2*	*18.4 - 100.0*	**17**	*60.7*	37.3 - 84.1	**50**	*68.0*	45.9 - 90.2	**8**	*38.4*	6.6 - 70.2						
	2005-2009	**15**	*64.3*	*38.5 - 90.0*	**22**	*65.6*	45.4 - 85.9	**72**	**55.0**	45.9 - 64.1	**20**	*60.9*	39.0 - 82.8						
	2010-2014	**17**	*42.4*	*18.0 - 66.8*	**33**	**79.1**	64.8 - 93.4	**85**	**58.2**	47.9 - 68.4	**10**	*47.5*	14.8 - 80.3						
Taiwan *	2000-2004	**90**	**47.3**	36.3 - 58.3	**105**	**44.5**	35.1 - 53.9	**551**	**52.7**	47.6 - 57.8	**58**	**21.3**	11.7 - 30.9						
	2005-2009	**105**	**46.4**	35.6 - 57.2	**116**	**42.6**	33.9 - 51.3	**712**	**59.0**	54.7 - 63.2	**58**	**22.9**	13.1 - 32.8						
	2010-2014	**128**	**45.6**	35.2 - 56.1	**160**	**47.0**	38.3 - 55.8	**803**	**58.4**	54.1 - 62.6	**95**	**19.5**	11.2 - 27.9						
Thailand §	2000-2004	**17**	*83.3*	*54.3 - 100.0*	**21**	*36.7*	15.5 - 58.0	**44**	*37.9*	22.1 - 53.8	**20**	*47.1*	25.2 - 68.9						
	2005-2009	**42**	*62.5*	*45.8 - 79.2*	**23**	*28.2*	5.6 - 50.8	**122**	**31.4**	22.0 - 40.7	**67**	**38.9**	25.4 - 52.5						
	2010-2014	**31**	**48.4**	34.1 - 62.8	**34**	*18.2*	4.2 - 32.2	**124**	**27.5**	18.8 - 36.3	**33**	**18.1**	8.6 - 27.6						
Turkey	2000-2004	**79**	**76.5**	64.6 - 88.3	**66**	*58.2*	44.0 - 72.5	**92**	**60.5**	50.1 - 71.0	**44**	*38.2*	20.3 - 56.2						
	2005-2009	**397**	**66.7**	61.3 - 72.0	**255**	**50.9**	43.8 - 58.0	**396**	**62.1**	56.9 - 67.4	**177**	**35.4**	27.8 - 43.0						
	2010-2014	**441**	**68.0**	63.0 - 73.1	**241**	**56.2**	49.0 - 63.5	**464**	**63.5**	58.2 - 68.9	**190**	**40.8**	32.8 - 48.9						

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (both sexes, 15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

BOTH SEXES

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs, women			Genital organs, men		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
EUROPE																			
Austria *	2000-2004	**737**	**87.5**	84.0 - 91.0	**1,437**	**91.3**	*88.8 - 93.8*	**1,867**	**89.1**	87.2 - 91.0	**1,461**	**66.0**	63.2 - 68.7	**24**	*43.8*	*22.5 - 65.1*			
	2005-2009	**842**	**91.0**	88.1 - 93.9	**1,721**	**91.8**	*89.7 - 94.0*	**2,059**	**91.3**	89.5 - 93.1	**1,455**	**61.7**	58.9 - 64.5	**25**	*33.7*	*13.0 - 54.4*			
	2010-2014	**1,125**	**90.6**	87.9 - 93.4	**2,182**	**95.1**	*93.2 - 97.1*	**2,700**	**92.7**	91.0 - 94.3	**1,481**	**66.9**	64.2 - 69.7	**27**	*35.9*	*15.6 - 56.2*			
Belgium *	2000-2004	**194**	**79.0**	71.3 - 86.7	**343**	**84.9**	79.3 - 90.6	**610**	**89.6**	86.2 - 93.0	**333**	**83.4**	78.4 - 88.4	**11**	*34.0*	0.0 - 72.2			
	2005-2009	**1,275**	**83.9**	81.1 - 86.8	**2,338**	**85.9**	83.9 - 88.0	**4,046**	**91.6**	90.3 - 92.8	**832**	**87.1**	83.9 - 90.4	**48**	*45.4*	27.6 - 63.1			
	2010-2014	**1,740**	**87.9**	85.4 - 90.3	**3,763**	**90.1**	88.3 - 91.8	**6,057**	**92.5**	91.4 - 93.7	**265**	**78.6**	73.5 - 83.7	**36**	*63.7*	41.2 - 86.3			
Bulgaria *	2000-2004	**305**	**43.9**	36.9 - 50.9	**617**	**47.3**	*42.6 - 52.0*	**549**	**62.5**	57.4 - 67.6	**117**	**28.9**	20.5 - 37.3	**10**	*22.1*	*0.0 - 45.7*			
	2005-2009	**353**	**53.5**	46.7 - 60.3	**771**	**51.6**	*47.4 - 55.7*	**682**	**66.1**	61.9 - 70.3	**105**	**18.2**	10.2 - 26.2	**7**	*67.5*	*29.0 - 100.0*			
	2010-2014	**417**	**58.2**	51.6 - 64.9	**979**	**58.8**	*54.9 - 62.6*	**834**	**68.2**	64.4 - 72.0	**120**	**28.5**	20.3 - 36.8	**8**	*43.1*	*9.3 - 76.8*			
Croatia *	2000-2004	**255**	**69.3**	61.7 - 76.9	**395**	**61.5**	55.5 - 67.5	**279**	**70.1**	64.2 - 75.9	**1,261**	**66.0**	62.8 - 69.2						
	2005-2009	**416**	**78.7**	73.5 - 83.8	**734**	**74.2**	70.2 - 78.2	**533**	**78.0**	74.1 - 82.0	**1,107**	**71.3**	68.0 - 74.6						
	2010-2014	**367**	**71.8**	66.1 - 77.5	**821**	**76.2**	72.6 - 79.8	**679**	**82.6**	79.0 - 86.3	**985**	**76.2**	72.8 - 79.6						
Czech Republic *	2000-2004	**1,025**	**78.6**	75.0 - 82.1	**3,376**	**80.8**	*79.0 - 82.6*	**2,876**	**83.9**	82.2 - 85.7	**445**	**57.8**	52.3 - 63.2	**20**	*33.3*	*9.4 - 57.1*			
	2005-2009	**1,292**	**81.6**	78.6 - 84.5	**4,167**	**85.5**	*84.0 - 87.0*	**3,512**	**87.0**	85.4 - 88.5	**368**	**56.2**	50.3 - 62.0	**20**	*43.4*	*20.6 - 66.1*			
	2010-2014	**1,443**	**82.7**	79.9 - 85.6	**4,863**	**86.9**	*85.6 - 88.2*	**3,970**	**87.5**	86.1 - 88.9	**386**	**54.4**	48.4 - 60.5	**31**	*40.4*	*19.1 - 61.7*			
Denmark *	2000-2004	**602**	**86.8**	82.9 - 90.7	**1,979**	**87.1**	*85.0 - 89.2*	**2,193**	**90.4**	88.5 - 92.3	**763**	**77.0**	73.1 - 80.8	**8**	*44.6*	*7.6 - 81.6*			
	2005-2009	**837**	**86.8**	83.7 - 89.8	**3,326**	**91.4**	*89.9 - 92.9*	**2,987**	**95.2**	93.8 - 96.6	**1,102**	**66.7**	63.5 - 69.9	**16**	*80.3*	*56.7 - 100.0*			
	2010-2014	**1,258**	**89.7**	87.2 - 92.2	**4,834**	**93.4**	*92.0 - 94.7*	**4,160**	**95.6**	94.4 - 96.9	**547**	**61.3**	57.6 - 65.0	**14**	*49.4*	*22.1 - 76.7*			
Estonia *	2000-2004	**96**	**69.7**	59.2 - 80.2	**240**	**63.8**	56.7 - 70.9	**252**	**76.1**	70.2 - 82.0	**16**	*56.7*	29.0 - 84.5						
	2005-2009	**96**	**68.9**	58.8 - 79.1	**312**	**70.2**	64.3 - 76.1	**346**	**81.8**	77.1 - 86.5	**17**	*24.8*	4.9 - 44.7						
	2010-2014	**64**	**95.6**	88.3 - 100.0	**290**	**76.3**	69.1 - 83.6	**222**	**87.5**	81.9 - 93.0	**21**	*26.5*	8.3 - 44.7						
Finland *	2000-2004	**553**	**81.0**	76.6 - 85.4	**1,312**	**83.7**	*81.0 - 86.4*	**1,213**	**89.5**	87.1 - 91.8	**485**	**78.5**	74.1 - 82.9	**14**	*32.9*	*6.3 - 59.4*			
	2005-2009	**733**	**86.5**	82.9 - 90.1	**1,758**	**86.3**	*84.2 - 88.5*	**1,713**	**91.2**	89.3 - 93.1	**563**	**77.6**	73.5 - 81.6	**15**	*36.9*	*11.6 - 62.2*			
	2010-2014	**983**	**88.8**	85.7 - 92.0	**2,183**	**88.0**	*86.1 - 89.9*	**2,324**	**91.1**	89.4 - 92.8	**1,073**	**83.0**	79.6 - 86.4	**22**	*42.1*	*18.1 - 66.1*			
France	2000-2004	**761**	**86.3**	82.9 - 89.7	**1,313**	**88.4**	85.7 - 91.0	**2,109**	**90.3**	88.6 - 92.0	**295**	**93.7**	89.4 - 98.1	**14**	*54.2*	27.2 - 81.1			
	2005-2009	**1,329**	**89.8**	87.3 - 92.3	**2,282**	**90.4**	88.5 - 92.2	**3,423**	**92.5**	91.0 - 94.0	**201**	**86.0**	79.9 - 92.0	**24**	*32.6*	9.3 - 56.0			
	2010-2014	**240**	**91.3**	86.2 - 96.4	**546**	**92.7**	88.9 - 96.5	**828**	**91.5**	88.4 - 94.5	**36**	**70.7**	57.5 - 84.0	**5**	*0.0*	0.0 - 0.1			
Germany	2000-2004	**2,950**	**89.5**	87.7 - 91.2	**6,137**	**92.7**	91.5 - 94.0	**9,215**	**92.5**	91.7 - 93.4	**1,507**	**75.5**	72.9 - 78.1	**81**	*62.0*	48.8 - 75.3	**7**	*34.5*	1.2 - 67.8
	2005-2009	**3,729**	**89.8**	88.2 - 91.5	**8,154**	**92.7**	91.8 - 93.7	**11,677**	**94.4**	93.7 - 95.1	**1,377**	**71.1**	68.2 - 74.0	**71**	*47.4*	34.2 - 60.7	**6**	*39.6*	1.5 - 77.8
	2010-2014	**3,431**	**91.0**	89.4 - 92.5	**8,103**	**94.0**	93.1 - 94.9	**11,258**	**95.1**	94.4 - 95.7	**1,229**	**73.1**	70.3 - 75.9	**72**	**66.1**	54.4 - 77.9	**9**	**40.0**	7.0 - 72.9
Gibraltar *	2000-2004				**5**	*62.9*	23.9 - 100.0	**5**	*44.8*	1.5 - 88.1									
	2005-2009				**9**	*95.3*	74.2 - 100.0	**4**	*100.0*	100.0 - 100.0									
	2010-2014				**11**	*100.0*	100.0 - 100.0	**1**	*100.0*	100.0 - 100.0									
Iceland *	2000-2004	**35**	*75.7*	*56.7 - 94.8*	**92**	*93.8*	87.4 - 100.0	**109**	**88.7**	79.6 - 97.7	**18**	*89.1*	74.8 - 100.0						
	2005-2009	**48**	*87.2*	*69.2 - 100.0*	**107**	**83.7**	74.9 - 92.5	**89**	**82.7**	74.3 - 91.1	**5**	*100.0*	-						
	2010-2014	**27**	*86.9*	*69.5 - 100.0*	**83**	**84.7**	76.8 - 92.6	**93**	**89.7**	80.9 - 98.4	**3**	*67.1*	23.1 - 100.0						
Ireland *	2000-2004	**668**	**86.8**	83.1 - 90.6	**442**	**81.1**	75.3 - 86.8	**1,342**	**86.2**	83.7 - 88.7	**51**	*59.9*	44.3 - 75.4	**8**	*47.8*	7.8 - 87.7			
	2005-2009	**1,019**	**87.1**	84.2 - 90.0	**651**	**82.8**	79.1 - 86.4	**1,627**	**88.3**	86.2 - 90.5	**57**	*53.1*	39.2 - 67.1	**20**	*56.7*	20.1 - 93.2			
	2010-2014	**939**	**88.2**	85.2 - 91.2	**770**	**88.6**	84.9 - 92.3	**1,784**	**91.0**	88.9 - 93.2	**67**	**62.6**	48.7 - 76.5	**18**	*38.0*	8.9 - 67.1			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (both sexes, 15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

BOTH SEXES

		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs, women			Genital organs, men		
		No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Italy	2000-2004	**1,636**	**80.3**	77.7 - 82.9	**4,737**	**84.2**	82.8 - 85.6	**5,571**	**87.1**	86.0 - 88.2	**2,147**	**77.5**	75.5 - 79.5	**69**	*42.4*	27.6 - 57.1			
	2005-2009	**2,403**	**82.9**	80.9 - 84.9	**8,155**	**86.8**	85.8 - 87.8	**8,923**	**88.1**	87.2 - 88.9	**3,347**	**80.2**	78.6 - 81.8	**83**	*47.5*	34.9 - 60.0			
	2010-2014	**1,001**	**82.1**	79.4 - 84.8	**3,467**	**86.3**	85.0 - 87.6	**3,715**	**88.1**	87.0 - 89.2	**971**	**78.0**	75.6 - 80.3	**30**	**59.5**	47.8 - 71.2			
Latvia *	2000-2004	**122**	**67.6**	58.0 - 77.3	**245**	**66.6**	59.3 - 73.8	**304**	**65.6**	59.4 - 71.8	**25**	*48.6*	26.4 - 70.8						
	2005-2009	**131**	**58.6**	48.1 - 69.1	**308**	**64.3**	57.8 - 70.7	**352**	**71.0**	65.4 - 76.5	**38**	*28.2*	13.6 - 42.8						
	2010-2014	**129**	**60.6**	48.1 - 73.1	**408**	**69.6**	63.6 - 75.6	**403**	**77.7**	72.4 - 82.9	**36**	**52.6**	37.5 - 67.7						
Lithuania *	2000-2004	**156**	**73.5**	65.1 - 81.8	**380**	**61.2**	55.1 - 67.3	**491**	**74.1**	69.4 - 78.8	**76**	**39.0**	28.9 - 49.2						
	2005-2009	**208**	**71.9**	63.7 - 80.0	**396**	**63.6**	58.1 - 69.0	**540**	**73.7**	69.5 - 78.0	**98**	**70.4**	60.2 - 80.7						
	2010-2014	**162**	**83.9**	74.8 - 93.0	**348**	**66.2**	59.7 - 72.7	**409**	**78.8**	73.9 - 83.7	**38**	**73.3**	61.0 - 85.6						
Malta *	2000-2004	**19**	*94.6*	*69.3 - 100.0*	**62**	**87.9**	78.8 - 97.0	**67**	**76.5**	67.3 - 85.7	**8**	*82.0*	52.3 - 100.0						
	2005-2009	**18**	*63.4*	*35.3 - 91.4*	**69**	*83.6*	71.6 - 95.6	**82**	**88.1**	82.4 - 93.8	**15**	*61.4*	32.5 - 90.3						
	2010-2014	**19**	*70.7*	*40.8 - 100.0*	**91**	**75.9**	64.2 - 87.6	**82**	**88.2**	81.8 - 94.5	**9**	*35.5*	2.0 - 68.9						
Netherlands *	2000-2004	**1,941**	**87.7**	85.6 - 89.8	**5,047**	**87.0**	*85.4 - 88.6*	**7,087**	**90.1**	89.0 - 91.2	**44**	*76.3*	60.6 - 91.9	**47**	*45.2*	*27.1 - 63.4*			
	2005-2009	**2,490**	**86.5**	84.7 - 88.3	**7,235**	**88.1**	*86.8 - 89.3*	**9,288**	**92.3**	91.4 - 93.1	**60**	*74.7*	62.0 - 87.5	**48**	*35.0*	*19.8 - 50.1*			
	2010-2014	**3,499**	**86.7**	85.0 - 88.4	**10,137**	**90.0**	*88.9 - 91.0*	**12,044**	**93.2**	92.4 - 94.0	**57**	**80.6**	69.6 - 91.5	**47**	*36.5*	*20.8 - 52.1*			
Norway *	2000-2004	**779**	**81.6**	77.6 - 85.6	**1,955**	**84.6**	*82.5 - 86.6*	**2,282**	**89.5**	87.7 - 91.3	**75**	**59.7**	49.1 - 70.3	**18**	*64.3*	*34.4 - 94.2*			
	2005-2009	**889**	**86.0**	82.7 - 89.4	**2,453**	**85.3**	*83.5 - 87.0*	**2,710**	**89.9**	88.3 - 91.4	**104**	**70.8**	60.5 - 81.0	**23**	*53.2*	*29.9 - 76.5*			
	2010-2014	**1,154**	**86.8**	83.7 - 89.9	**3,613**	**88.6**	*87.1 - 90.2*	**3,804**	**90.6**	89.2 - 92.0	**103**	**88.1**	79.1 - 97.2	**27**	*49.9*	*28.4 - 71.4*			
Poland *	2000-2004	**1,186**	**64.5**	61.1 - 68.0	**2,903**	**65.3**	*63.1 - 67.5*	**3,629**	**71.0**	69.3 - 72.8	**1,661**	**40.6**	37.9 - 43.3	**41**	*43.5*	*27.3 - 59.7*			
	2005-2009	**1,587**	**64.7**	61.8 - 67.6	**3,834**	**67.5**	*65.8 - 69.3*	**4,632**	**74.2**	72.7 - 75.6	**1,849**	**49.2**	46.6 - 51.8	**44**	*37.8*	*21.5 - 54.0*			
	2010-2014	**1,904**	**69.1**	66.4 - 71.8	**4,905**	**69.9**	*68.2 - 71.5*	**5,699**	**75.5**	74.2 - 76.9	**1,882**	**52.9**	50.3 - 55.5	**65**	**34.6**	*21.7 - 47.5*			
Portugal	2000-2004	**460**	**79.7**	74.4 - 85.0	**590**	**76.1**	71.8 - 80.3	**901**	**79.6**	76.7 - 82.5	**561**	**74.3**	70.2 - 78.3	**20**	*24.6*	5.2 - 44.0			
	2005-2009	**591**	**84.6**	80.1 - 89.0	**1,008**	**79.2**	76.1 - 82.2	**1,487**	**81.9**	79.5 - 84.3	**648**	**79.2**	75.5 - 82.9	**21**	*35.5*	14.2 - 56.8			
	2010-2014	**493**	**87.8**	77.8 - 97.9	**990**	**76.5**	69.5 - 83.4	**1,222**	**83.4**	78.1 - 88.8	**346**	**79.7**	72.5 - 86.8	**15**	*41.9*	0.0 - 88.4			
Romania (Cluj)	2000-2004																		
	2005-2009	**31**	*70.3*	*48.3 - 92.2*	**97**	**67.3**	*59.1 - 75.4*	**75**	*73.9*	62.5 - 85.3	**12**	*18.5*	0.0 - 38.5						
	2010-2014	**29**	*70.8*	*46.6 - 95.0*	**85**	**77.2**	*64.9 - 89.5*	**85**	**74.9**	64.7 - 85.2	**21**	*42.1*	20.1 - 64.2						
Russia	2000-2004	**155**	**60.9**	51.6 - 70.2	**487**	**63.8**	57.9 - 69.6	**520**	**72.6**	67.7 - 77.6	**184**	**37.2**	29.0 - 45.4						
	2005-2009	**226**	**58.6**	50.8 - 66.4	**630**	**61.9**	56.9 - 66.8	**614**	**68.7**	64.0 - 73.4	**119**	**44.5**	34.8 - 54.3						
	2010-2014	**268**	**66.4**	58.6 - 74.1	**818**	**60.4**	55.8 - 65.0	**824**	**73.2**	69.0 - 77.5	**61**	**37.7**	25.2 - 50.2						
Slovakia *	2000-2004	**330**	**73.3**	66.9 - 79.7	**1,068**	**74.4**	*70.7 - 78.0*	**1,035**	**78.7**	75.3 - 82.0	**83**	**45.2**	34.3 - 56.1	**7**	*45.3*	*11.2 - 79.3*			
	2005-2009	**441**	**79.6**	73.3 - 85.9	**1,328**	**79.4**	*76.4 - 82.4*	**1,247**	**82.2**	79.4 - 85.0	**130**	**35.3**	25.6 - 45.0	**13**	*16.5*	*0.0 - 35.0*			
	2010-2014	**105**	**76.3**	63.4 - 89.3	**295**	**75.0**	*68.6 - 81.4*	**279**	**84.0**	77.9 - 90.1	**25**	**17.7**	6.2 - 29.1	**2**	*2.7*	*0.0 - 8.2*			
Slovenia *	2000-2004	**214**	**74.5**	66.9 - 82.2	**645**	**77.4**	*73.3 - 81.5*	**571**	**81.7**	77.7 - 85.7	**54**	*55.7*	37.8 - 73.6						
	2005-2009	**275**	**83.3**	77.3 - 89.3	**914**	**86.7**	*83.5 - 90.0*	**851**	**85.4**	82.4 - 88.4	**53**	*35.5*	21.2 - 49.7						
	2010-2014	**249**	**78.9**	72.3 - 85.4	**962**	**90.4**	*87.0 - 93.8*	**772**	**83.5**	80.3 - 86.6	**31**	**34.3**	20.6 - 48.0						
Spain	2000-2004	**610**	**80.4**	76.0 - 84.7	**1,131**	**82.1**	78.9 - 85.3	**1,525**	**86.4**	84.3 - 88.5	**498**	**85.5**	81.2 - 89.7	**20**	*41.2*	19.0 - 63.4			
	2005-2009	**851**	**83.0**	79.4 - 86.5	**1,585**	**86.8**	84.5 - 89.1	**1,921**	**88.1**	86.3 - 89.9	**385**	**85.9**	81.6 - 90.1	**23**	*39.2*	17.1 - 61.3			
	2010-2014	**489**	**78.7**	73.0 - 84.3	**1,017**	**86.4**	82.7 - 90.0	**1,081**	**90.7**	88.0 - 93.5	**95**	**81.0**	72.3 - 89.8	**14**	*39.5*	7.7 - 71.3			

Supplementary table 4.2: Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (both sexes, 15-99 years) diagnosed with melanoma of the skin by continent, country, anatomic location and calendar period of diagnosis (2000-2004, 2005-2009, 2010-2014)

BOTH SEXES

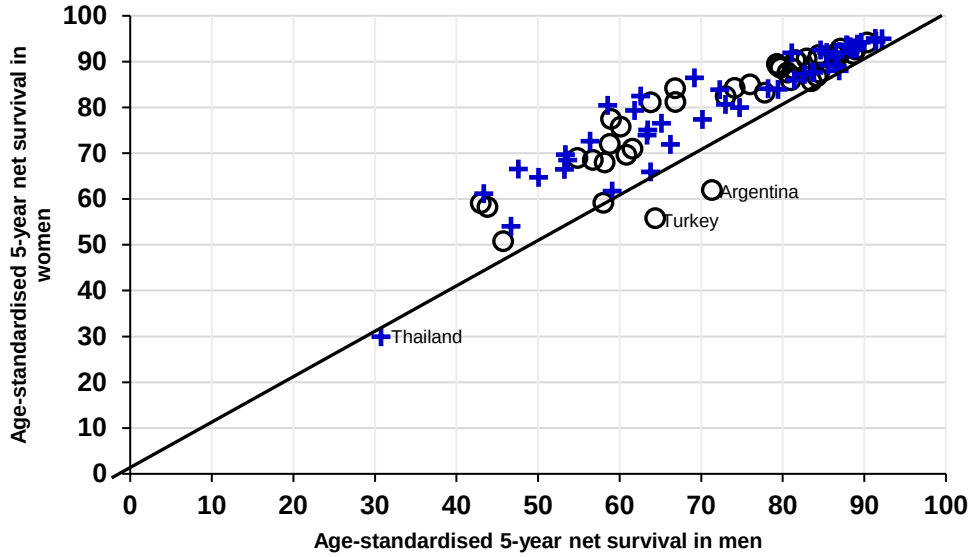
		Head and neck			Trunk			Upper and lower limbs			Overlapping and NOS			Genital organs, women			Genital organs, men		
		No.	**NS (%)**	**95% CI**	**No.**	**NS (%)**	**95% CI**	**No.**	**NS (%)**	**95% CI**	**No.**	**NS (%)**	**95% CI**	**No.**	**NS (%)**	**95% CI**	**No.**	**NS (%)**	95% CI
Sweden *	2000-2004	**1,251**	**84.5**	81.6 - 87.4	**3,695**	**88.9**	87.6 - 90.3	**3,900**	**90.7**	89.4 - 91.9	**326**	**84.2**	79.5 - 89.0	**38**	*47.4*	25.2 - 69.7			
	2005-2009	**1,611**	**86.2**	83.7 - 88.6	**4,770**	**89.4**	88.2 - 90.6	**5,230**	**92.0**	91.0 - 93.1	**281**	**92.6**	88.1 - 97.1	**42**	*40.2*	21.3 - 59.1			
	2010-2014	**1,981**	**88.0**	85.9 - 90.2	**6,495**	**90.2**	89.2 - 91.3	**7,183**	**93.8**	92.9 - 94.7	**79**	**84.6**	76.5 - 92.6	**35**	*41.8*	23.0 - 60.5			
Switzerland	2000-2004	**331**	**89.9**	84.3 - 95.4	**568**	**89.5**	86.0 - 93.0	**807**	**90.9**	87.6 - 94.2	**33**	*50.0*	31.9 - 68.1	**4**	*30.8*	0.0 - 69.3			
	2005-2009	**815**	**88.9**	85.7 - 92.1	**1,525**	**93.8**	91.8 - 95.9	**2,249**	**93.5**	92.0 - 95.0	**85**	**67.7**	58.1 - 77.3	**14**	*15.0*	0.0 - 33.3			
	2010-2014	**533**	**90.8**	87.5 - 94.1	**1,101**	**95.0**	93.0 - 97.1	**1,306**	**94.2**	92.6 - 95.8	**55**	**63.0**	49.2 - 76.8	**7**	*76.6*	41.5 - 100.0			
United Kingdom *	2000-2004	**7,153**	**84.9**	83.6 - 86.1	**10,664**	**84.5**	83.5 - 85.5	**19,800**	**90.5**	89.9 - 91.1	**2,485**	**60.1**	57.9 - 62.2	**206**	**57.0**	48.8 - 65.2	**17**	*24.2*	2.1 - 46.4
	2005-2009	**9,677**	**87.7**	86.7 - 88.8	**16,088**	**88.2**	87.4 - 88.9	**26,061**	**92.5**	92.0 - 93.0	**2,361**	**62.0**	59.8 - 64.2	**229**	**57.5**	49.4 - 65.5	**32**	*57.0*	34.7 - 79.3
	2010-2014	**12,754**	**89.1**	88.2 - 90.1	**20,997**	**90.4**	89.8 - 91.1	**33,030**	**93.5**	93.0 - 93.9	**1,518**	**57.5**	54.9 - 60.0	**236**	**45.3**	36.9 - 53.8	**29**	**54.4**	32.6 - 76.2
OCEANIA																			
Australia *	2000-2004	**8,857**	**90.6**	89.7 - 91.4	**15,919**	**93.6**	93.0 - 94.3	**21,673**	**95.0**	94.5 - 95.4	**2,061**	**54.2**	51.8 - 56.7	**38**	*53.5*	35.4 - 71.6			
	2005-2009	**10,409**	**90.4**	89.6 - 91.2	**18,100**	**94.0**	93.5 - 94.6	**24,616**	**95.8**	95.4 - 96.3	**2,044**	**49.4**	46.7 - 52.0	**55**	*35.5*	20.3 - 50.7			
	2010-2014	**9,749**	**90.2**	89.4 - 91.1	**17,357**	**94.8**	94.2 - 95.3	**23,490**	**96.2**	95.8 - 96.7	**1,874**	**48.0**	45.2 - 50.8	**47**	*36.4*	20.4 - 52.5			
New Zealand *	2000-2004	**1,550**	**88.4**	86.2 - 90.6	**2,734**	**92.1**	90.4 - 93.8	**4,249**	**94.2**	93.0 - 95.3	**473**	**45.2**	40.1 - 50.4	**15**	*33.5*	3.9 - 63.1			
	2005-2009	**1,800**	**87.9**	85.8 - 90.0	**3,213**	**93.4**	92.0 - 94.7	**5,112**	**95.7**	94.7 - 96.7	**531**	**41.5**	36.5 - 46.5	**10**	*32.4*	5.1 - 59.8			
	2010-2014	**1,957**	**90.2**	88.2 - 92.3	**3,586**	**94.4**	93.1 - 95.7	**5,457**	**95.3**	94.3 - 96.3	**501**	**41.3**	36.1 - 46.5	**19**	*23.9*	0.2 - 47.5			

* Data with 100% coverage of the national population

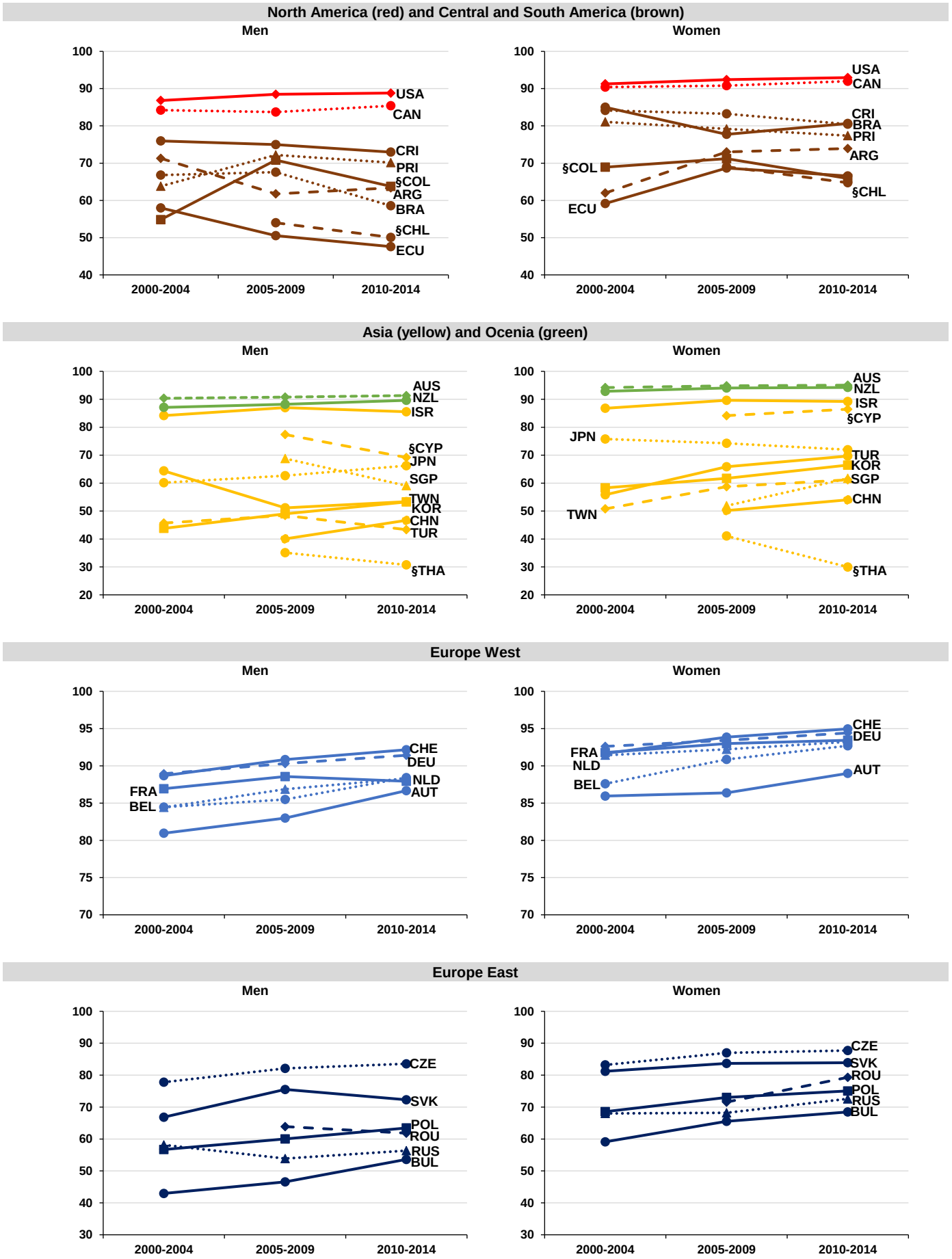
§ Survival estimate considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), ***or*** (b) registered only from a death certificate or at autopsy, ***or*** (c) registered with incomplete dates, i.e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status

Italics denote survival estimates that are not age-standardised

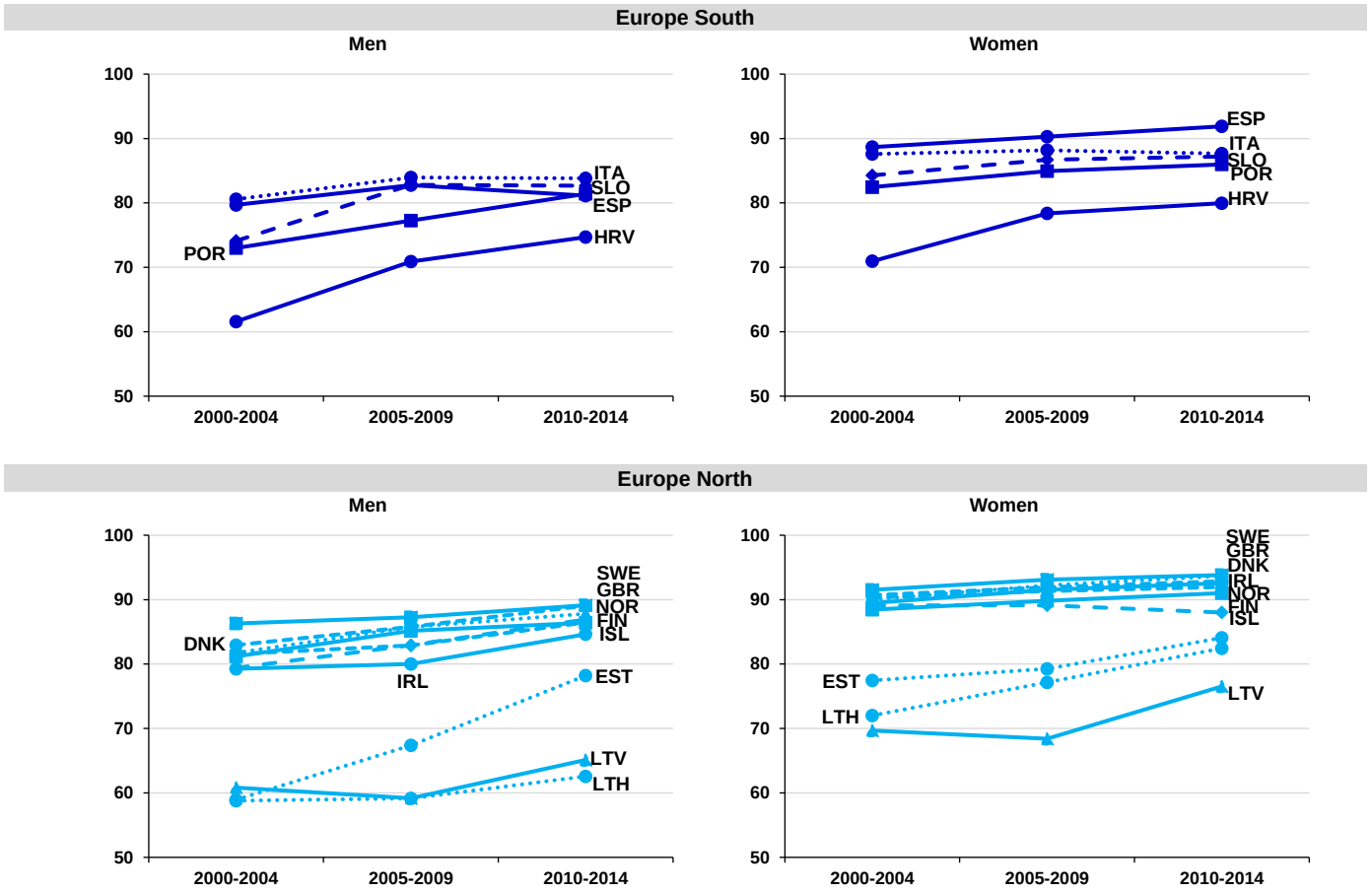
Supplementary Figure 4.1: Age-standardised 5-year net survival for men and women during 2000-2004 (circle) and 2010-2014 (dagger)



Supplementary Figure 4.2: Age-standardised 5-year net survival for men and women diagnosed with melanoma of the skin during 2000-2004, 2005-2009 and 2010-2014 by continent and country

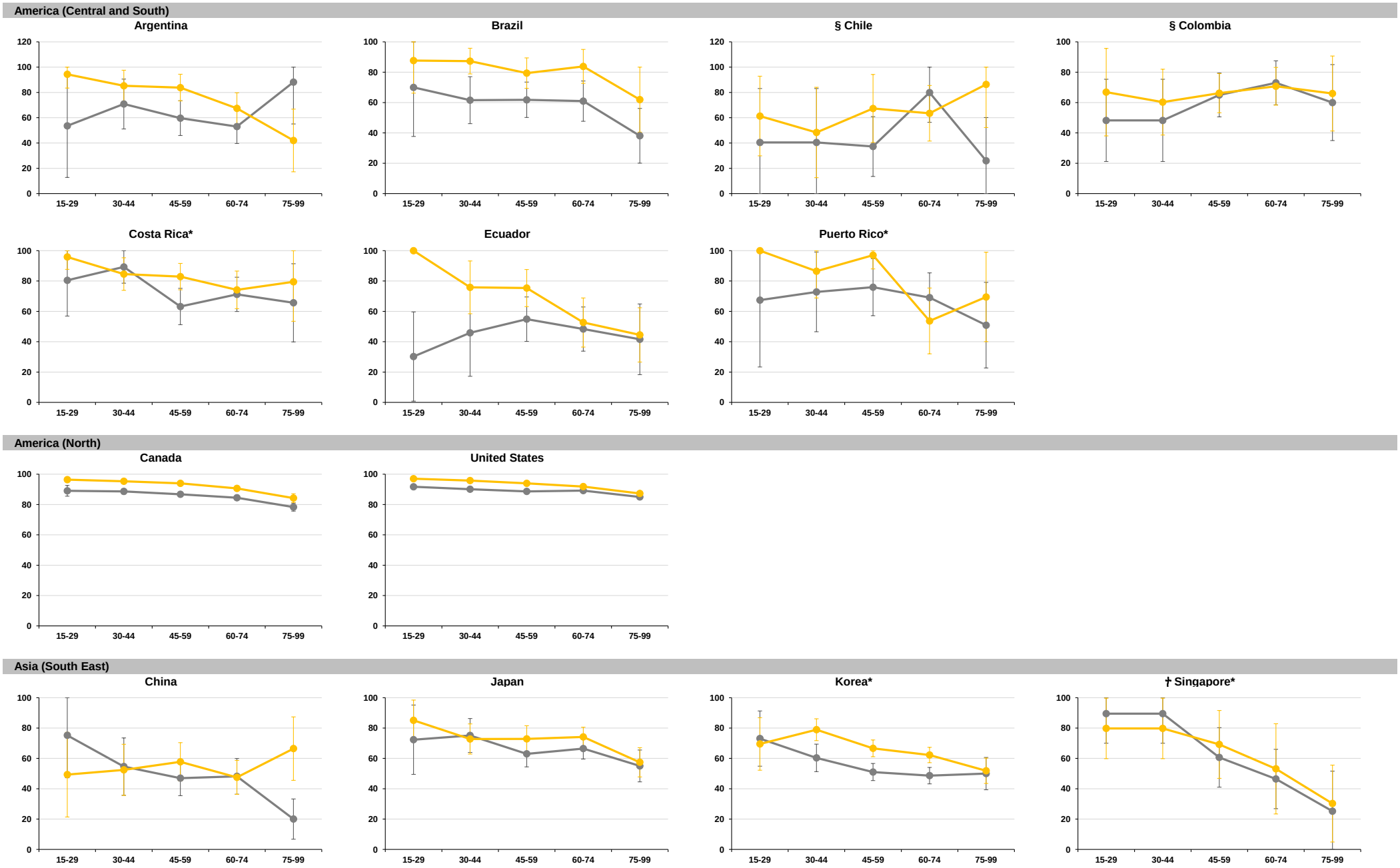


Supplementary Figure 4.2: Age-standardised 5-year net survival for men and women diagnosed with melanoma of the skin during 2000-2004, 2005-2009 and 2010-2014 by continent and country

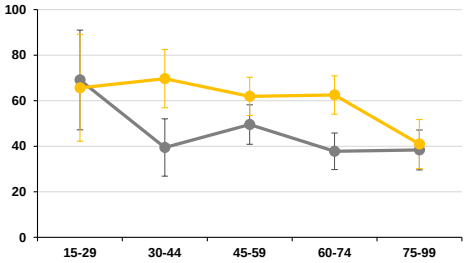


Standard ISO abbreviations for country names: Argentina - ARG; Australia - AUS; Austria - AUT; Belgium - BEL; Brazil - BRA; Bulgaria - BGR; Canada - CAN; Chile - CHL; China - CHN; Colombia - COL; Costa Rica - CRI; Croatia - HRV; Cyprus - CYP; Czech Republic CZE; Denmark - DNK; Ecuador - ECU; Estonia - EST; Finland - FIN; France - FRA; Germany - DEU; Iceland - ISL; India - IND; Ireland - IRL; Israel - ISR; Italy - ITA; Japan - JPN; Latvia -LVA; Lithuania - LTU; Malta - MLT; Netherlands - NLD; New Zealand - NZL; Norway -NOR; Poland - POL; Portugal - PRT; Puerto Rico - PRI; Republic of Korea -KOR; Romania - ROU; Russian Federation - RUS; Singapore - SGP; Slovakia - SVK; Slovenia - SVN; Spain - ESP; Sweden - SWE; Switzerland - CHE; Taiwan - TWN; Thailand - THA; Turkey - TUR; United Kingdom of Great Britain and Northern Ireland - GBR; United States of America - USA

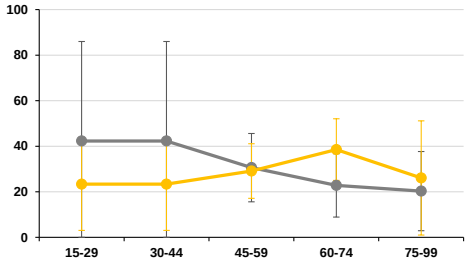
Supplementary Figure 4.3: Five-year net survival by age group (15-29, 30-44, 45-59, 60-74, 75-99) for men (gray) and women (yellow) diagnosed with melanoma of the skin during 2010-2014, by continent and country



Taiwan*

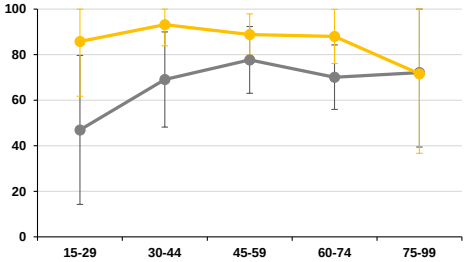


§ Thailand

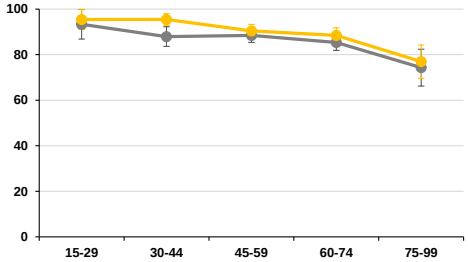


Asia (West)

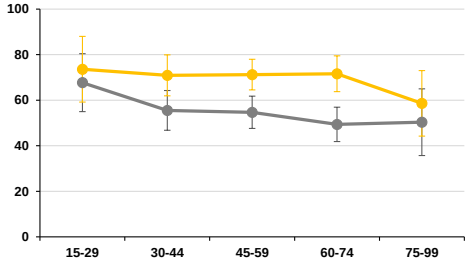
§ Cyprus*



Israel*

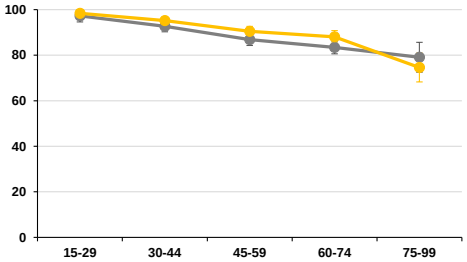


Turkey

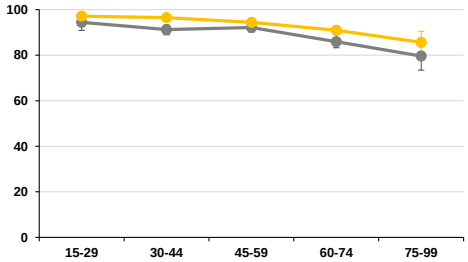


Europe (West)

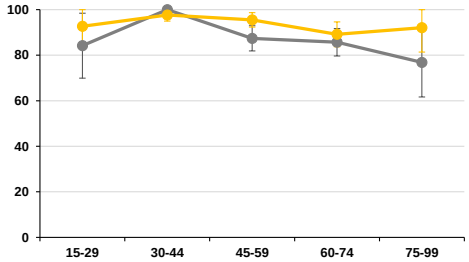
Austria*



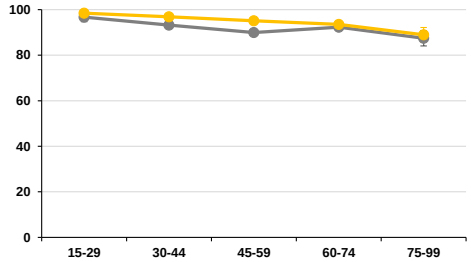
Belgium*



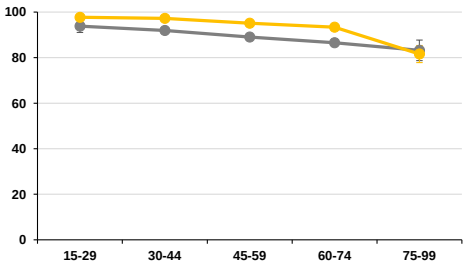
France



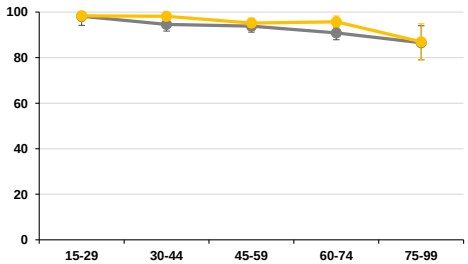
Germany



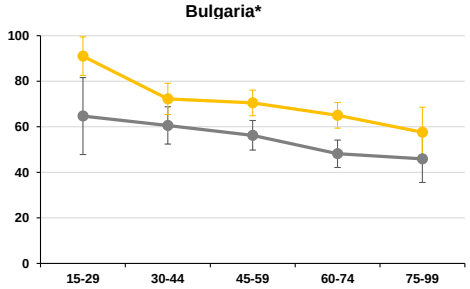
Netherlands*

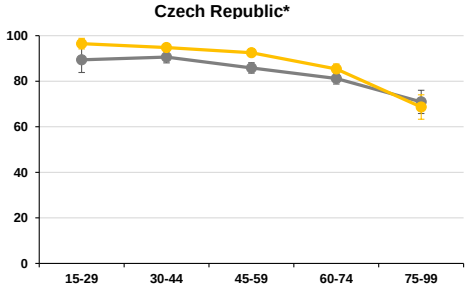


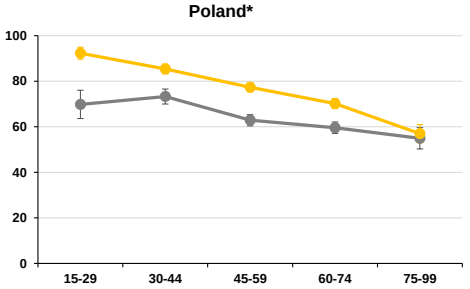
Switzerland

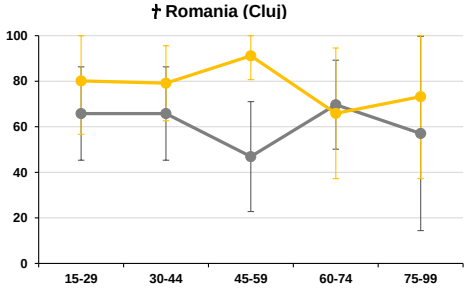


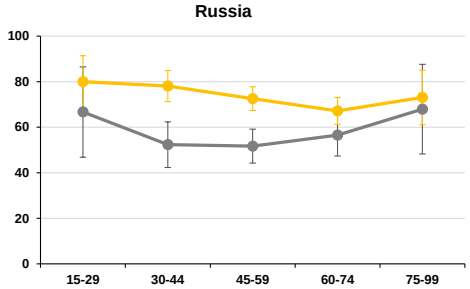
Europe (East)

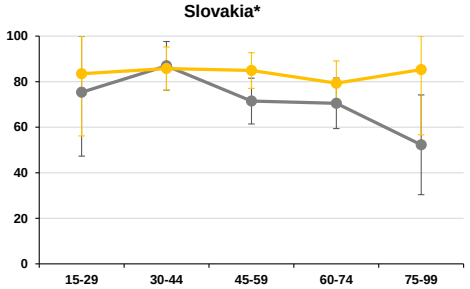




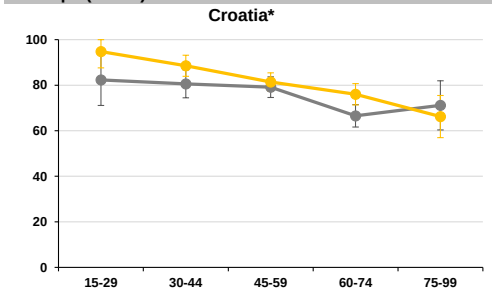


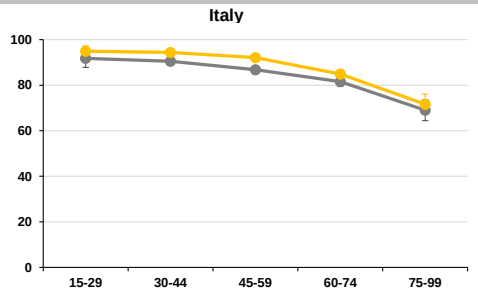


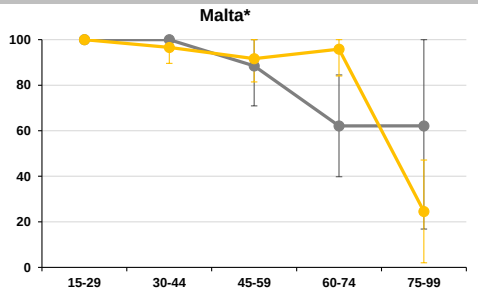


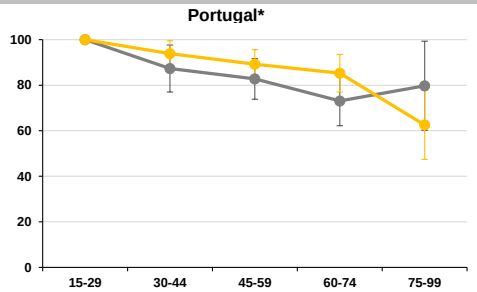


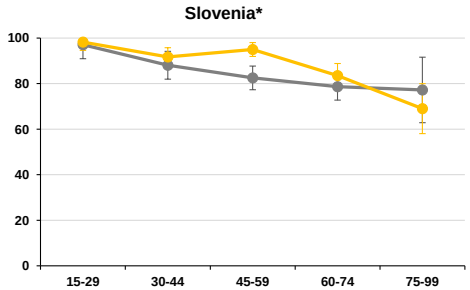
Europe (South)

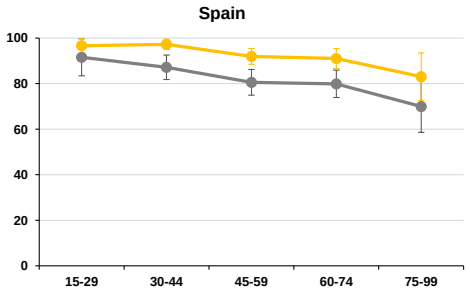




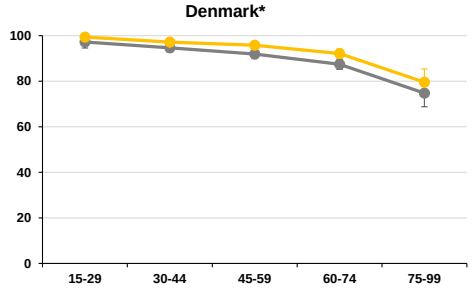


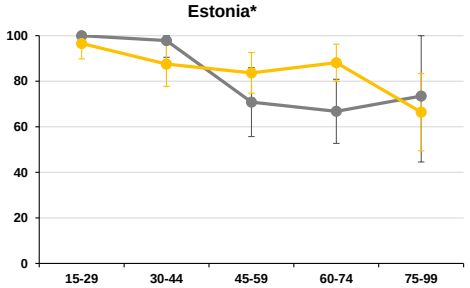


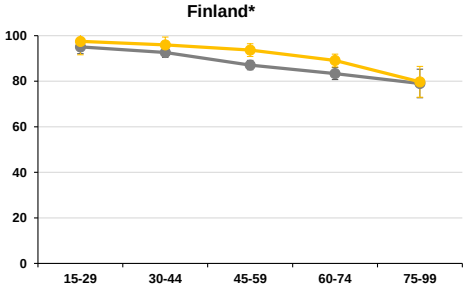


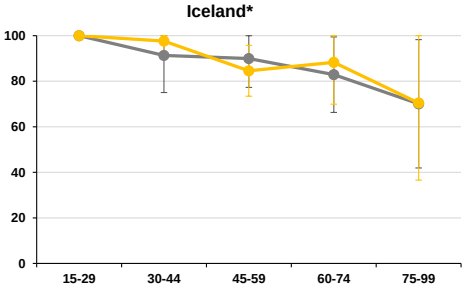


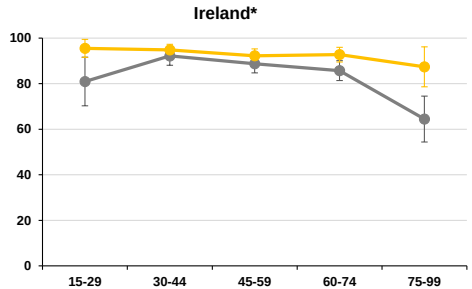
Europe (North)

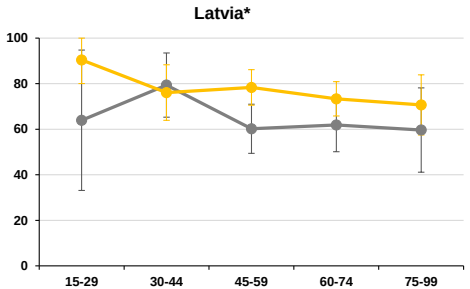


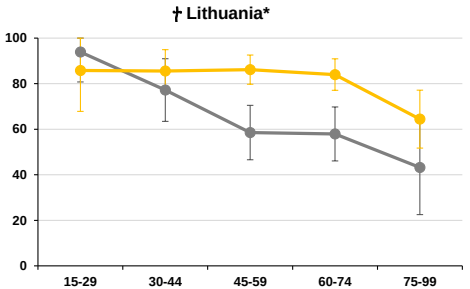


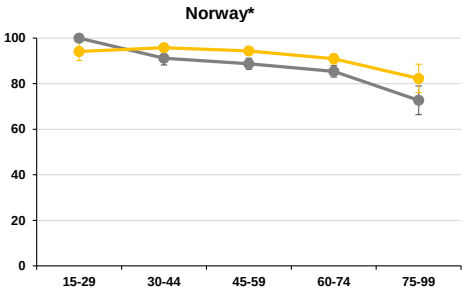


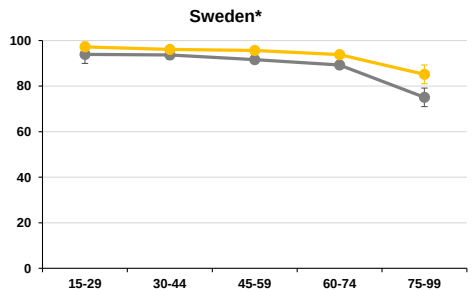


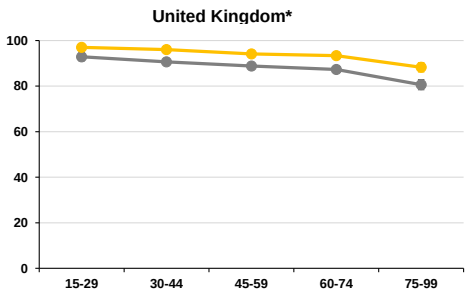




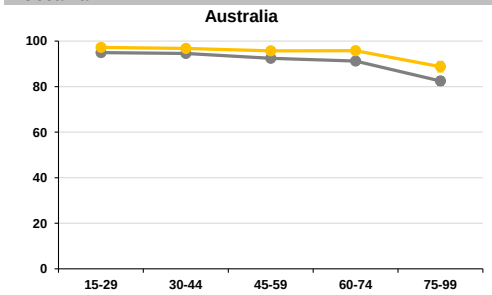


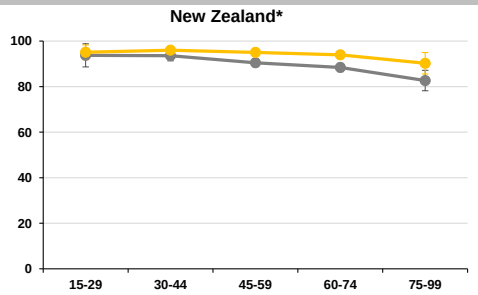






Oceania

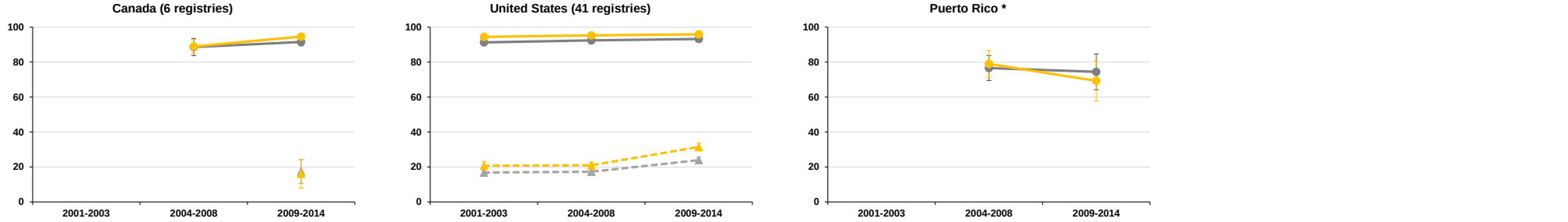




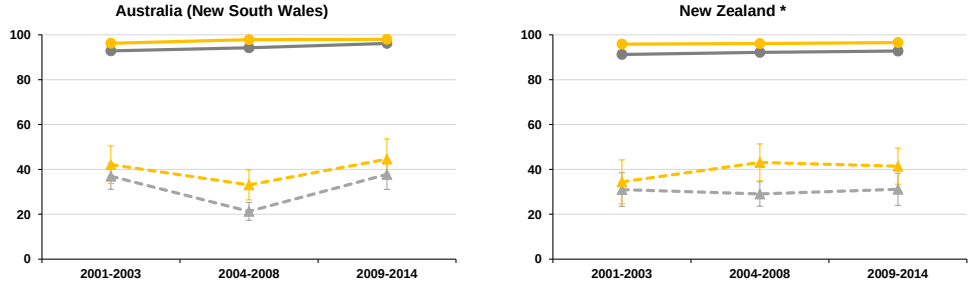
* 100% coverage of the national population
§ estimates flagged as less reliable
† data from two-adjacent age groups have been combined to obtain survival estimates

Supplementary Figure 4.4: Trends in age-standardised five-year net survival (%) for men (grey) and women (yellow) diagnosed with non-metastatic (continuous line) and metastatic (dotted line) melanoma of the skin during 2001-2003, 2004-2008 and 2009-2014 by continent (or continental region) and country.

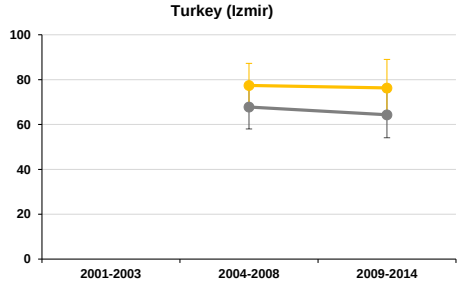
North and Central America



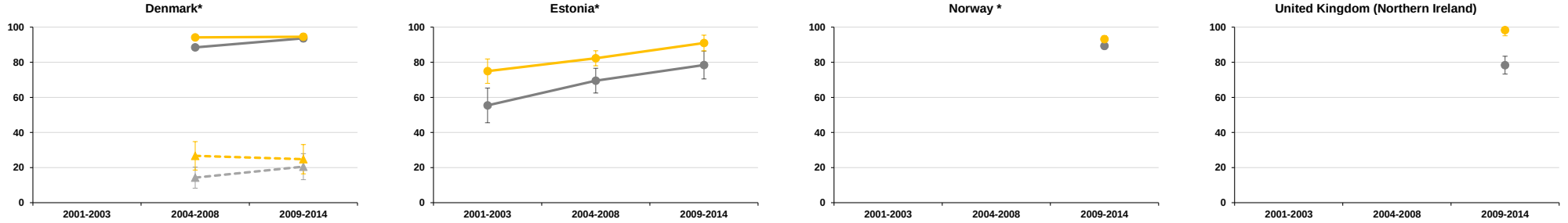
Oceania



Asia

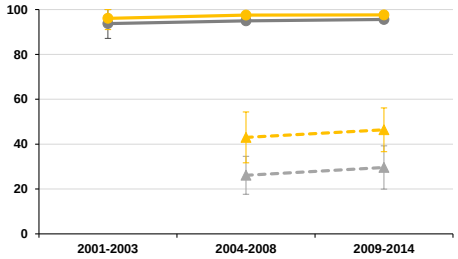


Europe (North)

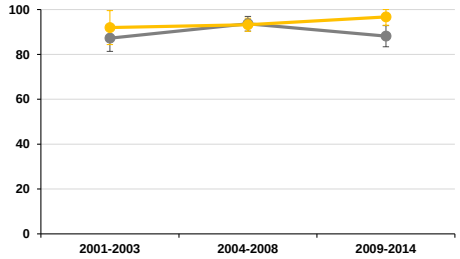


Europe (West)

Germany (3 registries)

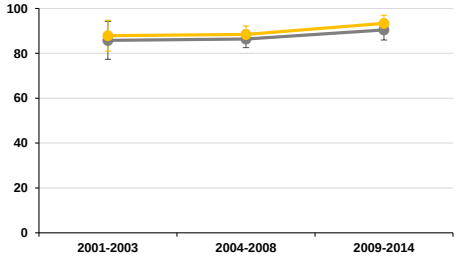


Switzerland (3 registries)

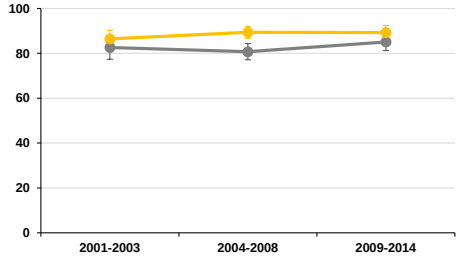


Europe (South)

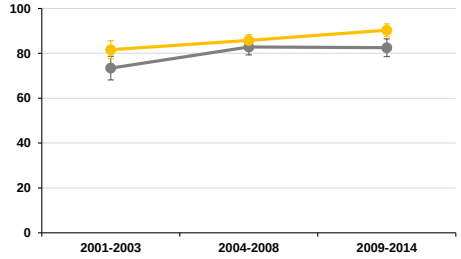
Italy (3 registries)



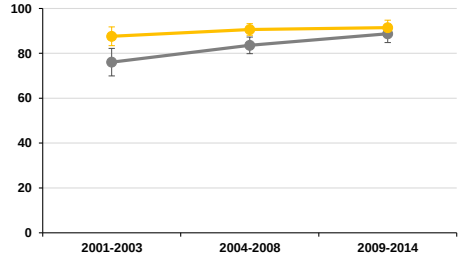
Portugal (South)



Slovenia *

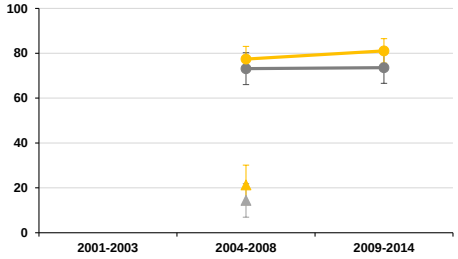


Spain (2 registries)

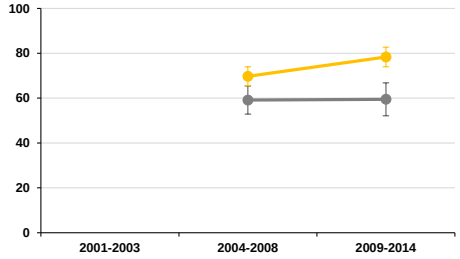


Europe (East)

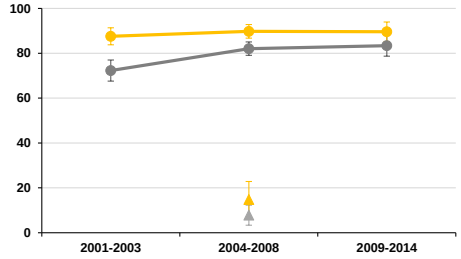
Poland (Lower Silesia)



Russian Federation (3)



Slovakia *



5. **Discussion**

In my doctoral research project, I set out to provide a comprehensive examination of world-wide variation in survival from melanoma of the skin, and to identify the reasons for the generally poor prognosis for patients in Asia and in Central and South America.

The first objective focused on stage at diagnosis, the most relevant prognostic factor. Analyses were performed on a small proportion of melanomas, those diagnosed when metastatic. I analysed data on patients diagnosed in the United States only, because stage data were available only for a few countries (Canada, Denmark, Germany, Netherlands and New Zealand) and the proportion of missing data on stage at diagnosis was low (10% or lower) and stable for all years 2000-2014 for all the 41 US population-based cancer registries that provided data for CONCORD-3. These cancer registries covered over 80% of the US population.

Metastatic melanoma was a uniformly deadly disease until the last decade. It was mainly treated with chemotherapy, but with purely palliative intent. During the first decade of 2000s, randomised clinical trials showed a dramatic improvement in observed short-term survival for patients diagnosed with metastatic or unresectable melanoma with targeted treatments[44] or immunotherapies.[41,42] The US FDA approved both the first immunotherapy (ipilimumab) and the first targeted treatment (vemurafenib) for metastatic or unresectable melanoma in 2011. The scope of *Research Paper 1* was to assess whether the improvement in short-term survival observed in clinical trials was also seen at a population level in the United States, for men and women, and for all ages and races. Randomised trials examine short-term survival for a small proportion of selected patients, usually within a single healthcare facility and under optimal clinical conditions. On the contrary, population-based survival is a measure of the average survival achieved by all cancer patients in a country or region covered by a population-based cancer registry, whether the patients are rich or poor, young or old, with or without comorbidity, with advanced or late disease, and whatever their race or ethnicity. These patients are seen in a wide range of healthcare facilities that offer different levels of rigour in the application of clinical protocols and compliance with treatment guidelines, a wide range of treatments, and equipment of dissimilar quality. Some patients may withdraw from treatment due to costs, or the length of travel to the clinic, or side-effects of treatment. For these reasons, population-based survival reflects the overall outcome of cancer care in the entire population of a country or region. That is why population-based survival estimates are so valuable to inform strategies for cancer control.

Few population-based studies focused on patients with metastatic melanoma, because they generally represent a very small proportion of all melanomas, e.g., around 5% of all cases in the United States. *Research paper 1* was the largest population-based study to date to show an improvement in short-term survival for metastatic melanoma in the United States. The availability of data from 41 US population-based cancer registries over 15 years allowed me to produce robust estimates of one- and two-year net survival trends over time, and also to analyse survival by age, sex and race. *Research Paper 1* showed a dramatic improvement in one- and two-year net survival in the United States starting from 2010.[91] The improvement was more pronounced among Whites and younger patients. While *Research Paper 1* focused on the most relevant prognostic factor for cutaneous melanoma, in *Research Paper 2,* I examined the most controversial prognostic factor: morphology.

The role of morphology has been debated at length from a clinical perspective. International clinical guidelines have disregarded morphology as a relevant prognostic factor in melanoma treatment, because the results of small single-centre studies conducted in the late 1980s suggested that melanomas of different morphologies converge in their behaviour once they metastasise.[148] I aimed to conduct the first world-wide comparison of the distribution of melanoma morphology, and of survival trends for each by morphologic type. I found a less favourable distribution of morphological sub-types in Asia and in Central and South America, where the proportion of nodular and acral melanomas was higher than in other world regions.

Nearly two third of melanomas occurring in lighter-skinned people are superficial spreading melanomas.[47] This subtype is linked to repeated sunburns in childhood and intermittent sun exposure throughout life. Tanning bed use has also been linked to an increased risk of superficial spreading melanoma in young women.[49] In several European countries the increasing incidence of melanoma reflected the increasing number of thin lesions, mainly superficial spreading melanomas.[175,220,221] Five-year net survival for this subtype is over 90% in most European countries, the US and Oceania, as shown in *Research Paper 3*.

Superficial spreading melanoma is less common among Hispanic, Asian and African populations, where the incidence of cutaneous melanoma is also low.[22] Acral lentiginous melanoma is the most frequent subtype in East Asia.[222] Acral sites are not UV radiation-exposed and the results of anatomical mapping of acral melanoma on the plantar surface suggest a possible association with mechanical of physical distress.[58,60] Its clinical features and prognosis are generally poor.[223,224]

In *Research Paper 2*, acral lentiginous and nodular melanoma have shown poorer prognosis than the superficial spreading melanoma. Further multivariable analysis of data from five

European cancer registries with complete information on stage and morphology, showed that sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes. In other words, the higher excess risk of death for those subtypes than for superficial spreading melanoma is not fully explained by later diagnosis.[193]

The results from *Research Paper 2* should be considered when reviewing national and international clinical guidelines for treatment of melanoma. Dermatologists, surgeons and pathologists need to be persuaded of the importance of a precise pathological diagnosis, both in managing individual patients. The importance of obtaining a more accurate picture of melanoma pathology and of population-level survival, by subtype, must also be stressed.

Despite the increasing incidence of superficial spreading melanoma in the US and other countries,[225] studies have not observed a consequent decrease in the incidence of thicker lesions, that are, on the contrary, increasing.[175,226,227] A possible explanation is that the respective pools of thick and thin melanomas are made up of different histological subtypes of melanoma, i.e., superficial spreading and nodular melanoma, which have long been recognized to differ in their biologic behaviour. As a consequence, early detection campaign may be not as effective for nodular melanoma as for superficial spreading melanoma.

The main limitation of *Research Paper 2* was the high proportion of melanoma with poorly specified histological sub-type (43%), i.e., coded as “malignant melanoma, not otherwise specified (NOS)”, even in countries with excellent cancer registry data. However, data on patients diagnosed with unspecified morphologies were included in the analyses and their age-standardised 5-year net survival was estimated separately. I found that, in most countries, age-standardised 5-year net survival for malignant melanoma, NOS was higher than that of nodular and acral lentiginous melanoma but lower than superficial spreading melanoma. It therefore appears that the tumours registered as malignant melanoma, NOS are an heterogeneous group of cutaneous melanoma, and the lack of more detailed information on histological subtype does not depend on a more aggressive clinical features.

In *Research Paper 3*, I explored the reasons behind the poor prognosis in men than in women with cutaneous melanoma world-wide, for the first time. Men were generally older than women, and more likely to be diagnosed with lesions located on the scalp and neck, that are known to have poorer prognosis at a clinical level. Men also tend to present with a higher proportion of metastatic disease. When I stratified the analysis by the main prognostic factors, I found that five-year net survival was higher in women than men for all age groups and anatomic locations. During 2001-2014, stage-specific analyses also demonstrated a poorer survival in men than women.

Immune function can also play a role in the survival advantage for women. Women mount more effective cellular and humoral immune responses and are less likely to succumb to bacterial and viral infections than men.[228] The immune system is especially critical to detecting and destroying melanoma tumours.

The poorer survival in men than women is documented for many solid cancers.[229,230] A large part of the women's advantage is likely attributable to biological factors, including hormonal status or more favourable molecular subtypes. However other factors, such as co-morbidities, treatment compliance and/or health behaviour (including degree of change in health behaviour after diagnosis) could be contributors to sex disparities and merit further investigation using high-resolution approach.

Research Paper 3 also highlights the poor prognosis for both men and women with melanoma in South-East Asia, which extends to all ages at diagnosis. In particular, five-year net survival for older men (75-99 years) was in the range 20-55% compared to 69-93% for younger men (15-29). Despite the relatively low incidence of cutaneous melanoma in Asian populations, public health efforts should still be directed to raising awareness of the disease among the general public, since it is typically lethal when metastatic, but with much higher survival if diagnosed early. Guidelines should also promote specific training in the diagnosis of melanoma for clinicians. This would be expected to reduce the time between first consultation and a definitive diagnosis, leading to a better prognosis.

My PhD project provides a comprehensive examination of world-wide variation in survival from melanoma of the skin. It also suggests the need for additional research project with more detailed data on stage and treatment to be collected by population-based cancer registries.

In *Research Paper 1*, I estimated trends in one- and two-year net survival for advanced melanoma in the United States, and showed increasing survival trends, particularly among younger patients. Subsequent analyses confirmed these findings at population level in Canada,[231] Germany,[232] Italy,[233] Sweden[234] and the Nordic European countries.[235]

The improvement in short-term survival is deemed to be related to the introduction of new systemic treatments for patients with metastatic disease. In Europe, the registration of new medicine is harmonized for all countries and directed by the European Medicine Agency (EMA). On the contrary, the degree and timing of reimbursement is decided at national level and varies widely among health care systems. This factor contributes to explain the wide inequality in access to innovative treatment.[236] In 2017, a study on access to innovative treatment for patients with metastatic melanoma including 30 European countries found that

targeted treatments and immunotherapies were not available in Romania, Montenegro, Belarus and Bosnia and Herzegovina, and the proportion of patients treated ranged from less than 5% in Spain and Serbia to 80% in Belgium.[237] The differential access to innovative treatment can contribute explaining the differences in survival for metastatic disease, also observed in *Research Paper 3.*

It was not possible to estimate trends in short-term survival for metastatic melanoma in countries other than the United States, because the availability and completeness of stage information in the vast majority of the other registries and countries was much more limited. In CONCORD-3, registries were invited to submit data on stage at diagnosis using one of three stage classifications: TNM stage,[36] condensed TNM[167] and SEER Summary Stage 2000.[107] Registries could also provide information on the tumour size, and on the number of lymph nodes examined and involved, as recorded in the pathological report. However, all these variables were optional information in the CONCORD-3 protocol, because population-based cancer registries often hold incomplete information on stage at diagnosis.[238-240] However, some recent studies highlighted improved accuracies and completeness of stage data in more recent years.[241,242]

It was not possible to evaluate longer-term survival, i.e., at five years after diagnosis, because five years of follow-up were not available for patients diagnosed during 2010-2014; patients were only followed up until 31 December 2014. The use of the period approach[78] could have enabled prediction of five-year survival for patients diagnosed in 2010-14, but we considered this approach less appropriate when analysing survival by stage. This is because the predictions would be obtained using data from patients who were diagnosed in earlier years and were still alive in 2010-2014, and therefore would not entirely reflect the most recent stage distribution, likely to be more favourable. In due course, I plan to update *Research Paper 1* using more recent data on incidence, and longer follow-up. These data are currently being collected for the fourth cycle of the CONCORD programme (CONCORD-4).

In the CONCORD-4 study, population-based cancer registries have been invited to submit data on patients diagnosed with one of 22 cancers or group of cancers, including melanoma, during 2000-2019 or later years, and followed up to 31 December 2019 or a later year. Data collection is ongoing. I will update the analysis of trends in short-term survival for the US. I may also be able to extend the analyses to other countries for which complete information on stage at diagnosis will be available. I also plan to estimate trends in longer-term net survival, to estimate whether the gain in short-term survival for metastatic melanoma that has occurred

after the introduction of immunotherapy and targeted therapy in some countries is maintained in the longer run.

The CONCORD-4 protocol requests data on the type of systemic treatment, i.e., chemotherapy, targeted therapy, including monoclonal antibody therapy and immunotherapy. These variables are optional rather than core variables. Some registries do not collect data on treatment, and treatment data may not be submitted by all the cancer registries that do collect such data. For those registries that provide complete data on stage and treatment, I will aim to assess whether the distribution of treatment for metastatic disease differs between younger and older patients, and to estimate whether the odds of receiving new lines of treatment differs by age, sex, race and socio-economic status, where relevant.

My research highlights the importance of accurate information on the morphologic subtype of melanoma to help understand the reasons behind the poorer survival in Central and South America and in Asia than in Europe, North America and Oceania. Further investigations may involve a high-resolution study, where detailed data on morphology, ulceration, mitotic rate, genetic profile and treatment would contribute towards explaining the poor prognosis in Asian and Latin American countries. Several recent studies have highlighted the importance of morphology on the prognosis of cutaneous melanoma.[54,154,243] The current evidence from population-based studies should persuade experts and clinicians to update clinical guidelines and to include morphology as a relevant prognostic factor, particularly in the light of the different distributions of morphology among populations with lower incidence of melanoma of the skin, i.e., Asians and Dark-skinned people.

In *Research Paper 3,* I built upon the findings of the first two research studies, and I tried to understand the reasons for the poorer prognosis in men than in women. The findings from *Research Paper 3* highlighted that, in most countries, men are generally older than women, they develop melanoma more often at anatomic sites that are known to have a poorer prognosis, and they present with a higher proportion of metastatic disease. However, the magnitude of the sex gap in five-year survival varies widely between countries, and it is much larger in countries in South America. To disentangle further the reasons for the gender gap, more detailed information on the route to diagnosis, stage at diagnosis, comorbidities and treatments are needed, particularly from cancer registries in countries where awareness of the early signs of melanoma is limited. In this context, granular and detailed data on ulceration, mitotic rate, Clark level, BRAF, MEK and NRAS mutations, surgical margins, number of lymph nodes removed, type of systemic treatment, insurance status and socio-economic status

(*high-resolution* variables) will be key to assessing adherence to clinical guidelines and to highlight whether any group of patients received sub-optimal treatment.

Some of the remaining questions raised in my research may be answered with data from CONCORD-4, for which data collection is currently ongoing. Currently, we have made preliminary assessment of the data submitted by 136 registries in 37 countries, which include cancer registrations for 46,041,726 cancer patients, including 3,006,989 diagnosed with a melanoma of the skin.[a] Among these data sets, 40 registries in 15 countries have submitted data on patients diagnosed up to 2020; a further 11 registries in 10 countries up to 2021 and one registry up to 2022.

A recent population-based study on 17,984 patients diagnosed with melanoma of the skin in the United States showed that patients diagnosed in 2020 tended to have thicker, more ulcerated and more advanced tumours.[244] A Dutch nation-wide study on 524 patients diagnosed with metastatic or unresectable melanoma in 2020 showed that advanced melanoma care in the Netherlands was severely affected by the COVID-19 pandemic.[245] Systemic treatment was more often delayed, and treatment more often postponed for patients diagnosed in 2020 than for those diagnosed in 2018-2019. CONCORD-4 data will give me a unique opportunity to examine the world-wide impact of the COVID-19 pandemic on the stage at diagnosis and the type of treatment. For a limited number of registries, I will also be able to assess whether the pandemic has had an impact on the time between diagnosis and treatment, both for localised and advanced tumours.

[a] The data for a further 100 registries have not yet been evaluated.

References

1. Miller C, Weinstock MA. Non-melanoma skin cancer in the United States: Incidence. *Journal of American Academy of Dermatology* 1994: 774-8.
2. Eisemann N, Jansen L, Castro FA*, et al.* Survival with nonmelanoma skin cancer in Germany. *British Journal of Dermatology* 2015; **174**: 778-85.
3. Kwiatkowska M, Ahmed S, Ardern-Jones M*, et al.* An updated report on the incidence and epidemiological trends of keratinocyte cancers in the United Kingdom 2013–2018. *Skin Health and Disease* 2021; **1**(4): e61.
4. International Agency for Research and Cancer. Solar and Ultraviolet Radiation (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 55). Lyon, France. ; 1992.
5. Garbe C, Büttner P, Weiss J*, et al.* Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. *J Invest Dermatol* 1994; **102**(5): 695-9.
6. Gandini S, Sera F, Cattaruzza MS*, et al.* Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**(14): 2040-59.
7. Newton-Bishop JA, Chang Y-M, Iles MM*, et al.* Melanocytic Nevi, Nevus Genes, and Melanoma Risk in a Large Case-Control Study in the United Kingdom. *Cancer Epidemiology, Biomarkers & Prevention* 2010; **19**(8): 2043-54.
8. Olsen CM, Zens MS, Stukel TA*, et al.* Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. *Int J Cancer* 2009; **124**(4): 937-44.
9. Williams ML, Sagebiel RW. Melanoma risk factors and atypical moles. *West J Med* 1994; **160**(4): 343-50.
10. Silva JH, Sá BC, Avila AL*, et al.* Atypical mole syndrome and dysplastic nevi: identification of populations at risk for developing melanoma - review article. *Clinics (Sao Paulo)* 2011; **66**(3): 493-9.
11. Tannous ZS, Mihm MC, Jr., Sober AJ*, et al.* Congenital melanocytic nevi: clinical and histopathologic features, risk of melanoma, and clinical management. *J Am Acad Dermatol* 2005; **52**(2): 197-203.
12. Slade J, Marghoob AA, Salopek TG*, et al.* Atypical mole syndrome: Risk factor for cutaneous malignant melanoma and implications for management. *Journal of the American Academy of Dermatology* 1995; **32**(3): 479-94.
13. Raj RC, Patil R. Familial atypical multiple mole melanoma syndrome in an adult Indian male-case report and literature review. *Indian J Dermatol* 2015; **60**(2): 217.
14. de Vries E, Coebergh JW. Cutaneous malignant melanoma in Europe. *European Journal of Cancer* 2004; **40**(16): 2355-66.
15. Stang A, Valiukeviciene S, Aleknaviciene B*, et al.* Time trends of incidence, mortality, and relative survival of invasive skin melanoma in Lithuania. *European Journal of Cancer* 2006; **42**(5): 660-7.
16. MacKie RM, Bray C, Vestey J*, et al.* Melanoma incidence and mortality in Scotland 1979-2003. *British Journal of Cancer* 2007; **96**(11): 1772-7.
17. Franco-Lie I, Iversen T, Robsahm TE*, et al.* Incidence trends of melanoma of the skin compared with other localisations, in the Norwegian population, 1956-2005. *Annals of Oncology* 2011; **22**: 1443-50.
18. Hollestein LM, van den Akker SA, Nijsten T*, et al.* Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Annals of Oncology* 2012; **23**(2): 524-30.
19. Vranova J, Arenbergerova M, Arenberger P*, et al.* Malignant melanoma in the Czech Republic: incidence and mortality according to sex, age and disease stage. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic* 2014; **158**(3): 438-46.

20. Bay C, Kejs AM, Storm HH*, et al.* Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: a Danish Population-based Register Study 1989-2011. *Cancer Epidemiology* 2015; **39**(1): 1-7.
21. Padrik P, Valter A, Valter E*, et al.* Trends in incidence and survival of cutaneous malignant melanoma in Estonia: a population-based study. *Acta Oncologica* 2017; **56**(1): 52-8.
22. Global Cancer Observatory. Cancer today. 2020. https://gco.iarc.fr/today/home.
23. Global Cancer Observatory. Cancers attributable to UV radiations. 2018. https://gco.iarc.fr/causes/uv/.
24. Chen YJ, Wu CY, Chen JT*, et al.* Clinicopathologic analysis of malignant melanoma in Taiwan. *Journal of the American Academy of Dermatology* 1999; **41**: 945-9.
25. Ishihara K, Saida T, Otsuka F*, et al.* Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. *International Journal of Clinical Oncology* 2008; **13**: 33-41.
26. Teh YL, Goh WL, Tan SH*, et al.* Treatment and outcomes of melanoma in Asia: Results from the National Cancer Centre Singapore. *Asia-Pacific Journal of Clinical Oncology* 2018; **14**: e95-e102.
27. Armstrong A, Powell C, Powell R*, et al.* Are we seeing the effects of public awareness campaigns? A 10-year analysis of Breslow thickness at presentation of malignant melanoma in the South West of England. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2014; **67**: 324-30.
28. Miller DR, Geller AC, Wyatt SW*, et al.* Melanoma awareness and self-examination practices: results of a United States survey. *Journal of American Academy of Dermatolgy* 1996; **34**(6): 962-70.
29. Weinstock MA, Risica PM, Martin RA*, et al.* Melanoma early detection with thorough skin self-examination: the "Check It Out" randomized trial. *Am J Prev Med* 2007; **32**(6): 517-24.
30. Walker H, Maitland C, Tabbakh T*, et al.* Forty years of Slip! Slop! Slap! A call to action on skin cancer prevention for Australia. *Public Health Res Pract* 2022; **32**(1).
31. Tabbakh T, Volkov A, Wakefield M*, et al.* Implementation of the SunSmart program and population sun protection behaviour in Melbourne, Australia: Results from cross-sectional summer surveys from 1987 to 2017. *PLOS Medicine* 2019; **16**(10): e1002932.
32. Hansen MR, Bentzen J. High-risk sun-tanning behaviour: a quantitative study in Denmark, 2008-2011. *Public Health* 2014; **128**(9): 777-83.
33. Abbasi NR, Shaw HM, Rigel DS*, et al.* Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA* 2004; **292**: 2771-6.
34. Robinson JK, Mallett KA, Turrisi R*, et al.* Engaging patients and their partners in preventive health behaviors: the physician factor. *Arch Dermatol* 2009; **145**(4): 469-73.
35. Swetter SM, Layton CJ, Johnson TM*, et al.* Gender differences in melanoma awareness and detection practices between middle-aged and older men with melanoma and their female spouses. *Arch Dermatol* 2009; **145**(4): 488-90.
36. 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; **17**: 1471-4.
37. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. *Expert Rev Anticancer Ther* 2018; **18**(8): 775-84.
38. Lakshmi A, Shah R, Begaj A*, et al.* NICE 2022 guidelines on the management of melanoma: Update and implications. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2023; **85**: 401-13.
39. Dummer R, Hauschild A, Guggenheim M*, et al.* Melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2010; **21**: v194-v7.
40. Hodi FS, O'Day S, McDermott F*, et al.* Improved survival with Ipilimumab in patients with metastatic melanoma. *New England Journal of Medicine* 2010; **363**(8): 711-23.
41. Robert C, Long GV, Brady B*, et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *New England Journal of Medicine* 2015; **372**(4): 320-30.
42. Robert C, Schachter J, Long GV*, et al.* Pembrolizumab versus ipilimumab in advanced melanoma. *New England Journal of Medicine* 2015; **372**(26): 2521-32.

43. Davies H, Bignell GR, Futreal PA. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**: 949-54.
44. Chapman PB, Hauschild A, Robert C*, et al.* Improved survival with Vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine* 2011; **364**(26): 2507-16.
45. Dummer R, Hauschild A, Santinami M*, et al.* Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. *New England Journal of Medicine* 2020; **383**(12): 1139-48.
46. Fritz A, Percy C, Jack A*, et al.* International classification of diseases for oncology (ICD-O) – first revision of 3rd edition. Geneva: World Health Organization; 2013.
47. International Agency for Research and Cancer. WHO Classification of Skin Tumours. Lyon, France. ; 2018.
48. Holman CD, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J Natl Cancer Inst* 1986; **76**(3): 403-14.
49. Lazovich D, Isaksson Vogel R, Weinstock MA*, et al.* Association Between Indoor Tanning and Melanoma in Younger Men and Women. *JAMA Dermatol* 2016; **152**(3): 268-75.
50. Mihm Jr MC, Lopansri S. A review of the classification of malignant melanoma. *The Journal of Dermatology* 1979; **6**(3): 131-42.
51. Clark WH, From L, Bernardino EA*, et al.* The histogenesis and biologic behaviour of primary human malignant melanomas of the skin. *Cancer Research* 1969; **29**: 705-26.
52. Greenwald HS, Friedman EB, Osman I. Superficial spreading and nodular melanoma are distinct biological entities: a challenge to the linear progression model. *Melanoma research* 2012; **22**(1): 1-8.
53. Mar V, Roberts H, Wolfe R*, et al.* Nodular melanoma: a distinct clinical entity and the largest contributor to melanoma deaths in Victoria, Australia. *Journal of the American Academy of Dermatology* 2013; **68**: 568-75.
54. Allais BS, Beatson M, Wang H*, et al.* Five-year survival in patients with nodular and superficial spreading melanomas in the US population. *J Am Acad Dermatol* 2021; **84**(4): 1015-22.
55. Smalberger GJ, Siegel DM, Khachemoune A. Lentigo maligna. *Dermatologic Therapy* 2008; **21**(6): 439-46.
56. Kvaskoff M, Siskind V, Green AèC. Risk Factors for Lentigo Maligna Melanoma Compared With Superficial Spreading Melanoma: A Case-Control Study in Australia. *Archives of Dermatology* 2012; **148**(2): 164-70.
57. Merkel EA, Gerami P. Malignant melanoma of sun-protected sites: a review of clinical, histological, and molecular features. *Laboratory Investigation* 2017; **97**(6): 630-5.
58. Jung HJ, Kweon SS, Lee JB*, et al.* A clinicopathologic analysis of 177 acral melanomas in Koreans: relevance of spreading pattern and physical stress. *JAMA Dermatol* 2013; **149**(11): 1281-8.
59. Zhang N, Wang L, Zhu GN*, et al.* The association between trauma and melanoma in the Chinese population: a retrospective study. *J Eur Acad Dermatol Venereol* 2014; **28**(5): 597-603.
60. Minagawa A, Omodaka T, Okuyama R. Melanomas and Mechanical Stress Points on the Plantar Surface of the Foot. *New England Journal of Medicine* 2016; **374**(24): 2404-6.
61. Lattanzi M, Lee Y, Simpson D*, et al.* Primary melanoma histologic subtype: impact on survival and response to therapy. *Journal of the National Cancer Institute* 2019; **111**: 180-8.
62. Coleman MP, Quaresma M, Berrino F*, et al.* Cancer survival in five continents: a worldwide population-based study (CONCORD). *The Lancet Oncology* 2008; **9**(8): 730-56.
63. Allemani C, Weir HK, Carreira H*, 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; **385**: 977-1010.
64. Allemani C, Matsuda T, Di Carlo V*, et al.* Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**: 1023-75.
65. Woods LM, Rachet B, Ellis L*, et al.* Full dates (day, month, year) should be used in population-based cancer survival studies. *International Journal of Cancer* 2012; **131**(7): E1120-E4.

66. McGivern L, Shulman L, Carney JK*, et al.* Death Certification Errors and the Effect on Mortality Statistics. *Public Health Reports* 2017; **132**(6): 669-75.
67. Lu T-H, Lee M-C, Chou M-C. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. *International Journal of Epidemiology* 2000; **29**(2): 336-43.
68. Percy C, Stanek E, 3rd, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981; **71**(3): 242-50.
69. Hoel DG, Ron E, Carter R*, et al.* Influence of death certificate errors on cancer mortality trends. *J Natl Cancer Inst* 1993; **85**(13): 1063-8.
70. Lakkireddy DR, Gowda MS, Murray CW*, et al.* Death certificate completion: how well are physicians trained and are cardiovascular causes overstated? *Am J Med* 2004; **117**(7): 492-8.
71. Schaffar R, Rapiti E, Rachet B*, et al.* Accuracy of cause of death data routinely recorded in a population-based cancer registry: impact on cause-specific survival and validation using the Geneva cancer registry. *BMC Cancer* 2013; **13**(1): 609.
72. Pohar Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68**: 113-20.
73. Rachet B, Maringe C, Woods LM*, et al.* Multivariable flexible modelling for estimating complete, smoothed life tables for sub-national populations. *BMC Public Health* 2015; **15**(1): 1240.
74. Ewbank DC, Gomez De Leon JC, Stoto MA. A reducible four-parameter system of model life tables. *Population Studies* 1983; **37**: 105-27.
75. Elandt-Johnson RC, Johnson NL. Survival models and data analysis. Indianapolis: Wiley; 1980.
76. Di Carlo V, Spika D, Rachet B*, et al.* Life tables for the CONCORD programme. http://csg.lshtm.ac.uk/life-tables.
77. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *European Journal of Cancer* 2004; **40**: 2307-16.
78. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996; **78**: 2004-10.
79. Xing Y, Chang GJ, Hu CY*, et al.* Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer* 2010; **116**: 2234-41.
80. Pollack LA, Li J, Berkowitz Z*, et al.* Melanoma survival in the United States, 1992 to 2005. *Journal of the American Academy of Dermatology* 2011; **65**: S78-86.
81. Uprety D, Bista A, Chennamadhavuni A*, et al.* Survival trends among patients with metastatic melanoma in the pretargeted and the post-targeted era: a US population-based study. *Melanoma Res* 2018; **28**(1): 56-60.
82. Hanna TP, Nguyen P, Baetz T*, et al.* A Population-based Study of Survival Impact of New Targeted and Immune-based Therapies for Metastatic or Unresectable Melanoma. *Clin Oncol (R Coll Radiol)* 2018; **30**(10): 609-17.
83. Enninga EAL, Moser JC, Weaver AL*, et al.* Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992-2011. *Cancer Medicine* 2017; **6**: 2203-12.
84. Eggermont A, Chiarion Sileni V, Grob JJ*, et al.* Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *New England Journal of Medicine* 2016; **375**.
85. Weber J, Mandala M, Del Vecchio M*, et al.* Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med* 2017; **377**(19): 1824-35.
86. Srikanthan A, Vera-Badillo F, Ethier J*, et al.* Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies. *Cancer Treat Rev* 2016; **43**: 67-73.
87. Unger JM, Barlow WE, Martin DP*, et al.* Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst* 2014; **106**(3): dju002.
88. Hutchins LF, Unger JM, Crowley JJ*, et al.* Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; **341**(27): 2061-7.
89. Unger JM, Hershman DL, Albain KS*, et al.* Patient income level and cancer clinical trial participation. *J Clin Oncol* 2013; **31**(5): 536-42.

90. Ward-Peterson M, Acuña JM, Alkhalifah MK*, et al.* Association between race/ethnicity and survival of melanoma patients in the United States over 3 decades. *Medicine* 2016; **95**(17).
91. Di Carlo V, Estève J, Johnson CH*, et al.* Trends in short-term survival from distant-stage cutaneous melanoma in the United States, 2001-2013 (CONCORD-3). *JNCI Cancer Spectrum* 2020; **4**(6).
92. van Zeijl MCT, Boer FL, van Poelgeest MIE*, et al.* Survival outcomes of patients with advanced mucosal melanoma diagnosed from 2013 to 2017 in the Netherlands – A nationwide population-based study. *European Journal of Cancer* 2020; **137**: 127-35.
93. Siming L, Xiaowen W, Xieqiao Y*, et al.* Toripalimab plus axitinib in patients with metastatic mucosal melanoma: 3-year survival update and biomarker analysis. *Journal for ImmunoTherapy of Cancer* 2022; **10**(2): e004036.
94. Wehbe J, Jaikaransingh D, Walker A. Immunotherapy as a treatment modality for mucosal melanoma of the head and neck: A systematic review. *Medicine (Baltimore)* 2022; **101**(31): e29979.
95. Boer FL, Ho VKY, Louwman MWJ*, et al.* Trends in Incidence and Survival of 1496 Patients with Mucosal Melanoma in The Netherlands (1990-2019). *Cancers (Basel)* 2023; **15**(5).
96. Furney SJ, Turajlic S, Stamp G*, et al.* Genome sequencing of mucosal melanomas reveals that they are driven by distinct mechanisms from cutaneous melanoma. *J Pathol* 2013; **230**(3): 261-9.
97. Shoushtari AN. Incorporating VEGF Blockade Into a Shifting Treatment Paradigm for Mucosal Melanoma. *Journal of Clinical Oncology* 2021; **39**(8): 867-9.
98. Hayward NK, Wilmott JS, Waddell N*, et al.* Whole-genome landscapes of major melanoma subtypes. *Nature* 2017; **545**(7653): 175-80.
99. International Agency for Research and Cancer. Cancer Incidence in Five Continents, Vol. XI. Lyon, France; 2017.
100. National Cancer Institute. Surveillance, Epidemiology, and End Results Programme. Cancer Stat Facts: Melanoma of the Skin. https://seer.cancer.gov/statfacts/html/melan.html (accessed August 2019).
101. U.S. Cancer Statistics Working Group. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute: U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016). June 2019. www.cdc.gov/cancer/dataviz.
102. Allemani C, Matsuda T, Di Carlo V*, et al.* Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**(17): 1023-75.
103. Schoffer O, Schülein S, Arand G*, et al.* Tumour stage distribution and survival of malignant melanoma in Germany 2002-2011. *BMC Cancer* 2016; **16**(1): 936-48.
104. Rockberg J, Amelio JM, Taylor A*, et al.* Epidemiology of cutaneous melanoma in Sweden. Stage-specific survival and rate of recurrence. *Int J Cancer* 2016; **139**(12): 2722-9.
105. Pollack LA, Li J, Berkowitz Z*, et al.* Melanoma survival in the United States, 1992 to 2005. *J Am Acad Dermatol* 2011; **65**(5): S78-86.
106. Xing Y, Chang GJ, Hu CY*, et al.* Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer* 2010; **116**(9): 2234-41.
107. Young JL, Roffers SD, Ries LAG*, et al.* SEER Summary Staging Manual-2000: codes and coding instructions; 2001.
108. Pohar-Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68**(1): 113-20.
109. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.; 2017.
110. Clerc-Urmès I, Grzebyk M, Hedelin G. Net survival estimation with stns. *Stata Journal* 2014; **14**(87-102).
111. Mariotto AB, Zou Z, Johnson CJ*, et al.* Geographical, racial and socio-economic variation in life expectancy in the US and their impact on cancer relative survival. *PloS one* 2018; **13**(7): e0201034-e.

112. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40**(15): 2307-16.
113. Bower H, Crowther MJ, Lambert PC. strcs: A command for fitting flexible parametric survival models on the log-hazard scale. *The Stata Journal* 2016; **16**(4): 989-1012.
114. Lambert PC. rcsgen: STATA module to generate restricted cubic splines and their derivatives. *Statistical Software Components* 2008.
115. Rutherford MJ, Ironmonger L, Ormiston-Smith N*, et al.* Estimating the potential survival gains by eliminating socioeconomic and sex inequalities in stage at diagnosis of melanoma. *British Journal of Cancer* 2015; **112**(Suppl 1): S116-23.
116. Enninga EAL, Moser JC, Weaver AL*, et al.* Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992-2011. *Cancer Med* 2017; **6**(10): 2203-12.
117. Crocetti E, Fancelli L, Manneschi G*, et al.* Melanoma survival: sex does matter, but we do not know how. *European Journal of Cancer Prevention* 2016; **25**(5): 404-9.
118. Kundu RV, Kamaria M, Ortiz S*, et al.* Effectiveness of a knowledge-based intervention for melanoma among those with ethnic skin. *J Am Acad Dermatol* 2010; **62**(5): 777-84.
119. Byrd KM, Wilson DC, Hoyler SS*, et al.* Advanced presentation of melanoma in African Americans. *J Am Acad Dermatol* 2004; **50**(1): 21-4.
120. Mahendraraj K, Sidhu K, Lau CS*, et al.* Malignant melanoma in African-Americans: a population-based clinical outcomes study involving 1106 African-American patients from the Surveillance, Epidemiology, and End Results (SEER) Database (1988-2011). *Medicine* 2017; **96**(15): e6258.
121. Wang Y, Zhao Y, Ma S. Racial differences in six major subtypes of melanoma: descriptive epidemiology. *BMC Cancer* 2016; **16**(1): 691.
122. Gamba CS, Clarke CA, Keegan TH*, et al.* Melanoma survival disadvantage in young, non-Hispanic white males compared with females. *JAMA Dermatology* 2013; **149**(8): 912-20.
123. Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application number: 125377Orig1s000 - Yervoy Ipilimumab. 2011.
124. Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application number: 202429Orig1s000 - Zelboraf vemurafenib.
125. Wolchok JD, Neyns B, Linette GP*, et al.* Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *The Lancet Oncology* 2010; **11**: 155-64.
126. Tang J, Yu JX, Hubbard-Lucey VM*, et al.* The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. *Nature Reviews Drug Discovery* 2018; **17**: 854-5.
127. U.S. Food & Drug Administration. Expanded Acccess Program. 2019. https://www.fda.gov/media/85675/download (accessed 8 Oct 2019).
128. Hanna TP, Nguyen P, Baetz T*, et al.* A population-based study of survival impact of new targeted and immune-based therapies for metastatic or unresectable melanoma. *Clinical Oncology* 2018; **30**(10): 609-17.
129. Hague W, Verma V, Butler EB*, et al.* Racial and socioeconomic disparities in the delivery of immunotherapy for metastatic melanoma in the United States. *Journal of Immunotherapy* 2019; **42**(6): 228-35.
130. Enewold L, Sharon E, Harlan LC. Metastatic melanoma: treatment and survival in the US after the introduction of ipilimumab and vemurafenib. *Oncology Research and Treatment* 2017; **40**(4): 174-83.
131. Bouchardy C, Rapiti E, Blagojevic S*, et al.* Older female cancer patients: importance, causes, and consequences of undertreatment. *Journal of Clinical Oncology* 2016; **14**(14): 1858-69.
132. Moore DH, Kauderer JT, Bell J*, et al.* An assessment of age and other factors influencing protocol versus alternative treatments for patients with epithelial ovarian cancer referred to member institutions: a Gynecologic Oncology Group study. *Gynecologic Oncology* 2004; **94**(2): 368-74.

133. Wiggins CL, Harlan LC, Harold EN*, et al.* Age disparity in the dissemination of imatinib for treating chronic myeloid leukaemia. *American Journal of Medicine* 2010; **123**(8): 764.e1-.e9.
134. Amini A, Rusthoven CG, Waxweiler TV*, et al.* Association of health insurance with outcomes in adults ages 18 to 64 years with melanoma in the Unities States. *Journal of the American Academy of Dermatology* 2016; **74**(2): 309-16.
135. Verma V, Sprave T, Haque W*, et al.* A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *Journal for ImmunoTherapy of Cancer* 2018; **6**(1): 128.
136. Shih V, ten Ham RM, Bui CT*, et al.* Targeted therapies compared to dacarbazine for treatment of BRAFV600E metastatic melanoma: a cost-effectiveness analysis. 2015; **2015**(2015): 8.
137. Al-Qurayshi Z, Crowther JE, Hamner JB*, et al.* Disparities of immunotherapy utilization in patients with stage III cutaneous melanoma: a national perspective. *Anticancer Res* 2018; **38**(5): 2897-901.
138. Jain V, Vanigalla S, Reddy V*, et al.* Association of insurance status with presentation, treatment, and survival in melanoma in the era of immune checkpoint inhibitors. *J Immunother* 2019 (published online ahead of print).
139. Pinheiro PS, Morris CR, Liu L*, et al.* The impact of follow-up type and missed deaths on population-based cancer survival studies for Hispanics and Asians. *JNCI Monographs* 2014; **2014**(49): 210-7.
140. Lariscy JT. Differential record linkage by Hispanic ethnicity and age in linked mortality studies: implications for the epidemiologic paradox. *Journal of aging and health* 2011; **23**(8): 1263-84.
141. Cress RD, Holly EA. Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians, and blacks: an analysis of California cancer registry data, 1988-93. *Cancer Causes Control* 1997; **8**(2): 246-52.
142. Cormier JN, Xing Y, Ding M*, et al.* Ethnic differences among patients with cutaneous melanoma. *Archives of Internal Medicine* 2006; **166**(17): 1907-14.
143. Wu XC, Eide MJ, King J*, et al.* Racial and ethnic variations in incidence and survival of cutaneous melanoma in the United States, 1999-2006. *Journal of the American Academy of Dermatology* 2011; **65**(5 Suppl 1): S26-37.
144. Berry DA, Cronin KA, Plevritis SK*, et al.* Effect of screening and adjuvant therapy on mortality from breast cancer. *New England Journal of Medicine* 2005; **353**(17): 1784-92.
145. Chia SK, Speers CH, D'yachkova Y*, et al.* The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007; **110**(5): 973-9.
146. Brenner H, Gondos A, Pulte D. Recent trends in long-term survival of patients with chronic myeloid leukaemia: disclosing the impact of advances in therapy on the population level. *Haematologica* 2008; **93**(10): 1544-9.
147. Ackerman AB, David KM. A unifying concept of malignant melanoma: biologic aspects. *Human Pathology* 1986; **17**: 438-40.
148. Balch CM, Murad TM, Soong SJ*, et al.* A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Annals of Surgery* 1978; **188**: 732-42.
149. Shaw HM, Balch CM, Soong SJ*, et al.* Prognostic histopathological factors in malignant melanoma. *Pathology* 1985; **17**(2): 271-4.
150. Eldh J, Boeryd B, Peterson L-E. Prognostic Factors in Cutaneous Malignant Melanoma in Stage I: A Clinical, Morphological and Multivariate Analysis. *Scandinavian Journal of Plastic and Reconstructive Surgery* 1978; **12**(3): 243-55.
151. Reyes E, Uribe C, de Vries E. Population-based incidence and melanoma-specific survival of cutaneous malignant melanoma in a Colombian population 2000-2009. *International Journal of Dermatology* 2018; **57**: 21-7.

152. Vazquez V L, Silva TB, Vieira Mde A*, et al.* Melanoma characteristics in Brazil: demographics, treatment, and survival analysis. *BMC Research Notes* 2015; **8**: 4.
153. Dessinioti C, Dimou N, Geller AC*, et al.* Distinct clinicopathological and prognostic features of thin nodular primary melanomas: an international study from 17 centers. *Journal of the National Cancer Institute* 2019; **111**: 1314-22.
154. Borges de Barros Primo R, Brito Nobre A, Santos BN*, et al.* Impact of clinical and histopathological characteristics on the disease-free survival of stage I-II acral melanoma patients. *International Journal of Dermatology* 2023; **62**(10): 1281-8.
155. Smithson SL, Pan Y, Mar V. Differing trends in thickness and survival between nodular and non-nodular primary cutaneous melanoma in Victoria, Australia. *Medical Journal of Australia* 2015; **203**(1): III-IV.
156. van der Esch EP, Muir CS, Nectoux J*, et al.* Temporal change in diagnostic criteria as a cause of the increase of malignant melanoma over time is unlikely. *International Journal of Cancer* 1991; **47**: 483-90.
157. Coleman MP, Estève J, Damiecki P*, et al.* Trends in cancer incidence and mortality. Lyon: International Agency for Research on Cancer; 1993.
158. Rockberg J, Amelio JM, Taylor A*, et al.* Epidemiology of cutaneous melanoma in Sweden. Stage-specific survival and rate of recurrence. *International Journal of Cancer* 2016; **139**: 2722-9.
159. Kemeny MM, Busch E, Stewart AK*, et al.* Superior survival of young women with malignant melanoma. *American Journal of Surgery* 1998; **175**: 437-44.
160. Galceran J, Uhry Z, Marcos-Gragera R*, et al.* Trends in net survival from skin malignant melanoma in six European Latin countries: Results from the SUDCAN population-based study. *European Journal of Cancer Prevention* 2017; **26**: S77-S84.
161. Crocetti E, Mallone S, Robsahm TE*, et al.* Survival of patients with skin melanoma in Europe increases further: Results of the EUROCARE-5 study. *European Journal of Cancer* 2015; **51**: 2179-90.
162. Downing A, Yu XQ, Newton-Bishop J*, et al.* Trends in prognostic factors and survival from cutaneous melanoma in Yorkshire, UK and New South Wales, Australia between 1993 and 2003. *International Journal of Cancer* 2008; **123**: 861-6.
163. Elder DE, Massi D, Scolyer RA*, et al.* WHO Classification of Skin Tumours. 4th ed; 2018.
164. Clerc-Urmès I, Grzebyk M, Hedelin G. Net survival estimation with stns. *Stata Journal* 2014; **14**: 87-102.
165. United Nations Statistic Division. Methodology; standard countries or area codes for statistical use (M49). 2022. https://unstats.un.org/unsd/methodology/m49/ (accessed 11 Feb 2022)).
166. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *The Stata Journal* 2009; **9**: 165-90.
167. Berrino F, Brown M, Moller C*, et al.* ENCR recommendation: Condensed TNM for Coding the Extent of Disease. Lyon: Europen Network of Cancer Registries; 2002.
168. Swetter SM, Tsao H, Bichakjian CK*, et al.* Guidelines of care for the management of primary cutaneous melanoma. *Journal of the American Academy of Dermatology* 2019; **80**: 208-50.
169. de Vries E, Sierra M, Pineros M*, et al.* The burden of cutaneous melanoma and status of preventive measures in Central and South America. *Cancer Epidemiology* 2016; **44**: 100-9.
170. Barbarić J, Coebergh JW, Šekerija M. Completeness of Data on Malignant Melanoma Skin Sites and Morphology in the Croatian National Cancer Registry 2000-2014: An Overview of Recent Progress. *Acta Dermatovenerol Croat* 2017; **25**: 285-91.
171. Green AC, Baade P, Coory M*, et al.* Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *Journal of Clinical Oncology* 2012; **30**: 1462-7.
172. Baade P, Meng X, Youlden D*, et al.* Time trends and latitudinal differences in melanoma thickness distribution in Australia, 1990–2006. *International Journal of Cancer* 2012; **130**: 170-8.

173. Montella A, Gavin A, Middleton R*, et al.* Cutaneous melanoma mortality starting to change: a study of trends in Northern Ireland. *European Journal of Cancer* 2009; **45**: 2360-6.
174. Lyth J, Eriksson H, Hansson J*, et al.* Trends in cutaneous malignant melanoma in Sweden 1997-2011: thinner tumours and improved survival among men. *British Journal of Dermatology* 2015; **172**: 700-6.
175. Sacchetto L, Zanetti R, Comber H*, et al.* Trends in incidence of thick, thin and in situ melanoma in Europe. *European Journal of Cancer* 2018; **92**: 108-18.
176. Shaikh WR, Dusza SW, Weinstock MA*, et al.* Melanoma thickness and survival trends in the United States, 1989 to 2009. *Journal of the National Cancer Institute* 2016; **108**.
177. Rubio-Casadevall J, Puig-Vives M, Puigdemont M*, et al.* Patterns of increased incidence and survival of cutaneous melanoma in Girona (Spain) 1994-2013: a population-based study. *Clinical and Translational Oncology* 2018: 1-9.
178. Singapore Cancer Registry. 50 years of cancer registration (1968-2017). Singapore; 2019.
179. Lv J, Dai B, Kong Y*, et al.* Acral melanoma in Chinese: a clinicopathological and prognostic study of 142 cases. *Scientific Reports* 2016; **6**: 31432.
180. Wada M, Ito T, Tsuji G*, et al.* Acral lentiginous melanoma versus other melanoma: A single-center analysis in Japan. *Journal of Dermatology* 2017; **44**: 932-8.
181. Albreski D, Sloan SB. Melanoma of the feet: misdiagnosed and misunderstood. *Clinics in Dermatology* 2009; **27**: 556-63.
182. Bradford PT, Goldstein AM, McMaster ML*, et al.* Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. *Archives of Dermatology* 2009; **145**: 427-34.
183. Kundu RV, Kamaria M, Ortiz S*, et al.* Effectiveness of a knowledge-based intervention for melanoma among those with ethnic skin. *Journal of the American Academy of Dermatology* 2010; **62**: 777-84.
184. Byrd KM, Wilson DC, Hoyler SS*, et al.* Advanced presentation of melanoma in African Americans. *Journal of the American Academy of Dermatology* 2004; **50**: 21-4.
185. Mahendraraj K, Sidhu K, Lau CS*, et al.* Malignant melanoma in African-Americans: a population-based clinical outcomes study involving 1106 African-American patients from the Surveillance, Epidemiology, and End Results (SEER) Database (1988-2011). *Medicine* 2017; **96**: e6258.
186. Shaikh WR, Xiong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. *Archives of Dermatology* 2012; **148**: 30-6.
187. Balch CM, Buzaid AC, Soong SJ*, et al.* New TNM melanoma staging system: linking biology and natural history to clinical outcomes. *Seminars in Surgical Oncology* 2003; **21**: 43-52.
188. Brunssen A, Jansen L, Eisemann N*, et al.* A population-based registry study on relative survival from melanoma in Germany stratified by tumor thickness for each histologic subtype. *Journal of the American Academy of Dermatology* 2019; **80**: 938-46.
189. Minicozzi P, Walsh PM, Sánchez M-J*, et al.* Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? *European Journal of Cancer* 2018; **93**: 127-37.
190. De Giorgi V, Mavilia C, Massi D*, et al.* Estrogen receptor expression in cutaneous melanoma. A real-time reverse transcriptase–polymerase chain reaction and immunohistochemical rtudy. *Arch Dermatology* 2009; **145**: 30-6.
191. Coleman MP, Estève J, Damiecki P*, et al.* Trends in cancer incidence and mortality. *IARC Sci Publ* 1993; (121): 1-806.
192. Global Cancer Observatory. Cancer today. 2018. https://gco.iarc.fr/today/home.
193. Di Carlo V, Stiller CA, Eisemann N*, et al.* Does the morphology of cutaneous melanoma help to explain the international differences in survival? Results from 1 578 482 adults diagnosed during 2000–2014 in 59 countries (CONCORD-3)*. *British Journal of Dermatology* 2022; **187**(3): 364-80.
194. de Giorgi V, Gori A, Gandini S*, et al.* Oestrogen receptor beta and melanoma: a comparative study. *British Journal of Dermatology* 2013; **168**(3): 513-9.

195. Lasithiotakis KG, Leiter U, Eigentler T*, et al.* Improvement of overall survival of patients with cutaneous melanoma in Germany, 1976-2001: which factors contributed? *Cancer* 2007; **109**(6): 1174-82.
196. Joosse A, De Vries E, Eckel R*, et al.* Gender differences in melanoma survival: Female patients have a decreased risk of metastasis. *Journal of Investigative Dermatology* 2011; **131**(3): 719-26.
197. Mervic L, Leiter U, Meier F*, et al.* Sex differences in survival of cutaneous melanoma are age dependent: An analysis of 7338 patients. *Melanoma Research* 2011; **21**(3): 244-52.
198. de Vries E, Nijsten TEC, Visser O*, et al.* Superior survival of females among 10 538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. *Annals of Oncology* 2008; **19**: 583-9.
199. Hieken TJ, Glasgow AE, Enninga EAL*, et al.* Sex-Based Differences in Melanoma Survival in a Contemporary Patient Cohort. *Journal of Women's Health* 2020; **29**(9): 1160-7.
200. Khosrotehrani K, Dasgupta P, Byrom L*, et al.* Melanoma survival is superior in females across all tumour stages but is influenced by age. *Archives of Dermatological Research* 2015; **307**(8): 731-40.
201. Smith AJ, Lambert PC, Rutherford MJ. Understanding the impact of sex and stage differences on melanoma cancer patient survival: a SEER-based study. *British Journal of Cancer* 2021; **124**(3): 671-7.
202. Di Carlo V, Stiller CA, Eisemann N*, et al.* Does the morphology of cutaneous melanoma help to explain the international differences in survival? Results from 1 578 482 adults diagnosed during 2000–2014 in 59 countries (CONCORD-3)*. *Br J Dermatol* 2022; **187**(3): 364-80.
203. Collaborative Stage Data Collection Systmem. Schema. http://cancerstaging.org/cstage/about/Pages/default.aspx (accessed 1 Nov 2019).
204. Micheli A, Ciampichini R, Oberaigner W*, et al.* The advantage of women in cancer survival: An analysis of EUROCARE-4 data. *European Journal of Cancer* 2009; **45**(6): 1017-27.
205. Gupta A, Driscoll MS. Do hormones influence melanoma? Facts and controversies. *Clin Dermatol* 2010; **28**(3): 287-92.
206. Daryanani D, Plukker JT, De Hullu JA*, et al.* Pregnancy and early-stage melanoma. *Cancer* 2003; **97**(9): 2248-53.
207. Youl PH, Youlden DR, Baade PD. Changes in the site distribution of common melanoma subtypes in Queensland, Australia over time: implications for public health campaigns. *Br J Dermatol* 2013; **168**(1): 136-44.
208. Bulliard JL, De Weck D, Fisch T*, et al.* Detailed site distribution of melanoma and sunlight exposure: aetiological patterns from a Swiss series. *Annals of Oncology* 2006; **18**: 789-94.
209. Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 1998; **78**(3): 276-80.
210. Bulliard J-L, Cox B, Elwood JM. Comparison of the site distribution of melanoma in New Zealand and Canada. *International Journal of Cancer* 1997; **72**(2): 231-5.
211. Krüger S, Garbe C, Büttner P*, et al.* Epidemiologic evidence for the role of melanocytic nevi as risk markers and direct precursors of cutaneous malignant melanoma. Results of a case control study in melanoma patients and nonmelanoma control subjects. *J Am Acad Dermatol* 1992; **26**(6): 920-6.
212. Autier P, Boniol M, Severi G*, et al.* Sex Differences in Numbers of Nevi on Body Sites of Young European Children: Implications for the Etiology of Cutaneous Melanoma. *Cancer Epidemiology, Biomarkers & Prevention* 2004; **13**(12): 2003-5.
213. Chiarugi A, Quaglino P, Crocetti E*, et al.* Melanoma density and relationship with the distribution of melanocytic naevi in an Italian population: a GIPMe study — the Italian multidisciplinary group on melanoma. *Melanoma Research* 2015; **25**(1).

214. Ribero S, Osella-Abate S, Reyes-Garcia D*, et al.* Effects of sex on naevus body distribution and melanoma risk in two melanoma case–control studies at different latitudes. *British Journal of Dermatology* 2017; **176**(4): 1093-4.
215. Visconti A, Ribero S, Sanna M*, et al.* Body site-specific genetic effects influence naevus count distribution in women. *Pigment Cell Melanoma Res* 2020; **33**(2): 326-33.
216. Japan Skin Cancer Society. Japanese melanoma study: Annual report. 2016. http://www.skincancer.jp/report-skincancer_melanoma_2016e.pdf (accessed 26 January 2023).
217. Lachiewicz AM, Berwick M, Wiggins CL*, et al.* Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the Surveillance, Epidemiology, and End Results (SEER) program. *Archives of Dermatology* 2008; **144**: 515-21.
218. Koh HK, Miller DR, Geller AC*, et al.* Who discovers melanoma? Patterns from a population-based survey. *J Am Acad Dermatol* 1992; **26**(6): 914-9.
219. Xavier M, Drummond-Lage AP, Baeta C*, et al.* Delay in cutaneous melanoma diagnosis: Sequence analyses from suspicion to diagnosis in 211 patients. *Medicine (Baltimore)* 2016; **95**(31): e4396.
220. Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993-2003. *British Journal of Cancer* 2006; **95**(1): 91-5.
221. Holterhues C, Vries Ed, Louwman MW*, et al.* Incidence and Trends of Cutaneous Malignancies in the Netherlands, 1989–2005. *Journal of Investigative Dermatology* 2010; **130**(7): 1807-12.
222. Kim SY, Yun SJ. Cutaneous Melanoma in Asians. *Chonnam Med J* 2016; **52**(3): 185-93.
223. Bello DM, Chou JF, Panageas KS*, et al.* Prognosis of acral melanoma: a series of 281 patients. *Ann Surg Oncol* 2013; **20**(11): 3618-25.
224. Chang JW. Acral melanoma: a unique disease in Asia. *JAMA Dermatol* 2013; **149**(11): 1272-3.
225. Olsen CM, Pandeya N, Rosenberg PS*, et al.* Incidence of in Situ vs Invasive Melanoma: Testing the "Obligate Precursor" Hypothesis. *J Natl Cancer Inst* 2022; **114**(10): 1364-70.
226. Chen ML, de Vere Hunt IJ, John EM*, et al.* Differences in Thickness-Specific Incidence and Factors Associated With Cutaneous Melanoma in the US From 2010 to 2018. *JAMA Oncology* 2022; **8**(5): 755-9.
227. Olsen CM, Pandeya N, Whiteman DC. The rise in thick melanomas: can early detection reduce the burden? *British Journal of Dermatology* 2023; **188**(5): 687-8.
228. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Human Reproduction Update* 2005; **11**(4): 411-23.
229. Innos K, Padrik P, Valvere V*, et al.* Sex differences in cancer survival in Estonia: a population-based study. *BMC Cancer* 2015; **15**(1): 72.
230. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians* 2016; **66**(1): 7-30.
231. O'Sullivan DE, Boyne DJ, Gogna P*, et al.* Understanding Real-World Treatment Patterns and Clinical Outcomes among Metastatic Melanoma Patients in Alberta, Canada. *Curr Oncol* 2023; **30**(4): 4166-76.
232. Hellmund P, Schmitt J, Roessler M*, et al.* Targeted and Checkpoint Inhibitor Therapy of Metastatic Malignant Melanoma in Germany, 2000–2016. *Cancers* 2020; **12**(9): 2354.
233. Zamagni F, Bucchi L, Mancini S*, et al.* The relative contribution of the decreasing trend in tumour thickness to the 2010s increase in net survival from cutaneous malignant melanoma in Italy: a population-based investigation*. *British Journal of Dermatology* 2022; **187**(1): 52-63.
234. Vikström S, Mikiver R, Lapins J*, et al.* Increasing melanoma incidence and survival trend shifts with improved melanoma-specific survival between 1990 and 2020 in Sweden. *British Journal of Dermatology* 2023; **189**(6): 702-9.
235. Tichanek F, Försti A, Hemminki A*, et al.* Survival in melanoma in the nordic countries into the era of targeted and immunological therapies. *Eur J Cancer* 2023; **186**: 133-41.

236. Cherny N, Sullivan R, Torode J*, et al.* ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. *Ann Oncol* 2016; **27**(8): 1423-43.
237. Kandolf Sekulovic L, Peris K, Hauschild A*, et al.* More than 5000 patients with metastatic melanoma in Europe per year do not have access to recommendedfirst-line innovative treatments. *European Journal of Cancer* 2017; **75**: 313-22.
238. Eisemann N, Waldmann A, Katalinic A. Imputation of missing values of tumour stage in population-based cancer registration. *BMC Medical Research Methodology* 2011; **11**(1): 129.
239. Søgaard M, Olsen M. Quality of cancer registry data: completeness of TNM staging and potential implications. *Clin Epidemiol* 2012; **4 Suppl 2**(Suppl 2): 1-3.
240. Seneviratne S, Campbell I, Scott N*, et al.* Accuracy and completeness of the New Zealand Cancer Registry for staging of invasive breast cancer. *Cancer Epidemiology* 2014; **38**(5): 638-44.
241. Chiang C-J, You S-L, Chen C-J*, et al.* Quality assessment and improvement of nationwide cancer registration system in Taiwan: a review. *Japanese Journal of Clinical Oncology* 2015; **45**(3): 291-6.
242. Henson KE, Elliss-Brookes L, Coupland VH*, et al.* Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol* 2020; **49**(1): 16-h.
243. Rauwerdink DJW, van Doorn R, van der Hage J*, et al.* Systemic Therapy in Advanced Nodular Melanoma versus Superficial Spreading Melanoma: A Nation-Wide Study of the Dutch Melanoma Treatment Registry. *Cancers (Basel)* 2022; **14**(22).
244. Xiong DD, Bordeaux J. The impact of the COVID-19 pandemic in 2020 on the diagnosis, treatment, and outcomes of invasive cutaneous melanoma: A retrospective national cohort study. *J Am Acad Dermatol* 2023; **89**(6): 1167-76.
245. van Not OJ, van Breeschoten J, van den Eertwegh AJM*, et al.* The unfavorable effects of COVID-19 on Dutch advanced melanoma care. *International Journal of Cancer* 2022; **150**(5): 816-24.

Appendix 1: Published version of *Research Paper 1*

Di Carlo V, Estève J, Johnson CH, Girardi F, Weir HK, Wilson RJ, Minicozzi P, Cress RD, Lynch CF, Pawlish KS, Rees JR, Coleman MP, Allemani C, Group UCW. Trends in short-term survival from distant-stage cutaneous melanoma in the United States, 2001-2013 (CONCORD-3). *JNCI Cancer Spectrum* 2020; **4**(6).

JNCI Cancer Spectrum (2020) 4(6): pkaa078

doi: 10.1093/jncics/pkaa078
First published online 14 September 2020
Article

Trends in short-term survival from distant-stage cutaneous melanoma in the United States, 2001-2013 (CONCORD-3)

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Abstract

Background: Survival from metastatic cutaneous melanoma is substantially lower than for localized disease. Treatments for metastatic melanoma have been limited, but remarkable clinical improvements have been reported in clinical trials in the last decade. We described the characteristics of US patients diagnosed with cutaneous melanoma during 2001-2013 and assessed trends in short-term survival for distant-stage disease. **Methods:** Trends in 1-year net survival were estimated using the Pohar Perme estimator, controlling for background mortality with life tables of all-cause mortality rates by county of residence, single year of age, sex, and race for each year 2001-2013. We fitted a flexible parametric survival model on the log-hazard scale to estimate the effect of race on the hazard of death because of melanoma and estimated 1-year net survival by race. **Results:** Only 4.4% of the 425 915 melanomas were diagnosed at a distant stage, cases diagnosed at a distant stage are more commonly men, older patients, and African Americans. Age-standardized, 1-year net survival for distant-stage disease was stable at approximately 43% during 2001-2010. From 2010 onward, survival improved rapidly, reaching 58.9% (95% confidence interval = 56.6% to 61.2%) for patients diagnosed in 2013. Younger patients experienced the largest improvement. Survival for distant-stage disease increased in both Blacks and Whites but was consistently lower in Blacks. **Conclusions:** One-year survival for distant-stage melanoma improved during 2001-2013, particularly in younger patients and those diagnosed since 2010. This improvement may be a consequence of the introduction of immune-checkpoint-inhibitors and other targeted treatments for metastatic and unresectable disease. Persistent survival inequalities exist between Blacks and Whites, suggesting differential access to treatment.

The incidence of cutaneous melanoma has been rising in most Caucasian populations during the past 50 years (1). In the United States, the age-standardized incidence rate rose from 8 per 100 000 person-years in 1975 to 25 in 2016 (2). Cutaneous melanoma was the fourth and fifth most common cancer in men and women, respectively, in the United States in 2016, with a total of 82 476 new cases (3).

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3) highlighted increasing trends in age-standardized 5-year net survival from cutaneous melanoma in most countries during 2000-2014; 5-year net survival exceeded 90% for patients diagnosed during 2010-2014 in the United States, Australia, New Zealand, and most Nordic and Western European countries but was below 60% in Ecuador, China, and Taiwan (4). Stage at diagnosis is an important predictor of prognosis, and survival for disease diagnosed at an advanced stage is much lower than for localized disease. If detected at a localized stage (tumor node metastasis [TNM] stage I-II and resectable stage III), cutaneous melanoma can be surgically treated with a favorable outcome. Five-year

Received: 5 February 2020; **Revised:** 13 July 2020; **Accepted:** 19 August 2020

relative survival for localized melanoma of the skin diagnosed in the last 20 years was higher than 90% in Germany (5), Denmark (6), Estonia (7), Sweden (8), and the United States (9).

Until about 2010, when advanced disease (TNM stage III unresectable melanoma and stage IV disease) was mainly treated with chemotherapy (eg, dacarbazine) and cytokines (eg, interleukin-2), the prognosis for metastatic melanoma was generally poor, with survival as low as 16% at 5 years after diagnosis for patients diagnosed in the United States (9,10). In recent years, major improvements in treatment, involving the use of targeted therapies and immunotherapy, have led to unprecedented clinical benefit. Ipilimumab, the first immunotherapy, and vemurafenib, the first targeted treatment for metastatic and unresectable melanoma, were approved by the US Food and Drug Administration (FDA) in 2011.

The aim of this study is to describe the characteristics of patients diagnosed with cutaneous melanoma during 2001-2013 using data provided by 34 US population-based cancer registries included in CONCORD-3 and to assess trends in short-term (1-year) survival for distant-stage disease.

Methods

CONCORD-3 obtained anonymized, individual tumor records from 322 population-based cancer registries in 71 countries worldwide, for patients who had been diagnosed with one of 18 common cancers, including melanoma, during 2000-2014 and followed-up to December 31, 2014. Data acquisition, ethical approval, and data quality control for the CONCORD programme have been described elsewhere (4). Cancer registries submitted records on all patients diagnosed with a melanoma, defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision (ICD-O-3) (11). We restricted survival analysis to malignant melanoma (ICD-O-3 behavior code 3) arising in the skin (ICD-O-3 topography codes C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9), and scrotum (C63.2).

Records with incomplete data or for tumors that were benign, in situ, of uncertain behavior, metastatic from another organ, or unknown if primary or metastatic, or on patients with age outside the range 15-99 years, were considered ineligible for analysis.

We excluded tumors registered only from a death certificate or discovered at autopsy, because their duration of survival was unknown, as well as records for which the vital status or sex was unknown and those with an invalid date or sequence of dates.

We included in analysis only primary, invasive, malignant cutaneous melanoma. If two or more invasive primary malignant melanomas were detected in the same person but with different dates of diagnosis, the record with the earliest date of diagnosis was retained. Registry datasets in which 15.0% or more of patients were lost to follow-up were excluded from the survival analyses.

Patients diagnosed in 2014 were included in CONCORD-3 but were not included in this study, because a full year of follow-up was not available by the study closure date (December 31, 2014). To assess trends in survival for the same registries, we retained only registries that submitted data on patients diagnosed up to and including 2013, with follow-up to December 31, 2014.

The CONCORD protocol required information on stage of disease at the time of diagnosis for patients diagnosed from 2001 onward, because the completeness of data on stage in many countries and United States was known to be much lower before 2001.

Stage was categorized as localized, regional, and distant according to the Surveillance, Epidemiology, and End Results Summary Stage 2000 classification (12). "Distant stage" includes melanoma with distant lymph node involvement, metastatic skin lesions, further contiguous extension, or metastasis to other organs. Age at diagnosis was grouped into 15-44 years, 45-54 years, 55-64 years, 65-74 years, and 75-99 years. Race was categorized as White, Black, and other race or ethnicities (Asian or Pacific Islander; American Indian or Alaska Native; other, unspecified or unknown race).

Melanomas were defined by morphology (ICD-O-3 8720–8790). We selected melanomas of the skin on the basis of topographic codes C44.0-C44.9 (skin), C51.0 (including the skin of the labia majora), C51.9 (vulva), C60.9 (penis), or C63.2 (scrotum). Melanomas were further categorized by anatomic subsite as arising in the skin of the head and neck (C44.0-C44.4), the trunk (C44.5), the limbs (C44.6-C44.7), or the genital organs (C51.0, C51.9, C60.9, C63.2), as lesions overlapping 2 of those categories, or of the skin with anatomic location not otherwise specified (C44.8-C44.9). Histological subtypes were grouped according to the first revision of ICD-O-3 (11) as malignant melanoma, not otherwise specified (NOS, 8720), superficial spreading (8743), lentigo maligna (8742), nodular (8721), acral (8744), and all other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8743, 8745-8746, 8750, 8760-8761, 8770-8774, 8780, 8790).

We explored the distribution of stage at diagnosis by sex, age, race, topography, and morphology. Survival analyses were restricted to patients diagnosed with distant-stage melanoma. One-year net survival for patients diagnosed in each of the 13 years from 2001 to 2013 was estimated with the non-parametric Pohar Perme estimator (13) using the STATA (14) command *stns* (15). Net survival is the cumulative probability that cancer patients survive their cancer up to a given time since diagnosis (eg, 1 year) after correcting for other causes of death (background mortality). To control for background mortality, which varies by geographical area, demographic characteristics, and over time, we used life tables of all-cause mortality in the general population by single year of age, sex, single calendar year, race (Blacks, Whites, and others) and county within each state. These life tables were kindly provided by the National Cancer Institute (16).

We estimated trends in 1-year net survival for 5 age groups. We then obtained age-standardized estimates for all ages combined using the second of the 3 sets of International Cancer Survival Standard weights (0.28, 0.17, 0.21, 0.20, and 0.14) designed for cancers with broadly constant incidence by age (17). Survival was estimated for men and women, and for both sexes combined.

We fitted a flexible parametric survival model on the log-hazard scale to estimate the effect of race on the hazard of death because of distant-stage melanoma; excess mortality and net survival by race were also estimated (18), with race as a categorical variable. Restricted cubic splines for the effect of age at diagnosis (3 degrees of freedom) and year of diagnosis (4 degrees of freedom) were included with the command *rcsgen* (19), including time-dependent effects.

Results

The CONCORD database included individual records for 1 040 814 adults (15-99 years) diagnosed with a primary,

Table 1. Data quality indicators: patients diagnosed with malignant melanoma of the skin during 2000-2014 in the United States

US registries	Calendar period	No. of patients submitted	Ineligible, %[a]			No. of eligible patients	Excluded, %[b]		No. of patients included	Data quality indicators, %[c]	
			Incomplete dates	In situ	Other		DCO	Other		Lost to follow-up	Censored
All US registries	2000-2014	1 040 814	0.6	36.0	2.6	632 861	0.5	0.0	629 816	2.6	0.1
Alabama	2000-2014	23 564	0.9	41.3	2.3	13 084	0.6	0.0	13 012	0.0	0.0
Alaska	2000-2013	1533	4.4	30.6	3.5	944	0.4	0.0	940	0.0	0.0
Arkansas	2000-2011	7592	0.3	31.9	3.3	4897	0.3	0.0	4879	0.0	0.0
California	2000-2011	127 043	1.1	36.9	2.3	75 851	0.2	0.0	75 712	0.0	0.0
Colorado	2000-2013	21 135	0.3	33.1	3.1	13 427	0.7	0.0	13 338	0.0	0.0
Connecticut	2000-2014	21 602	0.4	40.9	2.2	12 211	0.2	0.0	12 185	5.5	0.0
Delaware	2000-2014	6283	0.2	44.0	1.4	3413	0.2	0.0	3406	0.0	0.0
Florida	2000-2013	89 847	0.1	35.4	2.7	55 590	0.7	0.1	55 134	0.0	0.0
Georgia	2000-2014	43 981	0.0	35.6	2.0	27 451	0.4	0.0	27 350	0.0	0.0
Hawaii	2000-2014	5753	0.3	33.7	1.5	3710	0.2	0.0	3704	7.5	0.0
Idaho	2000-2014	9032	0.6	40.8	2.2	5095	0.7	0.0	5059	0.0	0.0
Indiana	2000-2014	25 599	0.6	32.3	3.3	16 347	0.5	0.0	16 269	0.0	0.0
Iowa	2000-2014	15 612	0.6	32.6	3.7	9846	0.2	0.0	9822	2.8	0.0
Kentucky	2000-2014	23 097	0.0	33.3	2.8	14 764	0.2	0.0	14 729	6.4	0.0
Louisiana	2000-2014	15 105	0.5	37.1	2.8	9000	0.2	0.0	8982	6.4	0.1
Maine	2000-2013	7860	0.3	38.4	3.0	4581	0.3	0.0	4565	0.0	0.0
Maryland	2000-2014	29 516	0.4	40.2	1.8	16 981	0.6	0.1	16 868	0.0	0.0
Massachusetts	2000-2009	23 194	0.0	34.5	3.0	14 483	0.4	0.0	14 420	0.0	0.0
Michigan	2000-2013	41 986	0.2	36.5	2.5	25 505	0.6	0.0	25 335	0.0	0.0
Minnesota	2000-2013	27 449	0.0	38.1	1.9	16 472	0.3	0.0	16 421	0.0	0.0
Mississippi	2002-2014	9214	0.8	31.6	2.8	5968	0.6	0.0	5931	0.0	0.0
Montana	2000-2014	5595	0.6	37.8	2.9	3289	0.5	0.0	3272	0.0	0.0
Nebraska	2000-2014	7894	0.6	33.4	3.5	4930	0.5	0.0	4906	0.0	0.0
New Hampshire	2000-2014	9727	0.1	40.3	2.3	5575	0.3	0.0	5560	0.0	0.0
New Jersey	2000-2014	49568	0.8	42.7	1.9	27 024	0.4	0.0	26 910	48.2	0.0
New Mexico	2000-2014	8720	0.0	40.1	2.2	5030	0.6	0.0	5000	8.7	0.4
North Carolina	2000-2014	47 654	0.0	39.5	2.4	27 727	0.4	0.0	27 602	0.0	0.0
Ohio	2000-2014	54 382	0.1	35.7	3.0	33 292	0.6	0.0	33 079	0.0	0.0
Oklahoma	2000-2010	9135	0.4	24.8	3.9	6479	1.1	0.0	6407	0.0	0.0
Oregon	2000-2013	24 301	0.1	40.9	2.6	13 703	0.5	0.0	13 637	0.0	0.0
Pennsylvania	2000-2014	62 912	2.4	32.9	2.7	39 052	0.4	0.0	38 904	0.0	0.0
Rhode Island	2000-2014	6363	0.4	39.0	2.4	3703	0.4	0.0	3688	0.0	0.0
South Carolina	2000-2014	24 940	0.0	40.8	1.8	14 309	0.5	0.0	14 230	0.0	0.0
Tennessee	2000-2011	19 264	0.5	28.5	3.3	13 047	0.3	0.0	13 003	0.0	0.0
Texas	2000-2013	59 374	0.9	28.4	3.5	39 862	0.8	0.0	39 555	0.0	0.0
Utah	2000-2014	14 946	0.1	38.2	2.1	8893	0.1	0.0	8885	0.0	0.2
Vermont	2000-2013	4537	0.1	38.8	1.9	2688	0.3	0.0	2679	0.0	0.0
Washington	2000-2008	22 317	0.8	39.2	2.2	12 876	0.2	0.0	12 843	0.0	0.0
West Virginia	2000-2014	8894	1.3	31.1	3.4	5707	0.4	0.0	5682	0.0	0.0
Wisconsin	2000-2013	21 636	0.9	28.4	3.6	14 507	1.0	0.0	14 366	0.0	0.0
Wyoming	2000-2013	2658	0.2	38.6	2.9	1548	0.1	0.0	1547	0.0	0.1

[a]Incomplete dates: records in which the year of birth is unknown, the month and/or year of diagnosis is unknown, or the year of last known vital status is unknown. Other: records with incomplete data or for tumors that are benign (behavior code 0), of uncertain behavior (1), metastatic from another organ (6), or unknown if primary or metastatic (9); or for patients with age outside the range of 15-99 years. DCO = Tumours registered only from a death certificate.
[b]Other: vital status or sex unknown; invalid date or sequence of dates.
[c]Censored: patients whose last known vital status is "alive" and who were censored within 5 years of diagnosis or, if diagnosed in 2010 or later, before December 31, 2014.

malignant cutaneous melanoma in 41 state-wide cancer registries in the United States covering a total population of 257 million people (80.2% of the US population). Data quality was generally high. The proportion of patients excluded for incomplete dates or for other reasons ranged from 0.0% to 4.4% (Table 1). Overall, 36.0% of patients were diagnosed with an in situ tumor.

Of the 632 861 patients eligible for inclusion in survival analyses, we excluded 3045 (0.5%) because the cancer was registered only from a death certificate or discovered at autopsy; survival time for these patients is unknown. Only 2.7% of the remaining 629 816 patients were lost to follow-up or censored within 5 years from diagnosis, but this proportion was much lower among patients with distant-stage disease (0.3%). The diagnosis was histologically confirmed in 99.3% of tumors (data not shown).

New Jersey was excluded because of the high proportion of patients lost to follow-up (48.2%). A further 118 239 patients were excluded from 6 state-wide registries (Arkansas, California, Massachusetts, Oklahoma, Tennessee, and

Table 2. Adults (15-99 years) diagnosed with primary malignant melanoma of the skin during 2001-2013 in 34 US registries: distribution by sex, age at diagnosis, race, anatomic location, morphology, and SEER Summary Stage 2000[a]

Patient and tumor characteristics	Localized No. (%)	Regional No. (%)	Distant No. (%)	Unknown No. (%)	Total No. (%)
Sex					
Male	182 150 (75.3)	24 747 (10.2)	12 443 (5.1)	22 470 (9.4)	241 810 (56.8)
Female	146 022 (79.3)	15 365 (8.3)	6158 (3.3)	16 560 (9.1)	184 105 (43.2)
Age group, y					
15-44	61 321 (79.7)	7039 (9.1)	2074 (2.7)	6510 (8.5)	76 944 (18.1)
45-54	58 041 (78.2)	6857 (9.2)	2942 (4.0)	6386 (8.6)	74 226 (17.4)
55-64	69 434 (77.4)	8296 (9.2)	4131 (4.6)	7848 (8.8)	89 709 (21.1)
65-74	66 251 (76.8)	7739 (9.0)	4204 (4.9)	8116 (9.3)	86 310 (20.3)
75-99	73 125 (74.1)	10 181 (10.3)	5250 (5.3)	10 170 (10.3)	98 726 (23.2)
Race					
White	315 166 (77.3)	39 200 (9.6)	18 052 (4.4)	35 550 (8.7)	407 968 (95.8)
Black	1286 (51.8)	500 (20.1)	363 (14.6)	333 (13.5)	2482 (0.6)
Other	11 720 (75.8)	412 (2.7)	186 (1.2)	3147 (20.3)	15 465 (3.6)
Anatomic location					
Head and neck	67 980 (77.6)	9140 (10.4)	2036 (2.3)	8405 (9.7)	87 561 (20.6)
Trunk	111 247 (81.3)	12 071 (8.8)	2817 (2.1)	10 754 (7.8)	136 889 (32.1)
Limbs	146 001 (81.5)	16 259 (9.1)	3314 (1.9)	13 561 (7.5)	179 135 (41.1)
Overlapping region or NOS	2014 (9.7)	2297 (11.0)	10 321 (49.6)	6191 (29.7)	20 823 (4.9)
Skin of genital organs	930 (61.7)	345 (22.9)	113 (7.5)	119 (7.9)	1507 (0.4)
Morphology					
Malignant melanoma, NOS	156 892 (1.8)	17 992 (8.2)	14 538 (6.7)	29 031 (13.3)	225 635 (51.9)
Superficial spreading	115 022 (89.0)	7906 (6.1)	1077 (0.8)	5285 (4.1)	129 782 (29.8)
Lentigo maligna	23 590 (88.0)	808 (3.0)	162 (0.6)	2258 (8.4)	27 163 (6.2)
Nodular	19 161 (62.1)	8963 (29.1)	1653 (5.4)	1064 (3.4)	31 329 (7.2)
Acral lentiginous	2990 (68.2)	1017 (23.2)	189 (4.3)	186 (4.3)	4428 (1.0)
Others	10 517 (65.2)	3426 (21.2)	982 (6.1)	1206 (7.5)	16 518 (3.8)
Total	328 172 (77.1)	40 112 (9.4)	18 601 (4.4)	39 030 (9.1)	425 915 (100.0)

[a] NOS = not otherwise specified; SEER = Surveillance, Epidemiology, and End Results.

Washington), because data were not available for patients diagnosed up to and including 2013. Finally, we explored the distribution of 425 915 patients by sex, age, race, topography, morphology, and stage at diagnosis.

Most patients diagnosed during 2001-2013 were men (56.8%), and they were generally older than women (median age at diagnosis = 64 vs 57 years, respectively). Only 0.6% of patients were Black (Table 2). Data on stage at diagnosis were available for 386 885 (90.8%) patients.

A majority of patients (77.1%) were diagnosed with localized disease. This proportion was stable over time (76.4%-79.8%, data not shown) and slightly higher in women (79.3% vs 75.3%) and in younger patients (79.7% vs 74.1% in patients aged 15-44 years and 75-99 years, respectively). Of melanomas, 4.4% were diagnosed at a distant stage, with a slightly higher proportion in men than women (4.6% vs 2.8% respectively, in 2001; 6.2% vs 4.5% in 2013, data not shown). There were 14.6% of Blacks diagnosed with distant-stage disease compared with only 4.4% in Whites and 1.2% in the "other race" category. Patients with distant-stage melanoma were generally older (median age = 65 years) than those diagnosed with localized (61 years) or regional (62 years) disease (data not shown).

Melanomas arose mostly on the skin of the limbs (42.1%), the trunk (32.1%), and the head and neck (20.6%) and were diagnosed at a distant stage in 2.0% of those cases (Table 2). Melanomas arising in overlapping or unspecified locations accounted for only 4.9% of all cases, but about one-half of these (49.6%) were diagnosed at an advanced stage. The proportion of melanomas registered with an unspecified morphology was 51.9%, followed by superficial spreading (29.8%) and nodular melanoma (7.2%). Distant-stage melanomas represented less than 1% of the superficial spreading and lentigo maligna morphologies (0.8% and 0.6%, respectively), but up to 6.7% of those classified as malignant melanoma NOS.

We restricted survival analysis to 18 601 patients diagnosed with distant-stage disease (Figure 1). In 2001, age-standardized 1-year net survival was 42.8% (95% confidence interval [CI] = 39.3% to 46.3%) and remained stable until 2010 (Table 3). Survival improved rapidly from 2010 onward, reaching 58.9% (95% CI = 56.6% to 61.2%) for patients diagnosed in 2013. The trend was similar for men and women, although survival was slightly but consistently higher in women (Table 3).

One-year net survival increased for all ages (Figure 2; Table 3). The youngest patients (15-44 years) experienced the largest absolute improvement, particularly from 2010, increasing from 44.4% (95% CI = 35.9% to 52.8%) in 2001 to 67.8% (95% CI = 62.0% to 73.6%) in 2013. For patients aged 45-54 years, 1-year survival increased from 45.7% (95% CI = 38.4% to 53.1%) in 2001 to 62.7% (95% CI = 57.6% to 67.8%) in 2013. We observed similar trends in patients aged 55-64 years and 65-74 years starting from 2011; both survival curves reached 56% (56.1%, 95% CI = 51.6% to 60.6%; and 56.7%, 95% CI = 52.4% to 60.9%, respectively) in 2013. One-year survival for patients aged 75 years or older remained at 44.5% (95% CI = 39.9% to 49.1%) or lower throughout the period 2001-2013.

Age-standardized 1-year net survival increased for both Whites and Blacks with distant-stage melanoma (Figure 3). Survival for Whites increased from 42.3% (95% CI = 39.9% to

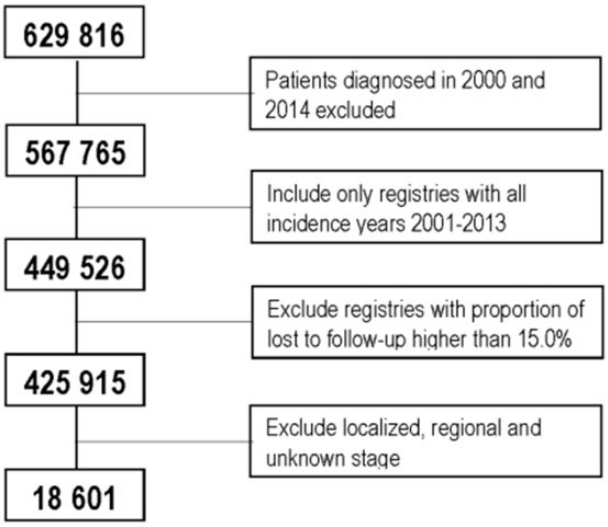

Figure 1. Patients included in survival analysis.

44.8%) in 2001 to 56.1% (95% CI = 54.6% to 57.6%) in 2013. Among Blacks, 1-year survival improved from 37.0% (95% CI = 32.0% to 42.7%) to 50.7% (95% CI = 46.3% to 55.7%) over the same period. The excess hazard of death because of melanoma within 1 year of diagnosis was 13% higher in Blacks than Whites (excess hazard ratio = 1.13, 95% CI = 1.00 to 1.27; data not shown).

Discussion

This study includes data from 34 state-wide cancer registries, covering 56.9% of the US population and is the largest population-based analysis to date of trends in 1-year survival for distant-stage cutaneous melanoma. It shows a dramatic improvement in survival, particularly between 2010 and 2013.

The proportion of melanomas diagnosed at a distant stage remained stable over time (4%-5%) and was slightly lower in women than men. Sex inequalities in stage at diagnosis are well known (20–22); they are commonly attributed to differences in health-seeking behavior (23). Traditionally, women tend to visit their health-care provider and perform skin checks more frequently than men; this can translate to a higher proportion of women being diagnosed with localized disease.

Blacks were more likely to be diagnosed with distant-stage melanoma than Whites. The perception among African Americans that melanoma risk is low is considered a major cause for delayed diagnosis (24,25). Consistent with previous studies (26–29), patients diagnosed at a distant stage were generally older.

One-year net survival improved noticeably for men and women and in both Blacks and Whites. This improvement may reflect the recent introduction of new treatments for metastatic and unresectable disease.

The first immune checkpoint inhibitor approved by the FDA, ipilimumab (30), in March 2011 showed 1-year overall survival for patients diagnosed with metastatic melanoma in a phase III randomized clinical trial as high as 45.6% compared with less than 30% (25.3%) for patients treated with standard therapy (31).

Vemurafenib, the first licensed targeted treatment for patients with metastatic disease and the BRAF V600E mutation, was also shown to increase short-term survival. A phase III randomized trial of 675 patients diagnosed with metastatic melanoma showed an overall 6-month survival of 84% (95% CI = 78% to 89%) in those treated with vemurafenib compared with 64% (95% CI = 56% to 73%) in those treated with dacarbazine (32). The FDA approved the drug on this evidence in August 2011 (33).

Our study has shown a substantial improvement in short-term survival since 2010-2011 for patients diagnosed with distant-stage melanoma of the skin, particularly for younger patients. Most of the improvement occurred from 2010, one year before FDA approval of the new lines of treatment. Some of these patients may have been recruited to clinical trials, which started well before 2010 (31,34–36). Additionally, they may have received the newer treatments through the FDA expanded access programs (37), which provide access to investigational drugs before their official approval to patients with life-threatening conditions who cannot be enrolled in clinical trials.

Data on whether the patients were recruited to a clinical trial or received systemic therapy for compassionate use were not available to us to explore these hypotheses. However, a population-based study of the impact of targeted and immune-based therapies for metastatic or unresectable melanoma in Ontario found that about 5% of patients were already being treated with the new therapies in 2007; this percentage increased to more than 82% by 2015 (38). That study confirmed the use of immunotherapy well before the approval of ipilimumab by Health Canada in 2012 and highlighted its widespread use in recent years. A similar study in the United States showed that the use of immunotherapy in patients younger than 65 years improved rapidly after 2010, from 8-12% during 2004-2010 to 30% in 2014 (39).

Patients aged 75 years or older with distant-stage disease experienced considerably less improvement in short-term survival. This may be due to less frequent use of the newer therapies. A recent study designed to identify factors associated with the treatment of metastatic melanoma in the United States (40) found that older patients were less likely to receive ipilimumab or to be tested for the BRAF mutation. This may have resulted from concerns about how they would tolerate the new treatments. Previous studies on solid tumors have shown that age can act as a barrier to receipt of optimal treatment because of a higher prevalence of comorbidity or absence of data on treatment efficacy from clinical trials and more frequent adverse effects (41,42). A US study showed that only 46% of patients aged 80 years or older received imatinib, a highly effective treatment for chronic myeloid leukaemia, compared with 89.7% of those aged 20-59 years (43).

The CONCORD-3 study protocol did not require detailed information on specific types of treatment, so it was not possible to estimate the proportion of patients who received immune-checkpoint inhibitors or targeted treatments. Data on socio-economic status and type of health insurance were not collected. That information might have helped to explain the disparities in the stage distribution and stage-specific survival by age and race. An analysis of 61 650 melanoma patients aged 18-64 years diagnosed in the United States during 2007-2012 estimated that the proportion of patients with metastatic disease ranged from only 3.7% in the non-Medicaid insurance group to 15.5% among Medicaid and 10.7% among uninsured patients (44). A recent systematic review of the cost-effectiveness of immune-checkpoint inhibitors in the United States estimated that the individual cost of treatment for metastatic melanoma ranged from US$152 000 to US$303 000 for a patient with a median survival time (45). The cost of targeted therapies for metastatic melanoma with the BRAF V600E

Table 3. Number of patients at risk together with age-standardized and age-specific 1-year net survival for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in 34 US registries overall, by sex, and by age at diagnosis[a]

			Sex				Age, y									
	US registries		Men		Women		15-44		45-54		55-64		65-74		75-99	
Calendar year	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)	No.	NS, % (95% CI)
2001	921	42.8 (39.3 to 46.3)	626	39.9 (35.7 to 44.1)	295	48.7 (42.5 to 54.9)	132	44.4 (35.9 to 52.8)	178	45.7 (38.4 to 53.1)	169	50.2 (42.6 to 57.8)	198	32.7 (26.1 to 39.4)	244	39.7 (33.0 to 46.3)
2002	1009	38.5 (35.2 to 41.7)	673	36.8 (32.9 to 40.7)	336	41.6 (35.9 to 47.2)	162	46.4 (38.7 to 54.0)	186	34.0 (27.2 to 40.8)	198	37.3 (30.5 to 44.0)	208	36.1 (29.5 to 42.7)	255	33.2 (27.1 to 39.3)
2003	1070	44.1 (40.7 to 47.4)	733	42.3 (38.3 to 46.3)	337	48.0 (42.1 to 53.9)	133	49.7 (41.3 to 58.2)	185	44.5 (37.4 to 51.7)	230	45.3 (38.8 to 51.7)	244	42.8 (36.5 to 49.2)	278	32.3 (26.5 to 38.1)
2004	1226	42.9 (39.8 to 46.0)	807	40.0 (36.2 to 43.9)	419	48.6 (43.4 to 53.8)	163	46.7 (39.1 to 54.3)	207	38.8 (32.2 to 45.4)	250	42.4 (36.3 to 48.6)	256	42.9 (36.7 to 49.1)	350	40.8 (35.2 to 46.3)
2005	1244	42.8 (39.6 to 46.0)	855	42.5 (38.5 to 46.4)	389	43.2 (37.8 to 48.7)	137	43.9 (35.6 to 52.1)	195	44.3 (37.3 to 51.3)	266	45.4 (39.3 to 51.4)	288	40.5 (34.7 to 46.2)	358	38.5 (33.0 to 43.9)
2006	1359	45.6 (42.5 to 48.7)	879	44.0 (40.2 to 47.8)	480	48.5 (43.4 to 53.7)	146	51.5 (43.4 to 59.5)	232	47.6 (41.2 to 54.0)	312	44.4 (38.8 to 49.9)	297	41.7 (36.0 to 47.4)	372	38.7 (33.4 to 44.0)
2007	1319	44.5 (41.3 to 47.7)	855	44.2 (40.1 to 48.2)	464	45.6 (40.3 to 50.8)	130	45.5 (37.0 to 54.0)	209	43.7 (37.0 to 50.5)	281	45.3 (39.4 to 51.1)	317	48.4 (42.8 to 54.1)	382	37 (31.8 to 42.1)
2008	1381	42.8 (39.7 to 45.9)	935	41.1 (37.2 to 45.0)	446	46.6 (41.5 to 51.8)	142	43 (34.9 to 51.1)	225	47.2 (40.7 to 53.7)	336	40.3 (35.0 to 45.5)	290	45.2 (39.4 to 51.0)	388	37.2 (32.1 to 42.3)
2009	1486	42.0 (39.1 to 45.0)	988	40.5 (36.8 to 44.1)	498	45 (40.0 to 49.9)	159	44.7 (37.0 to 52.4)	230	38.9 (32.6 to 45.2)	346	43.2 (37.9 to 48.4)	341	43.8 (38.4 to 49.2)	410	36.2 (31.3 to 41.2)
2010	1678	45.7 (43.0 to 48.3)	1151	44.5 (41.2 to 47.8)	527	47.9 (43.3 to 52.5)	207	57.1 (50.4 to 63.8)	277	46.1 (40.2 to 51.9)	385	41.4 (36.5 to 46.4)	366	41.4 (36.3 to 46.5)	443	34.9 (30.2 to 39.6)
2011	1725	51.9 (49.2 to 54.6)	1168	49.0 (45.4 to 52.6)	557	56.8 (52.5 to 61.1)	168	66.1 (58.9 to 73.2)	265	51.7 (45.7 to 57.8)	430	45.8 (41.1 to 50.5)	388	47.4 (42.4 to 52.5)	474	39.3 (34.6 to 44.0)
2012	2012	56.7 (54.3 to 59.2)	1355	54.6 (51.4 to 57.7)	657	60.3 (56.4 to 64.1)	226	70.3 (64.4 to 76.3)	297	58.2 (52.5 to 63.8)	485	51.0 (46.5 to 55.5)	486	51.1 (46.6 to 55.7)	518	44.5 (39.9 to 49.1)
2013	2171	58.9 (56.6 to 61.2)	1418	57.4 (54.4 to 60.5)	753	61.4 (57.7 to 65.1)	251	67.8 (62.0 to 73.6)	349	62.7 (57.6 to 67.8)	484	56.1 (51.6 to 60.6)	541	56.7 (52.4 to 60.9)	546	43.9 (39.4 to 48.3)

[a]CI = confidence interval; NS = net survival.

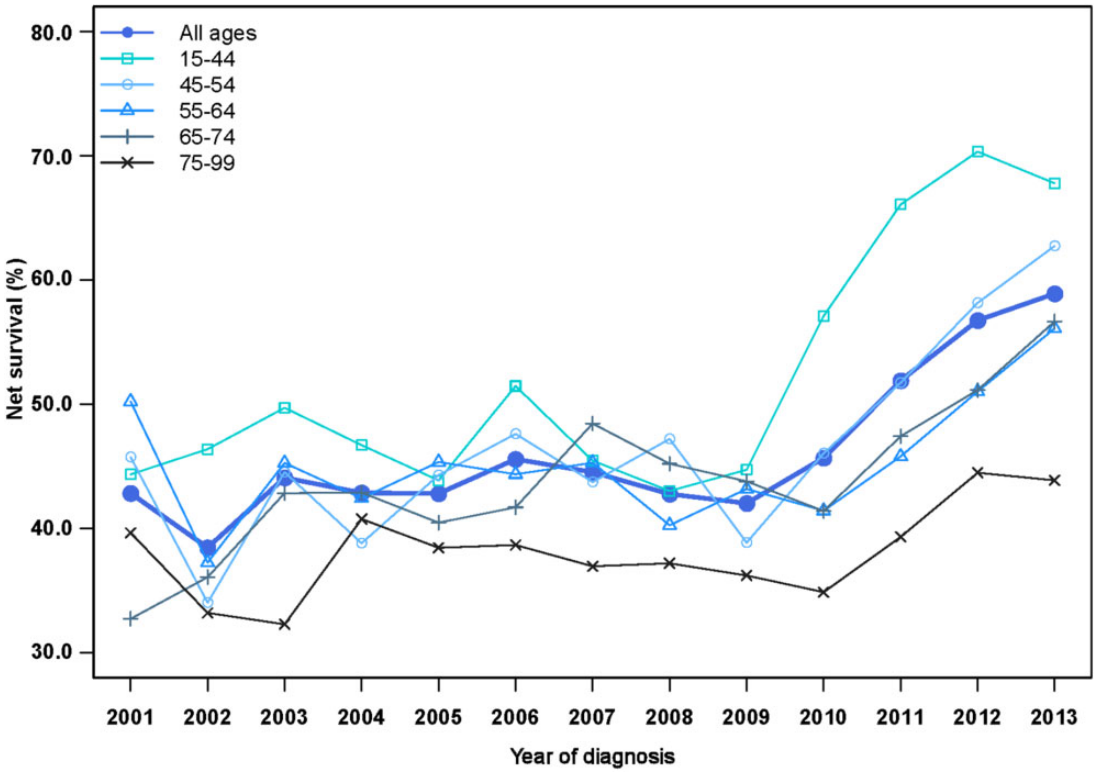

Figure 2. Trends in age-specific 1-year net survival (%) for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in the United States.

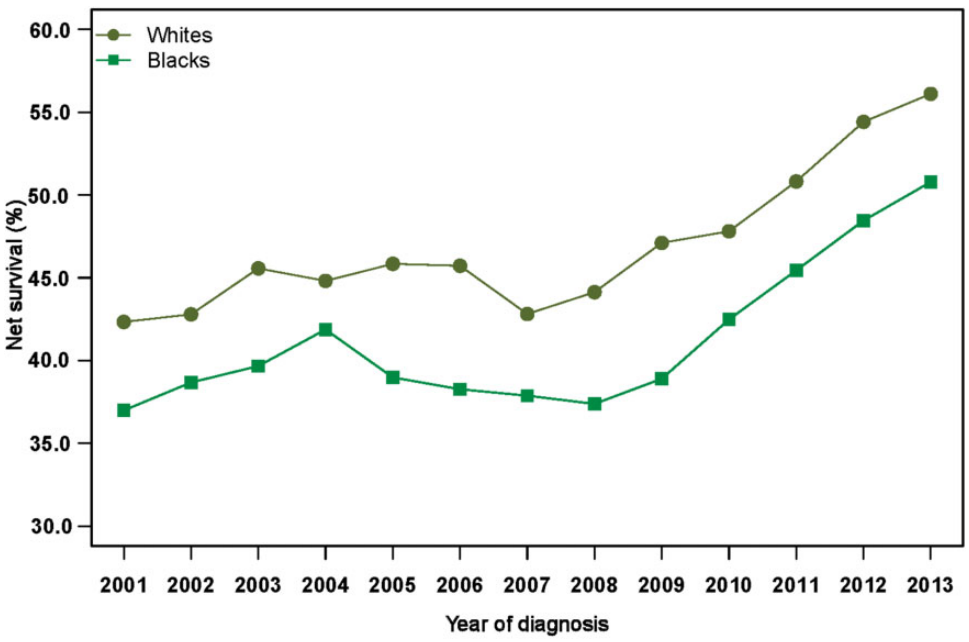

Figure 3. Trends in age-standardized 1-year net survival (%) for patients diagnosed with distant-stage cutaneous melanoma during 2001-2013 in the United States, by race.

mutation was estimated at between US$149 000 and US$319 000 (46). Recent analyses have shown that patients were less likely to receive immunotherapy if they had no insurance or only Medicaid coverage, received a lower income, or received care at a community practice rather than an academic center (39,47,48). Such differences in access to treatment may partly explain the racial disparities in the recent trends in short-term survival reported in this study.

One-year net survival was consistently lower in Blacks than Whites. Survival was not estimated for other races. The

proportion of patients lost to follow-up, including those whose deaths are missed by the cancer registries, is generally higher among Asians or Pacific Islanders than Whites and Blacks (49,50). Incomplete follow-up among Asians or Pacific Islanders and other minority groups may lead to overestimation of survival and biased comparisons.

Several studies have shown a survival disadvantage for Blacks diagnosed with melanoma in the United States. A study of more than 260 000 people diagnosed during 1988-2011 estimated an absolute gap of almost 20% (89% vs 70%) between Blacks and Whites in 5-year relative survival for all stages combined (26). Among Whites and Blacks of non-Hispanic origin, the difference in 5-year overall survival was almost 30% (82% vs 53%) during 1982-2011 (27).

Racial disparities in survival from melanoma have commonly been ascribed to a less favorable stage distribution of Black patients (26,51–53). However, we have shown that the proportion of distant-stage melanoma was higher among Blacks than Whites, and 1-year survival for distant-stage melanoma was consistently lower among Blacks than among Whites. This gap in survival suggests racial differences in treatment and access to care.

Despite the exclusion of about 2500 patients registered with a distant-stage melanoma in cancer registries for which incidence data were not complete for 2001-2013, we were nevertheless able to include 18 601 patients: this, to our knowledge, is the largest population-based analysis of trends in 1-year net survival for distant-stage disease.

In conclusion, to our knowledge, this is the first population-based study to show a recent improvement in short-term survival from distant-stage cutaneous melanoma in the United States. This may be due to the availability of new and more effective therapies for the treatment of metastatic or unresectable disease. The dramatic improvement since 2010 in short-term survival for melanoma of the skin diagnosed at the metastatic or unresectable stage is important, because for most other solid tumors, survival for metastatic disease has not changed for several decades (54–56). More detailed population-based studies would help evaluate access to novel treatments and their longer term survival benefit for patients diagnosed with distant-stage melanoma.

Funding

This project was supported by the American Cancer Society, Centers for Disease Control and Prevention, Swiss Re, Swiss Cancer Research Foundation, Swiss Cancer League, Institut National du Cancer, La Ligue Contre le Cancer, Rossy Family Foundation, US National Cancer Institute, and the Susan G. Komen Foundation.

Notes

Role of the funder: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: The authors have no conflicts of interest to declare.

Role of the authors: Conceptualization: VDC, CA; Data: all US authors in participating cancer registries; Methodology: VDC, CA; Formal analysis: VDC; Visualization: VDC, CA; Supervision: CA, MPC; Validation: all authors; Writing—original draft: VDC, CA, MPC; Writing—review and editing: all authors; Funding acquisition: CA, MPC.

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Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Data availability statement

The data underlying this article cannot be shared because they are personal data, provided in anonymized form by participating US cancer registries to the CONCORD programme under relevant ethical and statutory approvals in the United States and the United Kingdom, to protect the privacy of individuals.

Requests for data should be addressed to the registry or registries concerned.

References

1. International Agency for Research and Cancer. *Cancer Incidence in Five Continents*. Vol. XI. Lyon, France; 2017.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Programme. Cancer stat facts: melanoma of the skin. https://seer.cancer.gov/statfacts/html/melan.html. Accessed August 31, 2019.
3. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999–2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. www.cdc.gov/cancer/dataviz, June 2019.
4. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391(10125):1023–1075.
5. Schoffer O, Schülein S, Arand G, et al. Tumour stage distribution and survival of malignant melanoma in Germany 2002-2011. *BMC Cancer*. 2016;16(1):936–948.
6. Bay C, Kejs AM, Storm HH, et al. Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: a Danish population-based register study 1989-2011. *Cancer Epidemiol*. 2015;39(1):1–7.
7. Padrik P, Valter A, Valter E, et al. Trends in incidence and survival of cutaneous malignant melanoma in Estonia: a population-based study. *Acta Oncol*. 2017;56(1):52–58.
8. Rockberg J, Amelio JM, Taylor A, et al. Epidemiology of cutaneous melanoma in Sweden. Stage-specific survival and rate of recurrence. *Int J Cancer*. 2016;139(12):2722–2729.
9. Pollack LA, Li J, Berkowitz Z, et al. Melanoma survival in the United States, 1992 to 2005. *J Am Acad Dermatol*. 2011;65(5 Suppl 1):S78–S86.
10. Xing Y, Chang GJ, Hu CY, et al. Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer*. 2010;116(9):2234-2241.
11. Fritz A, Percy C, Jack A, et al. *International classification of diseases for oncology (ICD-O)*. 1st rev of 3rd ed. Geneva, Switzerland: World Health Organization; 2013.
12. Young JL, Roffers SD, Ries LAG, et al. SEER Summary Staging Manual-2000: Codes and coding instructions. Bethesda, MD: National Cancer Institute, NIH Pub. No. 01-4969; 2001.
13. Pohar-Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics*. 2012;68(1):113–120.
14. StataCorp. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC; 2017.
15. Clerc-Urmès I, Grzebyk M, Hedelin G. Net survival estimation with stns. *Stata J*. 2014;14(1):87–102.
16. Mariotto AB, Zou Z, Johnson CJ, et al. Geographical, racial and socio-economic variation in life expectancy in the US and their impact on cancer relative survival. *PLoS One*. 2018;13(7):e0201034-e.
17. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40(15):2307–2316.
18. Bower H, Crowther MJ, Lambert PC. STRCS: a command for fitting flexible parametric survival models on the log-hazard scale. *Stata J*. 2016;16(4):989–1012.
19. Lambert PC. rcsgen: STATA module to generate restricted cubic splines and their derivatives. Statistical Software Components S456986, Department of Economics, Boston College. https://ideas.repec.org/c/boc/bocode/s456986.html.
20. Rutherford MJ, Ironmonger L, Ormiston-Smith N, et al. Estimating the potential survival gains by eliminating socioeconomic and sex inequalities in stage at diagnosis of melanoma. *Br J Cancer*. 2015;112(S1):S116–S123.
21. Enninga EAL, Moser JC, Weaver AL, et al. Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992-2011. *Cancer Med*. 2017;6(10):2203–2212.
22. Crocetti E, Fancelli L, Manneschi G, et al. Melanoma survival: sex does matter, but we do not know how. *Eur J Cancer Prev*. 2016;25(5):404–409.
23. Miller DR, Geller AC, Wyatt SW, et al. Melanoma awareness and self-examination practices: results of a United States survey. *J Am Acad Dermatol*. 1996;34(6):962–970.
24. Kundu RV, Kamaria M, Ortiz S, et al. Effectiveness of a knowledge-based intervention for melanoma among those with ethnic skin. *J Am Acad Dermatol*. 2010;62(5):777–784.
25. Byrd KM, Wilson DC, Hoyler SS, et al. Advanced presentation of melanoma in African Americans. *J Am Acad Dermatol*. 2004;50(1):21–24.
26. Mahendraraj K, Sidhu K, Lau CS, et al. Malignant melanoma in African-Americans: a population-based clinical outcomes study involving 1106 African-American patients from the Surveillance, Epidemiology, and End Results (SEER) Database (1988-2011). *Medicine*. 2017;96(15):e6258.
27. Ward-Peterson M, Acuña JM, Alkhalifah MK, et al. Association between race/ethnicity and survival of melanoma patients in the United States over three decades. *Medicine*. 2016;95(17):e3315.
28. Wang Y, Zhao Y, Ma S. Racial differences in six major subtypes of melanoma: descriptive epidemiology. *BMC Cancer*. 2016;16(1):691.
29. Gamba CS, Clarke CA, Keegan TH, et al. Melanoma survival disadvantage in young, non-Hispanic white males compared with females. *JAMA Dermatol*. 2013;149(8):912–920.
30. Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application number: 125377Orig1s000 - Yervoy Ipilimumab; 2011.
31. Hodi FS, O'Day S, McDermott F, et al. Improved survival with Ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–723.
32. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507–2516.
33. Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application number: 202429Orig1s000. Zelboraf vemurafenib; 2011.
34. Eggermont A, Chiarion Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med*. 2016;375(19):1845–1855.
35. Wolchok JD, Neyns B, Linette GP, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol*. 2010;11(2):155–164.
36. Tang J, Yu JX, Hubbard-Lucey VM, et al. The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. *Nat Rev Drug Discov*. 2018;17(12):854–855.
37. U.S. Food & Drug Administration. Expanded Access Program. 2019. https://www.wepclinical.com/expanded-access-programs/. Accessed October 8, 2019.
38. Hanna TP, Nguyen P, Baetz T, et al. A population-based study of survival impact of new targeted and immune-based therapies for metastatic or unresectable melanoma. *Clin Oncol*. 2018;30(10):609–617.
39. Hague W, Verma V, Butler EB, et al. Racial and socioeconomic disparities in the delivery of immunotherapy for metastatic melanoma in the United States. *J Immunother*. 2019;42(6):228–235.
40. Enewold L, Sharon E, Harlan LC. Metastatic melanoma: treatment and survival in the US after the introduction of ipilimumab and vemurafenib. *Oncol Res Treat*. 2017;40(4):174–183.
41. Bouchardy C, Rapiti E, Blagojevic S, et al. Older female cancer patients: importance, causes, and consequences of undertreatment. *J Clin Oncol*. 2007;25(14):1858–1869.
42. Moore DH, Kauderer JT, Bell J, et al. An assessment of age and other factors influencing protocol versus alternative treatments for patients with epithelial ovarian cancer referred to member institutions: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;94(2):368–374.
43. Wiggins CL, Harlan LC, Harold EN, et al. Age disparity in the dissemination of imatinib for treating chronic myeloid leukaemia. *Am J Med*. 2010;123(8):764.e1–e9.
44. Amini A, Rusthoven CG, Waxweiler TV, et al. Association of health insurance with outcomes in adults ages 18 to 64 years with melanoma in the Unities States. *J Am Acad Dermatol*. 2016;74(2):309–316.
45. Verma V, Sprave T, Haque W, et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. *J Immunotherapy Cancer*. 2018;6(1):128.
46. Shih V, ten Ham RM, Bui CT, et al. Targeted therapies compared to dacarbazine for treatment of BRAFV600E metastatic melanoma: a cost-effectiveness analysis. *J Skin Cancer*. 2015;2015(2015):1–8.
47. Al-Qurayshi Z, Crowther JE, Hamner JB, et al. Disparities of immunotherapy utilization in patients with stage III cutaneous melanoma: a national perspective. *Anticancer Res*. 2018;38(5):2897–2901.
48. Jain V, Vanigalla S, Reddy V, et al. Association of insurance status with presentation, treatment, and survival in melanoma in the era of immune checkpoint inhibitors. *J Immunother*. 2020;43(1):8–15.
49. Pinheiro PS, Morris CR, Liu L, et al. The impact of follow-up type and missed deaths on population-based cancer survival studies for Hispanics and Asians. *JNCI Monogr*. 2014;2014(49):210–217.
50. Lariscy JT. Differential record linkage by Hispanic ethnicity and age in linked mortality studies: implications for the epidemiologic paradox. *J Aging Health*. 2011;23(8):1263–1284.
51. Cress RD, Holly EA. Incidence of cutaneous melanoma among non-Hispanic Whites, Hispanics, Asians, and Blacks: an analysis of California cancer registry data, 1988-93. *Cancer Causes Control*. 1997;8(2):246–252.
52. Cormier JN, Xing Y, Ding M, et al. Ethnic differences among patients with cutaneous melanoma. *Arch Intern Med*. 2006;166(17):1907–1914.
53. Wu XC, Eide MJ, King J, et al. Racial and ethnic variations in incidence and survival of cutaneous melanoma in the United States, 1999-2006. *J Am Acad Dermatol*. 2011;65(5 Suppl 1):S26–S37.
54. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–1792.
55. Chia SK, Speers CH, D'yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer*. 2007;110(5):973
56. Brenner H, Gondos A, Pulte D. Recent trends in long-term survival of patients with chronic myeloid leukaemia: disclosing the impact of advances in therapy on the population level. *Haematologica*. 2008;93(10):1544–1549.

Appendix 2: Published version of *Research Paper 2*

Di Carlo V, Stiller CA, Eisemann N, Bordoni A, Matz M, Curado MP, Daubisse-Marliac L, Valkov M, Bulliard J-L, Morrison D, Johnson C, Girardi F, Marcos-Gragera R, Šekerija M, Larønningen S, Sirri E, Coleman MP, Allemani C, CONCORD Working Group. Does the morphology of cutaneous melanoma help to explain the international differences in survival? Results from 1 578 482 adults diagnosed during 2000–2014 in 59 countries (CONCORD-3)*. *Br J Dermatol* 2022; **187**(3): 364-80.

BJD
British Journal of Dermatology

Does the morphology of cutaneous melanoma help to explain the international differences in survival? Results from 1 578 482 adults diagnosed during 2000–2014 in 59 countries (CONCORD-3)

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Accepted for publication
27 March 2022

DOI 10.1111/bjd.21274

Abstract

Background CONCORD-3 highlighted wide disparities in population-based 5-year net survival for cutaneous melanoma during 2000–2014. Clinical evidence suggests marked international differences in the proportion of lethal acral and nodular subtypes of cutaneous melanoma.

Objectives We aimed to assess whether the differences in morphology may explain global variation in survival.

Methods Patients with melanoma were grouped into the following seven morphological categories: malignant melanoma, not otherwise specified (International Classification of Diseases for Oncology, third revision morphology code 8720), superficial spreading melanoma (8743), lentigo maligna melanoma (8742), nodular melanoma (8721), acral lentiginous melanoma (8744), desmoplastic melanoma (8745) and other morphologies (8722–8723, 8726–8727, 8730, 8740–8741, 8746, 8761, 8770–8774, 8780). We estimated net survival using the nonparametric Pohar Perme estimator, correcting for background mortality by single year of age, sex and calendar year in each country or region. All-ages survival estimates were standardized using the International Cancer Survival

Standard weights. We fitted a flexible parametric model to estimate the effect of morphology on the hazard of death.

Results Worldwide, the proportion of nodular melanoma ranged between 7% and 13%. Acral lentiginous melanoma accounted for less than 2% of all registrations but was more common in Asia (6%) and Central and South America (7%). Overall, 36% of tumours were classified as superficial spreading melanoma. During 2010–2014, age-standardized 5-year net survival for superficial spreading melanoma was 95% or higher in Oceania, North America and most European countries, but was only 71% in Taiwan. Survival for acral lentiginous melanoma ranged between 66% and 95%. Nodular melanoma had the poorest prognosis in all countries. The multivariable analysis of data from registries with complete information on stage and morphology found that sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes.

Conclusions This study provides the broadest picture of distribution and population-based survival trends for the main morphological subtypes of cutaneous melanoma in 59 countries. The poorer prognosis for nodular and acral lentiginous melanomas, more frequent in Asia and Latin America, suggests the need for health policies aimed at specific populations to improve awareness, early diagnosis and access to treatment.

What is already known about this topic?

- The histopathological features of cutaneous melanoma vary markedly worldwide.
- The proportion of melanomas with the more aggressive acral lentiginous or nodular histological subtypes is higher in populations with predominantly dark skin than in populations with predominantly fair skin.

What does this study add?

- We aimed to assess the extent to which these differences in morphology may explain international variation in survival when all histological subtypes are combined.
- This study provides, for the first time, international comparisons of population-based survival at 5 years for the main histological subtypes of melanoma for over 1.5 million adults diagnosed during 2000–2014.
- This study highlights the less favourable distribution of histological subtypes in Asia and Central and South America, and the poorer prognosis for nodular and acral lentiginous melanomas.
- We found that later stage at diagnosis does not fully explain the higher excess risk of death for nodular and acral lentiginous melanoma compared with superficial spreading melanoma.

The incidence of cutaneous melanoma has been rising steadily in most white populations over the past 50 years.[1,2] It is now one of the 10 most common malignancies in Oceania, North America and Europe, with age-standardized incidence rates in the range of 7.0–36.6 per 100 000 person-years. By contrast, melanoma is rare in populations of Asian and African origin, where incidence rates are in the range of 0.4–3.0 per 100 000 person-years.[3] The histopathological features of cutaneous melanoma vary markedly worldwide. The proportion of melanomas with the more aggressive acral lentiginous or nodular histological subtypes is higher in populations with predominantly dark skin than in populations with predominantly fair skin.[4,5]

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3)[6] highlighted wide disparities in 5-year net survival from cutaneous melanoma, which was lower in Asian populations than in the rest of the world. Age-standardized 5-year net survival for adults (15–99 years) diagnosed during the period 2010–2014 was 90% or higher in the USA, Australia, New Zealand and most

Nordic countries, but was 60% or lower in Ecuador, China, Korea, Singapore and Taiwan.

Stage at diagnosis is recognized as the most important predictor of survival.[7–10] Age at diagnosis is also a prognostic factor, and several studies have shown much higher survival for younger patients.[11–15] However, the prognostic role of morphology in cutaneous melanoma is controversial. Traditionally, melanomas of the skin have been classified into the following three fairly well-defined subgroups, characterized by different patterns of growth: superficial spreading and lentigo maligna melanoma, which is characterized by a long period of superficial growth; nodular melanoma, which is more likely to penetrate into the deeper layers of the skin if not removed; and acral lentiginous melanoma, which mostly develops on the extremities but displays similar biological behaviour to that of nodular melanoma.[16] Despite the advent of high-resolution genomics and other proposed approaches for the classification of melanocytic tumours, the diagnosis of the different subtypes should continue to be based on the pathologist's interpretation of the histology and how it fits into the World Health Organization (WHO) Classification of Tumours, commonly known as the WHO 'Blue Books'.[17] However, the morphological classification has not been considered useful for prognostic purposes because of the commonly held view that the clinical development of all melanomas is similar, whatever the histological subtype, spreading horizontally within the epidermis and then extending vertically into the dermis, and that they converge in their biological behaviour once they metastasize.[18]

In this study, we aimed to describe the histological distribution of cutaneous melanoma for adults diagnosed during 2000–2014 in the 59 countries that contributed data to CONCORD-3 and to produce the first international comparison of trends in population-based age-standardized 5-year net survival by morphological subtype. We also aimed to examine the role of morphological subtype in the prognosis of cutaneous melanoma.

Materials and methods

Anonymized individual tumour registrations for patients diagnosed during 2000–2014 with one of 18 cancers or groups of malignancies, including melanoma, were provided for CONCORD-3 by 322 population-based cancer registries in 71 countries worldwide (full details of the CONCORD Working Group are provided in Appendix S1; see Supporting Information). Patients were followed up for their vital status up to 31 December 2014. Data acquisition, ethical approval and data quality control have been described elsewhere.[6]

We asked participating registries to submit all registrations for malignant melanoma, regardless of anatomical site. Melanoma was defined by morphology codes in the range 8720–8790 according to the International Classification of Diseases for Oncology, third revision (ICD-O-3).[19] We focused this analysis of survival on melanomas arising in the skin (ICD-O-3 topography C44.0–C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9) and scrotum (C63.2). Survival from melanomas arising in internal organs and in the eye will be examined in a subsequent analysis. To facilitate quality control and comparison of the intensity of early diagnostic and screening activity, we requested all melanoma registrations, regardless of behaviour, whether benign (behaviour code 0), uncertain (behaviour code 1), *in situ* (behaviour code 2) or invasive (behaviour code 3). However, survival analyses included only primary invasive melanomas.

Records with incomplete data, or of tumours that were benign, *in situ*, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or for patients aged outside the range 15–99 years, were not included in survival analyses. We excluded tumours registered only on the basis of a death certificate or discovered at autopsy, as the survival is unknown in these cases. We also excluded records for which sex or vital status was unknown, and records with an invalid date or sequence of dates were also omitted.

Patients were grouped according to the following seven morphological categories using the ICD-O-3 classification: malignant melanoma, not otherwise specified (NOS) (morphology code 8720), superficial spreading melanoma (8743), lentigo maligna melanoma (8742), nodular melanoma (8721), acral lentiginous melanoma (8744), desmoplastic melanoma (8745) and other morphologies (8722–8723, 8726–8727, 8730, 8740–8741, 8746, 8761, 8770–8774, 8780).

Patients were grouped according to calendar period of diagnosis, i.e. 2000–2004, 2005–2009 or 2010–2014. We examined time trends in the morphology distribution for each country. We also estimated trends in age-standardized 5-year net survival by country and morphology with the nonparametric Pohar Perme estimator,[20] using the STATA (StataCorp, College Station, TX, USA) command *stns*.[21] The cohort approach was used for patients diagnosed during the periods 2000–2004 and 2005–2009 because these patients had all been followed up for at least 5 years. We used the period approach[22] to estimate survival for patients diagnosed during 2010–2014 because 5-year follow-up for vital status was not available for all patients up to 31 December 2014.

To control for wide differences in background mortality based on geographical area, sex, and over time, we constructed life tables of all-cause mortality in the general population for each country or registry by single year of age, sex, calendar year and, where possible, by race/ethnicity (Israel, Singapore, USA, Australian Northern Territory and New Zealand).

We estimated 5-year net survival by morphology in each of five age groups (15–44 years, 45–54 years, 55–64 years, 65–74 years and 75–99 years). We obtained age-standardized estimates for all age groups combined using the International Cancer Survival Standard type 2 weights for the five age groups (0.28, 0.17, 0.21, 0.20 and 0.14).[23] We did not estimate survival if fewer than 10 patients were available for analysis in a given combination of morphological subtype and calendar period. If 10–49 patients were available for a given

calendar period, we only estimated survival for all ages combined. If 50 or more patients were diagnosed during the periods 2000–2004 and 2005–2009, we attempted survival estimation for each age group in each calendar period. For 2010–2014, we estimated net survival using the period approach, including in the analyses all patients diagnosed during the 5-year period from 2010 to 2014, plus those diagnosed before 2010 who were still alive at the beginning of 2010. Therefore, for the period 2010–2014 the threshold of 50 or more patients required to attempt age-standardization applies to the combined cohort of patients. If a single age-specific estimate could not be obtained, we merged the data for adjacent age groups and assigned the combined estimate to both age groups before standardization for age. If two or more age-specific estimates could not be obtained, we reported only the unstandardized estimate for all ages combined. The pooled estimates for countries with more than one registry do not include data from registries for which the estimates were less reliable. Less reliable estimates are shown with a footnote in Tables 1–3 when such estimates were the only available information from a given country or territory (see footnote in Tables 1–3 for the definition of less reliable estimates). Here, we comment only on reliable, age-standardized survival estimates. Continental regions were defined using the United Nations Geoscheme.[24]

To estimate the effect of morphology on the hazard of death owing to melanoma, we fitted a flexible parametric model on the log cumulative hazard scale, using *stpm2*[25] in STATA. We restricted this analysis to registries where at least 65% of registrations had a specific morphology code, i.e. not malignant melanoma, NOS. Among these registries, we further selected those for which data on stage were available for at least 75% of registrations using one of the following classifications: Union for International Control Tumour–Node–Metastasis staging system, 7th edition,[26] Condensed TNM[27] or Surveillance Epidemiology and End Results Summary Stage 2000.[28] Using this constraint, we were able to include data from one regional cancer registry in Germany (Lower Saxony), two registries in Spain (Basque Country and Granada) and the Norwegian national cancer registry.

For each country, we first fitted a model with only morphology as a covariable (model 1). We then included, as additional covariables, sex, a restricted cubic spline for the effect of age at diagnosis (four degrees of freedom) and stage at diagnosis (metastatic vs. nonmetastatic) (model 2). We excluded patients for whom stage at diagnosis was unknown (complete case analysis).

Results

We obtained data from 284 registries in 59 countries for 2 303 095 adults who were diagnosed with melanoma during 2000–2014 (Table 4). Of these patients, 49% were diagnosed in North America, 37% in Europe, 12% in Oceania, and only 2% in Asia and less than 1% in both Africa and in Central and South America.

A total of 637 957 patients (28%) who were diagnosed with an *in situ* tumour were excluded from survival analysis, which ranged from 11% in Central and South America to 35% in North America. The proportion of *in situ* melanoma was 20% or higher in 10 countries (Table 4), which suggests that the approach to early diagnosis in these countries was highly effective. We excluded a further 78 587 patients for other reasons (see footnote in Table 4). The proportion of melanomas of benign or uncertain behaviour was particularly high in Norway (22%), highlighting the intensive monitoring activity for atypical naevi and premalignant lesions in this country.

Of the 1 586 551 eligible patients, we further excluded 7139 patients (0.5%) who were diagnosed only on the basis of a death certificate or where melanoma was discovered at autopsy, and 930 patients (less than 0.1%) were excluded for other reasons. Finally, 1 578 482 patients diagnosed with a primary invasive melanoma of the skin were available for survival analysis (99.5% of those eligible). More than 99% of these tumours were microscopically confirmed, either cytologically or histologically.

About 42% of the tumours were registered as malignant melanoma, NOS. The proportion of such tumours was generally high in countries in Asia (76%), Central and South America (63%), North America (51%) and Africa (46%) and much lower in Oceania (33%). In Europe, the proportion of melanomas with a nonspecific morphology was higher in Eastern European countries (57%) than in Southern (37%), Northern (32%) and Western European countries (27%). The proportion of melanomas diagnosed with a nonspecific morphology fell substantially in Australia (from 40% in 2000–2004 to 26% in 2010–2014), Denmark (from 42% to 11%), Iceland (from 36% to 18%), Italy (from 32% to 19%), Lithuania (from 85% to 35%), Portugal (from 70% to 35%) and the UK (from 39% to 23%) (Table S1; see Supporting Information).

Overall, superficial spreading melanoma was the second most common histological subtype (36% of all cases). It accounted for more than half of the patients in Denmark, France, Iceland, the Netherlands, Norway, Sweden and Switzerland (Figure 1). Nodular melanoma accounted for 7% of all cases in North America and Asia, 9% in Oceania and 13% in Central and South America. In Europe, 12% of the cases were registered as nodular melanoma, with higher proportions in the Czech Republic, Ireland, Norway, Romania, Slovakia and Sweden. About 6% of adults were diagnosed with lentigo maligna melanoma, ranging from 2% in Asia to 8% in Oceania. Acral lentiginous melanoma was very rare in North America, Europe and Oceania (less than 2% of all cases) but the proportion was higher in Central and South America (more than 10% in Colombia, Costa Rica, Guadeloupe and Martinique) and Asia (more than 10% in Korea, Singapore and Taiwan). Less than 1% of the patients were diagnosed with desmoplastic melanoma. The proportion of patients diagnosed with other morphological subtypes was higher than 20% in Estonia, Italy and Latvia.

Table 1 Number of patients and age-standardized 5-year net survival (NS, %) with 95% confidence interval (CI): adults (15–99 years) diagnosed with melanoma of the skin in North, Central and South America, by country, morphology and calendar period of diagnosis (2000–2004, 2005–2009, 2010–2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI
America (Central and South)																						
Argentina	2000–2004							**30**	71.2	50.7–91.7							**131**	**66.7**	57.8–75.5	**10**	44.8	14.6–75.0
	2005–2009	**31**	98.5	92.3–100.0	**24**	100.0	85.9–100.0	**76**	**58.1**	45.8–70.4							**320**	**62.9**	57.0–68.8	**44**	72.6	55.6–89.5
	2010–2014	**26**	**100.0**	90.0–100.0	**21**	100.0	85.7–100.0	**44**	**71.9**	61.3–82.6							**277**	**65.2**	58.5–71.9	**11**	52.0	26.6–77.5
Brazil	2000–2004				**19**	100.0	100.0–100.0	**75**	**71.7**	61.8–81.7	**13**	65.8	36.0–95.6				**359**	**76.0**	70.1–81.9			
	2005–2009	**41**	84.4	65.0–100.0	**21**	96.5	77.2–100.0	**78**	**68.8**	56.7–80.8	**10**	32.1	3.4–60.7				**437**	**76.3**	71.5–81.1	**12**	67.8	40.8–94.8
	2010–2014	**43**	85.0	68.9–100.0	**10**	95.3	72.8–100.0	**43**	**64.8**	51.5–78.1							**251**	**69.7**	64.4–75.1	**13**	33.7	5.6–61.8
Chile	2000–2004							**12**	19.0	0.0–39.7							**59**	57.0	42.6–71.4			
	2005–2009	**11**	100.0	100.0–100.0	**10**	95.2	61.5–100.0	**28**	50.8	30.2–71.4	**18**	64.1	38.2–89.9				**57**	55.8	36.6–75.1			
	2010–2014	**16**	100.0 [b]	100.0–100.0	**20**	87.9 [b]	48.1–100.0	**36**	63.5 [b]	39.0–88.0	**25**	80.5 [b]	46.8–100.0				**154**	**55.6** [b]	43.1–68.1			
Colombia	2000–2004	**29**	85.0 [b]	70.0–100.0	**16**	100.0 [b]	85.1–100.0	**53**	41.8 [b]	24.8–58.8	**45**	81.6 [b]	62.1–100.0				**196**	**54.9** [b]	46.9–62.9			
	2005–2009	**49**	84.8 [b]	71.0–98.5	**53**	99.6 [b]	79.6–100.0	**83**	**63.4** [b]	51.3–75.4	**73**	75.6 [b]	61.4–89.7				**219**	**64.7** [b]	57.1–72.4	**15**	42.3 [b]	9.0–75.6
	2010–2014				**17**	**96.0** [b]	86.4–100.0	**23**	**56.7** [b]	43.7–69.7	**21**	**70.6** [b]	56.9–84.4				**43**	**55.8** [b]	46.6–65.0	**10**	35.0 [b]	7.2–62.8
Costa Rica[a]	2000–2004	**47**	100.0	95.8–100.0	**33**	100.0	100.0–100.0	**34**	72.6	55.2–90.1	**46**	75.3	59.0–91.5				**104**	**75.6**	67.0–84.2			
	2005–2009	**71**	**86.3**	78.9–93.7	**51**	**97.5**	89.9–100.0	**63**	**58.9**	49.3–68.5	**70**	**74.2**	62.1–86.2				**183**	**69.9**	62.5–77.4			
	2010–2014	**90**	**83.9**	74.4–93.4	**103**	**93.6**	85.3–100.0	**49**	**58.2**	44.6–71.9	**65**	**70.5**	58.8–82.2				**318**	**75.9**	69.2–82.6	**23**	88.2	59.1–100.0
Ecuador	2000–2004							**24**	69.1	46.1–92.2	**12**	47.5	17.8–77.2				**146**	**56.2**	47.3–65.1			
	2005–2009							**45**	61.0	44.3–77.7	**12**	27.6	2.9–52.3				**319**	**60.1**	53.5–66.6	**13**	54.7	23.2–86.3
	2010–2014							**53**	**67.6**	52.3–82.9	**17**	27.1	1.4–52.8				**332**	**57.0**	50.2–63.8			
Guadeloupe[a]	2000–2004																					
	2005–2009																					
	2010–2014	**16**	0.1 [b]	0.0–0.2				**11**	38.5	0.0–90.8												
Martinique[a]	2000–2004	**12**	92.6 [b]	76.2–100.0							**14**	78.0[b]	42.3–100.0				**28**	92.1[b]	76.0–100.0			
	2005–2009	**18**	100.0 [b]	89.5–100.0							**20**	84.0[b]	62.1–100.0									
	2010–2014	**18**	100.0 [b]	90.0–100.0																		
Puerto Rico[a]	2000–2004	**12**	62.4	28.2–96.6	**22**	100.0	92.9–100.0	**25**	50.9	27.4–74.5	**27**	56.4	33.4–79.5				**296**	**72.4**	66.4–78.4	**15**	68.1	34.7–100.0
	2005–2009	**19**	71.9	50.4–93.3				**36**	38.9	20.8–56.9	**14**	35.3	7.7–62.8				**340**	**79.9**	74.9–85.0	**11**	57.8	26.7–88.9
	2010–2014	**20**	70.8	41.0–100.0				**17**	62.0	31.3–92.8	**10**	50.5	18.2–82.8				**149**	**76.2**	68.5–83.9			
America (North)																						
Canada	2000–2004	**6720**	**95.1**	94.1–96.1	**1219**	**97.6**	95.9–99.4	**2076**	**72.1**	69.8–74.4	**297**	**86.1**	81.6–90.5	**131**	79.6	69.4–89.8	**8737**	**83.9**	82.9–84.9	**661**	**75.6**	71.7–79.4
	2005–2009	**8352**	**96.2**	95.4–97.0	**1492**	**97.8**	96.4–99.3	**2661**	**69.7**	67.6–71.8	**366**	**81.6**	77.0–86.2	**194**	**90.4**	85.3–95.5	**10 731**	**83.7**	82.9–84.6	**926**	**80.6**	77.6–83.6
	2010–2014	**10 737**	**96.8**	96.0–97.5	**2301**	**96.8**	94.6–99.0	**3119**	**72.3**	70.3–74.3	**391**	**77.9**	72.8–83.0	**266**	**91.8**	87.3–96.4	**11 139**	**84.8**	84.0–85.6	**762**	**80.9**	77.7–84.2
USA	2000–2004	**51 276**	**96.8**	96.5–97.2	**10 760**	**98.7**	98.0–99.5	**12 341**	**69.5**	68.6–70.5	**1771**	**82.2**	79.9–84.6	**2082**	**87.3**	85.3–89.3	**96 459**	**86.4**	86.1–86.7	**6317**	**84.1**	82.9–85.3
	2005–2009	**66 456**	**97.5**	97.1–97.8	**13 531**	**99.3**	98.7–99.9	**15 772**	**71.2**	70.3–72.0	**2229**	**82.6**	80.6–84.6	**2442**	**89.1**	87.3–91.0	**111 496**	**88.2**	87.9–88.4	**6469**	**85.3**	84.1–86.4
	2010–2014	**65 610**	**97.6**	97.3–97.9	**14 191**	**99.6**	98.9–100.0	**15 202**	**71.6**	70.7–72.4	**2317**	**81.6**	79.6–83.7	**2255**	**89.7**	87.8–91.5	**101 623**	**88.5**	88.2–88.8	**4988**	**84.2**	83.0–85.5

NOS, not otherwise specified. [a]Data with 100% coverage of the national population. [b]Survival estimate considered less reliable, because 15% or more of patients were (i) lost to follow-up or censored alive within 5 years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), or (ii) registered only from a death certificate or at autopsy, or (iii) registered with incomplete dates, i.e. unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status. Italics denote survival estimates that are not age-standardized. Bold values denote age-standardized survival estimates.

Table 2 Number of patients and age-standardized 5-year net survival (NS,%) with 95% confidence interval (CI): adults (15–99 years) diagnosed with melanoma of the skin in Asia and Oceania, by continent, country, morphology and calendar period of diagnosis (2000–2004, 2005–2009, 2010–2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI
Asia																						
China	2000–2004																**110**	**36.0**	26.0–46.0			
	2005–2009																**538**	**44.7**	39.8–49.5	**15**	63.2	37.1–89.4
	2010–2014																**623**	**48.4**	43.2–53.6	**17**	69.9	41.1–98.7
Cyprus[a]	2000–2004																**15**	84.7 [b]	59.6–100.0			
	2005–2009	**72**	96.2[b]	88.9–100.0				**59**	**73.8**[b]	62.8–84.7							**86**	**75.1**[b]	64.6–85.5	**13**	83.6 [b]	34.4–100.0
	2010–2014	**101**	**87.3** [b]	78.8–95.8				**94**	**71.4**[b]	59.9–82.9							**92**	**69.7**[b]	58.9–80.5	**20**	63.6 [b]	36.8–90.5
Israel[a]	2000–2004	**585**	**93.3**	90.1–96.5	**141**	**97.6**	92.2–100.0	**251**	**69.6**	63.0–76.2	**22**	66.6	41.0–92.2				**2648**	**84.8**	83.1–86.5	**58**	50.7	35.4–66.1
	2005–2009	**407**	**94.2**	90.4–98.0	**110**	97.5	88.4–100.0	**316**	**68.9**	62.5–75.3	**23**	80.8	51.6–100.0				**3614**	**89.3**	87.9–90.6	**42**	51.1	34.3–67.9
	2010–2014	**335**	**97.7**	93.8–100.0	**74**	**98.7**	93.6–100.0	**208**	**65.3**	57.4–73.2	**26**	79.3	56.6–100.0	**11**	51.0	20.7–81.2	**3314**	**87.8**	86.3–89.3	**64**	**64.6**	52.9–76.2
Japan	2000–2004																**703**	**68.7**	64.7–72.7			
	2005–2009	**36**	84.8	69.6–99.9	**31**	90.1	59.0–100.0	**53**	52.3	36.2–68.4	**78**	82.4	68.5–96.2				**1605**	**67.2**	64.3–70.1	**14**	35.8	7.9–63.6
	2010–2014	**42**	**88.4**	77.8–98.9	**25**	89.0	57.8–100.0	**57**	**56.5**	44.3–68.7	**71**	**93.2**	81.7–100.0				**999**	**68.0**	64.7–71.2	**14**	46.2	16.5–75.9
Korea[a]	2000–2004	**17**	83.1	61.5–100.0				**87**	**50.4**	39.2–61.6	**156**	**73.1**	64.6–81.6				**982**	**47.2**	43.8–50.6	**22**	41.6	20.9–62.3
	2005–2009	**27**	84.0	66.5–100.0	**16**	94.2	72.2–100.0	**113**	**38.0**	29.5–46.6	**247**	**80.3**	74.1–86.4				**1548**	**51.3**	48.5–54.1	**38**	64.2	47.9–80.5
	2010–2014	**39**	**86.3**	63.0–100.0	**20**	100.0	85.9–100.0	**192**	**41.5**	32.1–50.9	**399**	**79.4**	73.9–84.9	**16**	53.7	26.2–81.3	**1790**	**56.2**	53.5–59.0	**43**	**60.8**	48.5–73.2
Singapore[a]	2000–2004										**11**	71.2	35.8–100.0				**59**	**53.4**	40.8–66.1			
	2005–2009	**17**	66.9	41.3–92.5				**15**	39.8	13.2–66.3	**19**	62.2	34.6–89.8				**71**	**55.5**	45.2–65.9			
	2010–2014	**14**	100.0	100.0–100.0				**27**	25.2	8.8–41.6	**28**	65.2	38.9–91.5				**76**	**55.6**	43.5–67.6			
Taiwan[a]	2000–2004	**10**	93.3	73.8–100.0				**62**	**40.9**	29.1–52.8	**87**	**66.9**	65.6–77.3				**612**	**46.1**	41.6–50.7	**23**	51.0	26.8–75.1
	2005–2009	**33**	81.3	66.0–96.6				**81**	**41.8**	31.4–52.2	**167**	**68.2**	59.4–77.0				**667**	**49.6**	45.2–54.0	**34**	33.5	15.1–51.8
	2010–2014	**49**	**71.4**	54.6–88.2				**154**	**36.7**	27.0–46.5	**306**	**65.6**	57.4–73.8				**634**	**46.7**	42.1–51.3	**33**	**35.9**	21.2–50.6
Thailand	2000–2004																**103**	**44.9**	34.4–55.4			
	2005–2009																**248**	**35.9** [b]	28.6–43.2			
	2010–2014																**151**	**28.0** [b]	21.5–34.4			
Turkey	2000–2004	**21**	79.9 [b]	59.2–100.0	**20**	84.8 [b]	67.1–100.0	**48**	59.9 [b]	42.1–77.7	**10**	61.6 [b]	26.3–96.9				**181**	**51.9** [b]	42.9–60.8			
	2005–2009	**67**	**77.7**	66.4–88.9	**58**	97.3	85.8–100.0	**187**	**52.3**	44.3–60.4	**67**	**73.8**	62.3–85.3				**810**	**52.5**	48.6–56.4	**36**	63.2	45.2–81.3
	2010–2014	**91**	**80.1**	68.7–91.5	**94**	**96.4**	90.5–100.0	**192**	**53.9**	46.2–61.6	**65**	**72.5**	60.2–84.9				**858**	**56.4**	52.6–60.1	**33**	**55.9**	41.8–69.9
Oceania																						
Australia[a]	2000–2004	**18 244**	**97.4**	96.8–97.9	**3523**	**98.6**	97.5–99.7	**3930**	**79.3**	77.8–80.8	**230**	**78.1**	71.5–84.6	**805**	**84.6**	81.3–87.8	**19 244**	**88.5**	87.9–89.1	**2574**	**93.2**	91.8–94.7
	2005–2009	**24 151**	**97.5**	97.0–97.9	**5186**	**97.9**	96.9–98.9	**4574**	**79.5**	78.0–81.0	**274**	**82.3**	76.6–88.0	**918**	**84.9**	81.8–88.1	**17 740**	**87.9**	87.3–88.5	**2384**	**93.2**	91.7–94.7
	2010–2014	**26 279**	**97.5**	97.1–98.0	**4376**	**98.3**	97.3–99.2	**4643**	**80.2**	78.6–81.8	**288**	**81.2**	75.6–86.8	**894**	**84.8**	81.4–88.2	**13 506**	**87.2**	86.4–87.9	**2539**	**94.1**	92.6–95.6
New Zealand[a]	2000–2004	**3633**	**96.9**	95.6–98.2	**563**	**94.8**	91.9–97.7	**889**	**75.3**	71.7–78.8	**68**	**90.4**	82.5–98.4	**105**	**79.7**	70.4–89.1	**3617**	**86.3**	84.8–87.8	**146**	**84.9**	77.9–91.8
	2005–2009	**4998**	**97.2**	96.3–98.2	**488**	**95.4**	92.1–98.8	**1034**	**78.0**	74.7–81.2	**65**	**80.7**	71.2–90.3	**122**	**88.5**	82.3–94.8	**3891**	**86.6**	85.2–88.0	**70**	81.2	67.7–94.8
	2010–2014	**5786**	**97.9**	97.0–98.9	**617**	**90.0**	79.3–100.0	**1232**	**77.4**	74.2–80.6	**100**	**77.4**	68.5–86.3	**134**	**89.9**	83.9–95.8	**3523**	**87.0**	85.6–88.5	**129**	**81.6**	73.9–89.3

NOS, not otherwise specified. [a]Data with 100% coverage of the national population. [b]Survival estimate considered less reliable, because 15% or more of patients were (i) lost to follow-up or censored alive within 5 years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), or (ii) registered only from a death certificate or at autopsy, or (iii) registered with incomplete dates, i.e. unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status. Italics denote survival estimates that are not age-standardized. Bold values denote age-standardized survival estimates.

Table 3 Number of patients and age-standardized 5-year net survival (NS, %) with 95% confidence interval (CI): adults (15–99 years) diagnosed with melanoma of the skin in Europe, by country, morphology and calendar period of diagnosis (2000–2004, 2005–2009, 2010–2014)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI
Europe																						
Austria[a]	2000–2004	**1433**	**98.2**	96.1–100.0	**258**	97.3	88.3–100.0	**384**	**75.0**	70.0–80.1	**48**	60.9	45.6–76.1	**11**	70.3	40.7–99.9	**3306**	**77.9**	76.3–79.6	**89**	**60.2**	48.7–71.7
	2005–2009	**1236**	**95.6**	93.3–97.9	**245**	**99.6**	96.7–100.0	**405**	**67.2**	61.7–72.7	**55**	71.3	56.4–86.3	**22**	100.0	85.2–100.0	**4044**	**81.9**	80.5–83.4	**97**	**68.6**	59.4–77.9
	2010–2014	**1522**	**94.9**	92.4–97.3	**290**	**98.7**	95.5–100.0	**383**	**62.9**	57.3–68.6	**54**	**72.4**	59.2–85.6	**23**	100.0	100.0–100.0	**5180**	**87.1**	85.8–88.4	**65**	**70.5**	59.7–81.2
Belgium[a]	2000–2004	**619**	**93.9**	90.3–97.5	**50**	99.3	81.7–100.0	**121**	**75.6**	67.2–83.9	**23**	77.3	56.0–98.5				**645**	**80.8**	77.1–84.4	**31**	90.5	64.1–100.0
	2005–2009	**3852**	**94.3**	92.9–95.6	**380**	**98.0**	95.2–100.0	**785**	**70.7**	66.7–74.6	**146**	**85.5**	78.1–92.9	**25**	100.0	84.3–100.0	**3181**	**85.1**	83.5–86.7	**177**	**82.2**	75.5–88.9
	2010–2014	**5590**	**95.4**	94.1–96.7	**725**	**98.5**	96.1–100.0	**940**	**74.9**	71.3–78.5	**190**	**87.7**	81.5–94.0	**43**	72.4	48.7–96.1	**4128**	**88.5**	87.1–90.0	**250**	**83.3**	77.1–89.5
Bulgaria[a]	2000–2004	**20**	85.0	45.5–100.0				**151**	**46.2**	36.6–55.7							**1245**	**51.6**	48.3–54.9	**180**	**45.4**	36.7–54.0
	2005–2009	**27**	76.8	55.1–98.5				**271**	**57.9**	50.8–65.0							**1421**	**57.1**	54.1–60.2	**186**	**35.0**	27.2–42.8
	2010–2014	**90**	**86.6**	75.4–97.8				**379**	**64.0**	57.2–70.9							**1661**	**61.6**	58.8–64.4	**210**	**39.9**	32.0–47.8
Croatia[a]	2000–2004																**2174**	**66.3**	63.8–68.7			
	2005–2009	**39**	90.6	75.2–100.0				**122**	**70.4**	61.2–79.6							**2622**	**74.6**	72.5–76.6			
	2010–2014	**288**	**89.6**	81.6–97.7				**174**	**58.9**	49.8–68.1	**25**	67.9	33.9–100.0				**2298**	**77.1**	75.0–79.1	**57**	80.8	66.6–95.0
Czech Republic[a]	2000–2004	**2214**	**97.0**	95.1–98.9	**361**	**97.9**	93.9–100.0	**2016**	**71.2**	68.8–73.7	**53**	86.3	67.5–100.0	**46**	59.1	41.7–76.5	**2546**	**71.3**	69.2–73.4	**507**	**77.5**	72.6–82.3
	2005–2009	**3142**	**98.1**	96.7–99.6	**438**	**97.0**	93.3–100.0	**2080**	**73.0**	70.6–75.3	**93**	**83.5**	75.2–91.9	**106**	**77.9**	68.8–87.0	**2964**	**77.2**	75.4–79.1	**540**	**80.1**	75.8–84.3
	2010–2014	**4082**	**98.2**	96.9–99.6	**442**	**99.0**	96.3–100.0	**2033**	**73.0**	70.7–75.3	**93**	**82.3**	72.9–91.7	**142**	**80.2**	72.4–87.9	**3335**	**78.9**	77.2–80.7	**567**	**81.5**	77.3–85.6
Denmark[a]	2000–2004	**2597**	**92.7**	90.9–94.5	**136**	97.3	85.1–100.0	**444**	**72.3**	67.4–77.2	**17**	89.1	66.1–100.0				**2318**	**83.6**	81.6–85.5	**27**	85.5	66.8–100.0
	2005–2009	**5384**	**95.3**	94.1–96.4	**218**	88.6	78.8–98.4	**757**	**72.4**	68.8–76.0	**66**	**84.3**	73.9–94.7				**1778**	**78.1**	75.8–80.3	**61**	90.4	80.0–100.0
	2010–2014	**8123**	**96.0**	95.1–97.0	**329**	**93.6**	88.6–98.6	**943**	**74.8**	71.5–78.1	**77**	**75.3**	61.8–88.8	**43**	100.0	87.7–100.0	**1229**	**77.1**	74.7–79.5	**69**	**90.9**	79.9–100.0
Estonia[a]	2000–2004	**27**	100.0	93.0–100.0	**28**	100.0	85.5–100.0	**24**	82.7	58.1–100.0							**109**	**71.0**	62.0–80.1	**410**	**66.3**	60.8–71.8
	2005–2009	**32**	100.0	100.0–100.0	**15**	95.0	71.3–100.0	**14**	71.6	45.3–97.8							**203**	**70.0**	63.4–76.7	**500**	**73.7**	69.2–78.1
	2010–2014	**28**	**100.0**	100.0–100.0	**11**	100.0	96.1–100.0	**29**	**56.2**	34.4–78.0	**17**	64.0	17.3–100.0				**305**	**82.7**	74.0–91.4	**207**	**78.2**	72.5–83.8
Finland[a]	2000–2004																**3576**	**84.8**	83.3–86.4			
	2005–2009	**137**	**92.8**	87.0–98.5	**102**	100.0	93.8–100.0	**76**	**72.0**	62.6–81.5	**10**	79.1	42.8–100.0				**4452**	**87.0**	85.7–88.3			
	2010–2014	**539**	**93.9**	89.9–98.0	**260**	**100.0**	97.3–100.0	**216**	**76.0**	69.0–83.1	**16**	93.1	68.4–100.0				**5539**	**88.1**	86.9–89.3			
France	2000–2004	**2552**	**94.6**	93.0–96.2	**375**	**92.7**	87.6–97.8	**518**	**70.1**	65.5–74.8	**114**	**76.5**	67.7–85.3	**16**	69.6	37.9–100.0	**565**	**82.8**	79.2–86.5	**352**	**87.7**	83.3–92.1
	2005–2009	**4419**	**95.7**	94.5–96.9	**640**	**95.9**	92.9–99.0	**706**	**70.9**	66.5–75.2	**155**	**83.1**	75.2–91.0	**42**	75.5	56.1–94.9	**817**	**83.5**	79.7–87.4	**483**	**90.6**	87.1–94.2
	2010–2014	**1109**	**94.9**	92.4–97.4	**115**	**94.5**	88.6–100.0	**158**	**74.6**	65.4–83.7	**38**	**82.4**	73.1–91.7				**167**	**83.3**	76.4–90.1	**62**	**89.1**	80.7–97.4
Germany	2000–2004	**6566**	**99.2**	98.2–100.0	**1235**	**99.4**	98.0–100.0	**2415**	**74.4**	72.3–76.4	**319**	**85.4**	80.4–90.4	**39**	91.4	77.2–100.0	**3734**	**83.8**	82.3–85.3	**481**	**78.3**	73.9–82.7
	2005–2009	**11 019**	**98.8**	98.1–99.5	**2057**	**99.4**	97.9–100.0	**3394**	**77.7**	76.0–79.5	**478**	**83.7**	79.4–88.0	**56**	80.9	63.6–98.3	**5649**	**84.6**	83.4–85.9	**649**	**79.8**	75.9–83.7
	2010–2014	**11 676**	**99.0**	98.4–99.7	**1990**	**99.4**	97.9–100.0	**3188**	**77.2**	75.3–79.0	**450**	**84.7**	80.5–89.0	**78**	**91.6**	82.5–100.0	**6095**	**86.6**	85.4–87.8	**625**	**82.7**	78.8–86.7
Iceland[a]	2000–2004	**124**	**92.5**	85.6–99.3	**13**	78.2	48.1–100.0	**18**	78.9	59.4–98.3							**92**	88.6	79.8–97.3			
	2005–2009	**132**	**87.4**	79.7–95.2	**16**	82.3	55.9–100.0	**17**	61.6	31.3–91.9							**80**	87.7	78.8–96.6			
	2010–2014	**134**	**91.7**	85.6–97.8				**26**	56.0	29.6–82.5							**37**	**82.7**	71.1–94.4			
Ireland[a]	2000–2004	**771**	**94.8**	91.6–98.0	**184**	**95.7**	90.0–100.0	**418**	**71.6**	66.5–76.8	**36**	73.8	54.2–93.3	**20**	64.6	36.2–93.0	**1007**	**82.0**	79.0–85.1	**78**	**78.5**	68.1–89.0
	2005–2009	**980**	**95.0**	92.2–97.7	**294**	**97.5**	93.9–100.0	**527**	**73.4**	68.9–77.9	**52**	63.6	44.7–82.5	**35**	77.4	58.7–96.2	**1365**	**84.3**	81.8–86.8	**124**	**79.3**	71.0–87.7
	2010–2014	**1427**	**96.2**	93.6–98.8	**359**	**96.0**	92.3–99.8	**494**	**76.9**	72.1–81.7	**69**	**72.5**	58.5–86.5	**48**	**80.7**	67.1–94.3	**1121**	**86.8**	84.2–89.4	**61**	**81.1**	70.8–91.5
Italy	2000–2004	**5044**	**94.4**	93.2–95.6	**435**	**98.7**	96.4–100.0	**1411**	**68.5**	65.7–71.2	**155**	**84.1**	77.7–90.5	**54**	78.0	65.8–90.3	**4548**	**78.9**	77.6–80.3	**2515**	**79.4**	77.6–81.3
	2005–2009	**8677**	**94.6**	93.8–95.5	**626**	**99.2**	97.6–100.0	**2170**	**68.5**	66.2–70.8	**250**	**85.4**	80.3–90.6	**79**	77.1	62.8–91.4	**5983**	**81.8**	80.6–82.9	**5130**	**83.0**	81.8–84.2
	2010–2014	**3636**	**95.2**	94.1–96.2	**202**	**99.3**	97.0–100.0	**904**	**66.4**	63.3–69.5	**96**	**85.0**	78.0–92.0	**25**	**78.9**	64.7–93.1	**1768**	**79.7**	78.0–81.5	**2554**	**82.8**	81.3–84.3
Latvia[a]	2000–2004	**12**	100.0	76.7–100.0				**36**	44.5	26.3–62.7							**353**	**60.7**	54.7–66.8	**291**	**72.7**	66.2–79.1
	2005–2009							**45**	60.8	43.3–78.2							**424**	**64.1**	58.6–69.6	**357**	**66.0**	59.9–72.1
	2010–2014							**32**	**76.6**	63.9–89.2							**410**	**69.8**	64.3–75.3	**527**	**73.2**	67.8–78.5

(continued)

Table 3 (continued)

		Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
		N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI	N	NS (%)	95% CI
Lithuania[a]	2000–2004	**73**	**78.6**	67.3–89.9	**15**	87.8	62.9–100.0	**70**	**61.0**	49.8–72.2							**938**	**66.4**	62.8–70.0			
	2005–2009	**336**	**85.2**	80.1–90.3	**39**	100.0	85.8–100.0	**273**	**66.7**	60.0–73.4	**13**	93.7	68.4–100.0				**573**	**59.5**	54.8–64.2	**12**	83.5	56.5–100.0
	2010–2014	**331**	**88.3**	82.6–94.0	**41**	100.0	100.0–100.0	**226**	**65.5**	57.4–73.6	**13**	77.8	45.1–100.0				**339**	**63.3**	57.0–69.7			
Malta[a]	2000–2004	**59**	100.0	92.5–100.0				**29**	73.0	54.0–91.9							**54**	**83.8**	73.8–93.8			
	2005–2009	**85**	**87.6**	81.1–94.1				**15**	61.2	35.8–86.6							**72**	**76.5**	68.0–85.1			
	2010–2014	**88**	**90.1**	81.7–98.5	**11**	100.0	100.0–100.0	**25**	61.0	37.1–84.9							**71**	**72.4**	62.6–82.2			
The Netherlands[a]	2000–2004	**8326**	**93.9**	92.7–95.0	**509**	**97.2**	93.4–100.0	**2046**	**76.3**	74.1–78.6	**132**	**79.8**	71.9–87.8	**34**	86.4	68.3–100.0	**2630**	**82.5**	80.5–84.5	**499**	**79.4**	75.2–83.5
	2005–2009	**12 494**	**94.7**	93.9–95.5	**663**	**97.9**	95.4–100.0	**2473**	**73.0**	71.0–75.0	**138**	**80.3**	72.5–88.1	**60**	76.8	60.4–93.2	**2781**	**83.6**	81.9–85.4	**517**	**88.0**	84.3–91.8
	2010–2014	**18 354**	**95.1**	94.4–95.8	**1,317**	**98.0**	95.0–100.0	**2931**	**74.2**	72.2–76.1	**229**	**87.5**	80.9–94.2	**115**	**83.6**	76.4–90.7	**2385**	**84.3**	82.6–86.1	**455**	**85.8**	81.9–89.8
Norway[a]	2000–2004	**2780**	**93.7**	92.2–95.3	**158**	100.0	87.0–100.0	**1103**	**74.1**	71.0–77.2	**40**	93.6	76.3–100.0	**33**	71.9	49.8–94.1	**967**	**78.3**	75.2–81.4	**29**	85.1	56.3–100.0
	2005–2009	**3143**	**93.7**	92.3–95.1	**197**	97.1	85.4–100.0	**1304**	**74.0**	71.2–76.9	**32**	84.4	68.6–100.0	**44**	100.0	85.2–100.0	**1428**	**83.4**	81.0–85.8	**34**	64.2	45.2–83.3
	2010–2014	**4853**	**94.5**	93.2–95.8	**266**	**97.4**	93.6–100.0	**1642**	**77.2**	74.5–79.9	**38**	**85.5**	77.3–93.6	**46**	**75.9**	61.8–89.9	**1798**	**87.0**	84.9–89.0	**59**	**76.5**	63.9–89.1
Poland[a]	2000–2004	**509**	**84.2**	79.4–88.9	**205**	**98.4**	94.4–100.0	**566**	**63.2**	58.5–67.9	**37**	84.3	70.4–98.2				**7413**	**60.5**	59.2–61.8	**687**	**62.6**	58.4–66.8
	2005–2009	**847**	**88.9**	85.6–92.2	**259**	**99.0**	95.4–100.0	**956**	**59.0**	55.4–62.6	**48**	90.1	77.4–100.0				**9291**	**64.9**	63.7–66.0	**545**	**67.0**	62.5–71.6
	2010–2014	**1380**	**88.6**	85.7–91.6	**193**	**98.7**	94.6–100.0	**1216**	**58.3**	54.8–61.9	**60**	**84.0**	73.5–94.5	**19**	53.0	21.4–84.7	**10 938**	**68.1**	67.1–69.1	**655**	**66.5**	62.1–70.9
Portugal[a]	2000–2004	**323**	**92.6**	88.2–97.0	**81**	100.0	100.0–100.0	**233**	**59.2**	52.1–66.3	**80**	85.9	74.5–97.3				**1766**	**76.2**	73.8–78.5	**45**	72.1	56.5–87.6
	2005–2009	**748**	**91.7**	88.4–94.9	**157**	97.9	88.4–100.0	**355**	**63.0**	57.2–68.9	**136**	**82.4**	74.2–90.6	**12**	69.2	29.1–100.0	**2283**	**79.8**	77.9–81.8	**66**	82.8	71.5–94.1
	2010–2014	**1214**	**88.0**	80.3–95.7	**151**	**97.7**	90.9–100.0	**425**	**75.8**	65.3–86.2	**107**	**69.8**	58.6–81.0	**15**	45.5	3.4–87.6	**1064**	**81.8**	77.7–85.9	**92**	**74.4**	62.3–86.4
Romania (Cluj)	2000–2004																					
	2005–2009	**17**	75.5	52.7–98.3				**33**	61.2	40.3–82.1							**137**	**64.6**	56.1 – 73.0	**27**	89.5	73.5–100.0
	2010–2014	**58**	90.0	80.6–99.3				**53**	61.7	42.4–81.0							**85**	**63.3**	51.9 – 74.7	**19**	84.0	57.1–100.0
Russia	2000–2004							**21**	87.9	64.2–100.0							**943**	**62.1**	58.3–65.9	**377**	**70.2**	63.4–77.0
	2005–2009	**16**	85.4	56.2–100.0				**41**	56.7	39.2–74.2							**1316**	**61.5**	58.3–64.8	**210**	**69.9**	61.7–78.1
	2010–2014	**16**	86.0	58.9–100.0				**115**	**58.8**	47.0–70.6							**1623**	**66.4**	63.3–69.5	**216**	**66.6**	58.6–74.6
Slovakia[a]	2000–2004	**1141**	**88.3**	85.1–91.5	**130**	**86.4**	77.5–95.3	**553**	**59.5**	54.6–64.4	**38**	81.3	64.1–98.6				**542**	**63.0**	58.1–67.8	**115**	**61.9**	51.8–72.0
	2005–2009	**1494**	**91.0**	88.4–93.5	**138**	**93.5**	86.0–100.0	**689**	**69.3**	64.7–74.0	**31**	67.4	46.3–88.5	**11**	100.0	37.5–100.0	**720**	**63.5**	58.8–68.2	**77**	**48.8**	36.1–61.5
	2010–2014	**363**	**89.5**	83.5–95.4	**22**	**98.9**	90.9–100.0	**164**	**69.2**	60.2–78.2							**137**	**54.3**	44.3–64.4			
Slovenia[a]	2000–2004	**492**	**90.5**	86.5–94.6	**60**	90.2	75.0–100.0	**277**	**65.6**	59.4–71.8	**19**	72.5	43.8–100.0				**525**	**74.9**	70.3–79.4	**109**	**71.3**	61.8–80.8
	2005–2009	**882**	**95.1**	92.3–97.9	**74**	89.6	76.0–100.0	**284**	**71.8**	65.8–77.8	**18**	78.8	54.0–100.0				**724**	**78.5**	75.0–82.1	**114**	**71.5**	62.2–80.7
	2010–2014	**899**	**95.0**	92.1–97.9	**48**	**89.0**	77.0–100.0	**224**	**73.1**	66.6–79.5	**21**	65.2	51.1–79.3				**783**	**79.7**	76.0–83.3	**34**	**68.9**	57.1–80.8
Spain	2000–2004	**1465**	**92.9**	90.3–95.6	**268**	**95.4**	90.8–100.0	**501**	**68.9**	64.3–73.5	**144**	**71.9**	63.0–80.8	**20**	58.6	33.7–83.4	**1049**	**81.1**	78.3–84.0	**274**	**81.0**	75.2–86.8
	2005–2009	**1996**	**95.3**	93.5–97.0	**364**	**97.8**	94.7–100.0	**652**	**67.3**	63.3–71.3	**164**	**79.0**	71.9–86.1	**35**	65.5	46.1–84.9	**1167**	**82.8**	80.3–85.4	**300**	**85.6**	80.6–90.7
	2010–2014	**1198**	**96.8**	94.3–99.3	**188**	**97.8**	93.5–100.0	**411**	**60.4**	54.0–66.8	**83**	**82.8**	74.0–91.5	**28**	39.2	10.1–68.3	**659**	**84.6**	80.5–88.6	**130**	**80.6**	72.3–88.9
Sweden[a]	2000–2004	**4549**	**93.7**	92.6–94.9	**496**	**99.2**	96.7–100.0	**1509**	**71.9**	69.0–74.8	**103**	**84.0**	76.5–91.5	**32**	59.6	36.4–82.9	**2477**	**87.5**	85.8–89.2	**45**	87.5	66.8–100.0
	2005–2009	**6319**	**95.7**	94.8–96.6	**732**	**99.3**	97.4–100.0	**2077**	**71.4**	68.8–74.0	**125**	**81.1**	74.3–88.0	**67**	76.7	61.0–92.4	**2566**	**88.9**	87.3–90.5	**50**	75.6	57.6–93.6
	2010–2014	**9437**	**95.9**	95.1–96.7	**1041**	**96.3**	92.6–99.9	**2375**	**74.2**	71.8–76.6	**155**	**84.6**	78.4–90.7	**90**	**86.1**	75.1–97.0	**2620**	**90.8**	89.4–92.3	**56**	**83.0**	71.5–94.5
Switzerland	2000–2004	**1022**	**96.9**	94.6–99.3	**157**	91.8	75.5–100.0	**213**	**70.8**	62.8–78.7	**48**	86.9	61.5–100.0				**259**	**80.4**	74.6–86.2	**41**	62.2	45.7–78.7
	2005–2009	**2134**	**97.6**	96.1–99.2	**369**	**98.6**	96.0–100.0	**442**	**69.8**	64.6–74.9	**132**	**90.1**	84.3–96.0	**23**	78.8	57.5 – 100.0	**852**	**90.2**	87.5–93.0	**107**	**81.8**	74.0–89.7
	2010–2014	**1725**	**98.1**	96.6–99.5	**268**	**100.0**	97.8–100.0	**256**	**72.6**	66.7–78.5	**122**	**91.1**	85.6–96.5				**542**	**88.7**	85.7–91.6	**84**	**83.6**	75.6–91.7
UK[a]	2000–2004	**15 962**	**97.5**	95.5–99.5	**2142**	**98.0**	94.7–100.0	**5,109**	**73.1**	68.6–77.6	**519**	**81.7**	73.8–89.5	**155**	36.5	1.9–71.1	**15 485**	**79.2**	76.1–82.2	**951**	**70.3**	61.1–79.5
	2005–2009	**25 047**	**97.4**	96.8–97.9	**3254**	**98.0**	96.1–99.8	**6,925**	**74.5**	73.2–75.8	**714**	**79.7**	75.9–83.5	**225**	**83.3**	76.8–89.8	**17 094**	**82.1**	81.4–82.8	**1189**	**84.4**	81.8–87.1
	2010–2014	**37 002**	**97.5**	97.1–98.0	**4940**	**97.4**	95.6–99.3	**8,735**	**74.9**	73.7–76.2	**1,033**	**78.5**	74.8–82.1	**373**	**82.3**	75.3–89.3	**15 586**	**84.3**	83.6–85.1	**895**	**85.0**	82.1–87.9

NOS, not otherwise specified. [a]Data with 100% coverage of the national population. [b]Survival estimate considered less reliable, because 15% or more of patients were (i) lost to follow-up or censored alive within 5 years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), or (ii) registered only from a death certificate or at autopsy, or (ii) registered with incomplete dates, i.e. unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status. Italics denote survival estimates that are not age-standardized. Bold values denote age-standardized survival estimates.

Table 4 Data quality indicators, patients diagnosed with melanoma of the skin during 2000–2014, by continent and country

			Ineligible (%)				Exclusions (%)			Data quality indicators (%)			
	Calendar period	Patients submitted	Incomplete dates	*In situ*	Other[a]	Eligible patients	DCO	Other[b]	Available for analysis	MV	Nonspecific morphology	Lost to follow–up	Censored
Africa		498	9.6	0.0	9.2	404	0.0	8.9	368	91.3	45.9	3.0	54.1
Algerian registries	2000–2014	331	13.3	0.0	0.9	284	0.0	12.7	248	99.2	25.0	0.0	47.6
Mauritius[c]	2010–2012	5	0.0	0.0	20.0	4	0.0	0.0	4	100.0	100.0	0.0	0.0
Nigeria (Ibadan)	2005–2014	87	4.6	0.0	16.1	69	0.0	0.0	69	72.4	92.8	0.0	87.0
South Africa (Eastern Cape)	2000–2014	75	0.0	0.0	37.3	47	0.0	0.0	47	76.6	83.0	23.4	44.7
America (Central and South)		10 610	3.2	10.7	5.1	8599	1.4	0.3	8452	99.0	62.4	0.5	6.8
Argentinian registries	2000–2013	1196	4.7	0.8	3.3	1092	0.7	0.0	1084	99.6	67.7	0.0	0.0
Brazilian registries	2000–2014	2169	0.7	12.7	5.6	1758	4.8	0.0	1674	99.2	73.1	0.0	2.0
Chilean registries	2000–2012	569	0.0	0.0	2.5	555	0.2	0.0	554	99.5	60.1	0.0	19.3
Colombian registries	2000–2014	1698	3.8	5.2	10.0	1376	0.2	0.0	1373	98.8	49.4	0.0	25.0
Costa Rica[c]	2002–2014	1448	0.0	0.0	0.8	1436	0.0	0.3	1432	98.3	44.7	0.0	0.0
Ecuadorian registries	2000–2013	1483	11.2	8.4	6.5	1096	0.4	1.1	1080	98.8	78.0	0.2	5.3
Guadeloupe (France)[c]	2008–2013	60	0.0	13.3	0.0	52	0.0	0.0	52	100.0	0.0	0.0	71.2
Martinique (France)[c]	2000–2012	177	0.0	0.0	2.8	172	0.0	4.7	164	100.0	23.2	25.0	0.0
Puerto Rico[c]	2000–2011	1810	2.2	34.6	4.5	1062	2.2	0.0	1039	99.3	75.6	0.0	0.0
America (North)		1 134 825	0.6	35.2	2.7	706 357	0.5	0.0	703 094	99.2	51.1	3.8	0.1
Canadian registries	2000–2014	94 011	0.1	17.2	4.5	73 496	0.3	0.0	73 278	95.6	41.8	0.0	0.0
US registries	2000–2014	1 040 814	0.6	36.0	2.6	632 861	0.5	0.0	629 816	100.0	52.0	2.6	0.1
Asia		41 718	0.5	14.9	8.4	31 768	1.1	0.3	31 337	98.2	76.4	0.4	2.0
Chinese registries	2003–2013	1733	0.2	0.0	16.1	1450	0.1	0.0	1449	99.0	95.4	4.8	0.2
Cyprus[c]	2004–2014	687	3.6	3.1	6.1	599	1.7	0.0	589	99.7	32.8	0.0	53.7
Indian registries	2000–2014	61	0.0	0.0	8.2	56	0.0	7.1	52	98.1	94.2	3.8	5.8
Israel[c]	2000–2013	18 303	0.0	28.3	4.2	12 348	0.7	0.0	12 265	98.0	78.1	0.0	0.0
Japanese registries	2000–2014	6462	1.3	10.4	22.3	4263	5.7	0.0	4018	95.3	88.1	0.0	2.4
Jordan[c]	2000–2014	306	0.3	1.0	27.8	217	0.0	1.4	214	99.5	84.1	14.0	0.0
Korea[c]	2000–2014	5824	0.9	0.0	0.0	5771	0.0	0.0	5771	98.6	74.9	0.0	0.0
Kuwait[c]	2000–2013	21	0.0	0.0	14.3	18	0.0	0.0	18	100.0	72.2	0.0	0.0
Qatar[c]	2000–2014	61	0.0	1.6	8.2	55	0.0	0.0	55	98.2	87.3	0.0	70.9
Singapore[c]	2000–2014	521	0.0	9.0	20.3	368	0.3	0.0	367	100.0	56.1	0.0	0.0
Taiwan[c]	2000–2014	3123	0.3	3.4	0.6	2988	0.0	0.0	2988	100.0	64.0	0.0	0.0
Thai registries	2000–2014	817	0.0	0.0	5.9	769	0.0	9.6	695	99.7	95.0	0.3	3.9
Turkish registries	2000–2013	3799	1.4	4.8	18.4	2866	0.3	0.0	2856	99.3	64.8	0.2	4.8
Europe		842 368	0.1	16.8	5.3	651 577	0.5	0.1	647 719	99.3	34.1	1.7	3.9
Austria[c]	2000–2014	28 233	0.0	24.2	5.9	19 742	2.9	0.1	19 150	97.5	65.4	0.0	0.0
Belgium[c]	2004–2014	29 278	0.0	22.8	2.4	21 905	0.0	0.0	21 905	99.9	36.3	1.9	0.0
Bulgaria[c]	2000–2014	6057	0.0	0.0	0.0	6056	3.0	0.0	5875	100.0	73.7	0.0	0.0

(continued)

Table 4 (continued)

			Ineligible (%)				Exclusions (%)			Data quality indicators (%)			
	Calendar period	Patients submitted	Incomplete dates	*In situ*	Other[a]	Eligible patients	DCO	Other[b]	Available for analysis	MV	Nonspecific morphology	Lost to follow–up	Censored
Croatia[c]	2000–2014	8602	0.0	2.0	3.5	8126	3.4	0.0	7848	99.9	90.4	0.0	0.0
Czech Republic[c]	2000–2014	33 285	0.0	16.0	0.5	27 802	0.0	0.0	27 800	100.0	31.8	0.0	0.0
Denmark[c]	2000–2014	24 683	0.0	0.0	0.2	24 630	0.0	0.0	24 630	99.7	21.6	0.6	0.0
Estonia[c]	2000–2012	2556	0.0	11.8	9.9	2002	0.9	0.0	1983	98.4	31.1	1.2	0.0
Finland[c]	2000–2014	15 873	0.4	0.0	5.3	14 968	0.1	0.0	14 949	100.0	90.8	0.3	0.0
French registries	2000–2010	14 962	0.3	0.0	6.0	14 017	0.0	2.4	13 677	100.0	11.4	3.4	0.0
German registries	2000–2014	99 363	0.3	16.2	2.6	80 338	2.0	0.0	78 713	99.4	28.4	0.6	28.7
Gibraltar[c]	2000–2010	39	0.0	12.8	7.7	31	0.0	0.0	31	100.0	19.4	0.0	51.6
Iceland[c]	2000–2014	715	0.0	0.0	0.3	713	0.0	0.0	713	99.9	29.3	0.0	0.0
Ireland[c]	2000–2013	14 683	0.0	35.3	0.1	9475	0.1	0.0	9470	99.8	36.9	0.0	0.0
Italian registries	2000–2014	53 776	0.0	7.8	5.4	46 634	0.1	0.0	46 607	98.2	26.5	1.2	1.5
Latvia[c]	2000–2014	2507	0.0	0.0	0.2	2503	0.1	0.0	2501	99.8	47.5	0.0	0.0
Lithuania[c]	2000–2012	4129	0.0	6.3	13.4	3317	0.0	0.0	3317	100.0	55.8	0.0	0.9
Malta[c]	2000–2013	725	0.0	14.2	10.9	543	0.4	0.0	541	99.6	36.4	0.0	0.0
The Netherlands[c]	2000–2014	80 641	0.0	20.0	6.6	59 141	0.0	0.1	59 088	100.0	13.2	1.1	0.0
Norway[c]	2000–2014	31 469	0.0	8.6	27.9	19 997	0.0	0.0	19 994	99.9	21.0	0.3	0.0
Poland[c]	2000–2014	38 834	0.0	0.2	7.3	35 932	0.0	0.3	35 834	100.0	77.1	0.0	0.0
Portugal[c]	2000–2014	10 897	0.3	11.3	2.5	9358	0.0	0.0	9358	99.3	54.6	2.1	0.1
Romania (Cluj)	2006–2012	515	0.0	3.9	11.5	436	0.0	0.0	436	98.9	50.9	0.0	0.0
Russian registries	2000–2014	5081	0.0	0.1	2.9	4927	0.1	0.2	4914	99.5	79.0	2.5	0.7
Slovakia[c]	2000–2010	7933	0.0	11.1	7.3	6478	1.4	0.0	6389	100.0	21.9	0.0	0.0
Slovenia[c]	2000–2013	7442	0.0	18.8	5.9	5605	0.0	0.0	5603	100.0	36.3	0.1	0.0
Spanish registries	2000–2013	14 567	0.5	18.8	3.2	11 292	0.3	0.1	11 242	99.7	25.8	0.6	0.1
Sweden[c]	2000–2014	58 528	0.0	30.2	6.7	36 925	0.0	0.0	36 921	100.0	20.8	0.3	0.1
Swiss registries	2000–2014	19 030	0.0	19.4	2.1	14 923	0.1	0.1	14 893	99.9	20.0	7.2	7.9
UK[c]	2000–2014	227 965	0.1	22.9	4.8	163 761	0.2	0.0	163 337	98.5	30.8	4.3	0.0
Oceania		273 076	0.2	29.6	1.5	187 846	0.2	0.0	187 512	99.0	32.8	0.0	0.0
Australia[c]	2000–2014	241 133	0.2	33.5	1.4	156 531	0.1	0.0	156 302	98.9	32.3	0.0	0.0
New Zealand[c]	2000–2014	31 943	0.0	0.0	2.0	31 315	0.3	0.0	31 210	99.7	35.3	0.0	0.0
Total		2 303 095	0.4	27.7	3.5	1 586 551	0.5	0.0	1 578 482	99.2	43.2	2.5	1.6

DCO, death certificate only; MV, microscopically verified. [a]Other, records with incomplete data or for tumours that are benign (behaviour code 0), of uncertain behaviour (behaviour code 1), metastatic from another organ (behaviour code 6), or unknown if primary or metastatic (behaviour code 9); or for patients aged outside the range 15–99 years (adults); or with a topography code that is not in the range for skin (C440–C449), or the skin of the labia majora (C510), vulva (C519), penis (C609) or scrotum (C632). [b]Other, tumour coded with unknown vital status; or for patients for whom the sex is unknown. [c]Data with 100% coverage of the national population.

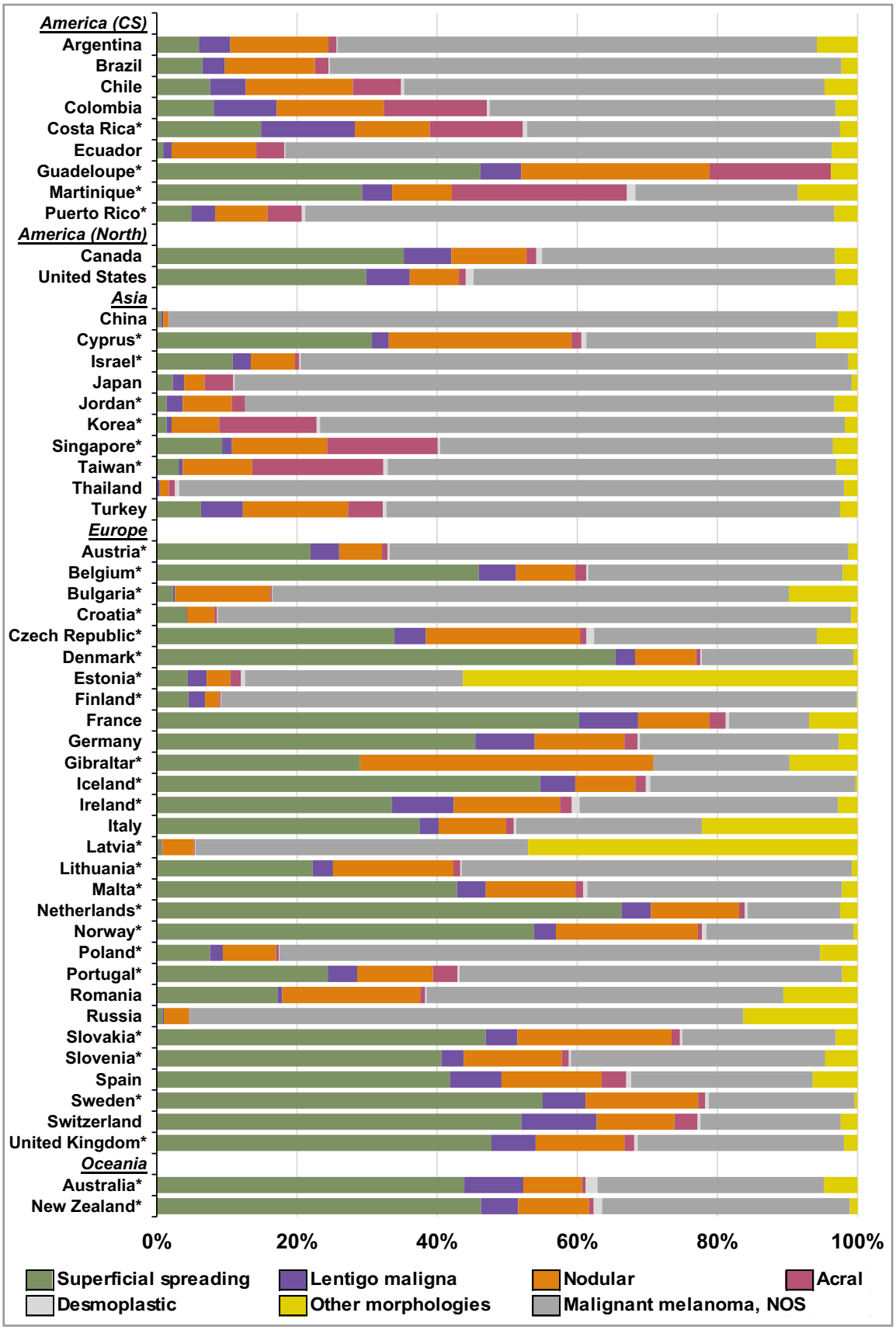

Fig 1 Morphology distribution by continent and country, all periods combined.NOS, not otherwise specified.

Malignant melanoma, not otherwise specified

Age-standardized 5-year net survival varied widely between world regions (Tables 1–3). It was in the range of 85–89% in Oceania and North America during 2010–2014. It was higher than 80% in all Western European countries and ranged from 54% to 79% in Eastern Europe. In Central and South America, age-standardized 5-year net survival ranged from 57% in Ecuador to 76% in Costa Rica and Puerto Rico. The 5-year survival was lower than 70% in all countries in the Asia region except Israel (88%), and was as low as 47% in Taiwan.

The 5-year survival increased between 2000–2004 and 2010–2014 by 10% or more in China (from 36% to 48%), Bulgaria (from 52% to 62%), Croatia (from 66% to 77%) and Estonia (from 71% to 83%).

Superficial spreading melanoma

Age-standardized 5-year net survival for patients diagnosed during 2010–2014 was 90% or higher in North America, Oceania and almost all European countries; survival was lower than 90% in only Slovakia, Poland, Lithuania, Portugal and Bulgaria. In the Asia region, survival ranged from 71% in Taiwan to 98% in Israel (Figure 2).

Lentigo maligna melanoma

The lentigo maligna melanoma subtype had the most favourable prognosis; age-standardized 5-year net survival was close to 100% in North America, Australia and most European countries. Estimates were not available for most countries in Central and South America and Asia because of the small numbers of patients diagnosed with this specific subtype.

Nodular melanoma

The prognosis for nodular melanoma was the poorest in all continents. Age-standardized 5-year net survival for patients diagnosed during 2010–2014 reached 72% in Canada and the USA, 77% in New Zealand and 80% in Australia. In Central and South America, it ranged from 58% in Costa Rica to 72% in Argentina, and in Europe, it ranged from 58% in Poland to 80% in Ireland. Survival improved dramatically in Bulgaria (from 46% in 2000–2004 to 64% in 2010–2014) and in Portugal (from 59% to 76%).

Acral lentiginous melanoma

The 5-year net survival for adults diagnosed during 2010–2014 was in the range of 77–82% in North America and Oceania and 70–95% in Europe. Most of the estimates for countries in Asia and Central and South America were not age-standardized because of the small numbers of patients available for survival analysis.

The 5-year net survival for adults diagnosed with desmoplastic melanoma during 2010–2014 ranged between 76% and 91%. Estimates were not available for Central and South America or for most countries in Asia because of the small numbers of patients available for analysis.

With the excess hazard of death for patients with superficial spreading melanoma taken as the reference category, the excess hazard ratio for patients diagnosed with nodular melanoma was 21.8 [95% confidence interval (CI) 14.7–32.3] in Germany, 12.1 (95% CI 8.1–18.1) in Spain and 6.7 (95% CI 5.7–7.9) in Norway (Table 5). The excess hazard ratios were lower after controlling for sex, age and stage at diagnosis, but the excess hazard of death for patients with nodular melanoma was still 13.5 (95% CI 9.6–18.9) times higher in Germany, 6.7 (95% CI 4.8–9.3) times higher in Spain and 4.1 (95% CI 3.6–4.8) times higher in Norway, than for patients in the same country diagnosed with superficial spreading melanoma.

The excess hazard ratio for patients diagnosed with acral lentiginous melanoma vs. superficial spreading melanoma was 15.2 (95% CI 9.0–25.5), 9.0 (95% CI 5.2–15.5) and 1.7 (95% CI 0.5–5.1) in Germany, Spain and Norway, respectively. After controlling for sex, age and stage at diagnosis, the excess hazard of death for patients with acral lentiginous melanoma was still 10.8-fold (95% CI 6.8–17.1) higher in Germany, fivefold (95% CI 3.1–8.1) higher in Spain and 2.2-fold (95% CI 1.0–4.9) higher in Norway, than for patients diagnosed with superficial spreading melanoma.

Discussion

This study of over 1.5 million adults diagnosed with cutaneous melanoma worldwide during 2000–2014 highlights wide international differences in the distribution of histological subtypes and differences in survival by subtype. For all countries investigated, the prognosis is poorest for nodular and acral lentiginous melanoma.

The prognostic role of the morphology of cutaneous melanomas is controversial. Clinical guidelines indicate that stage at diagnosis is the most important prognostic factor. The prevalent idea is that melanomas of different morphologies converge in their biological behaviour once they metastasize,[29] so the recommended treatment options do not differ between morphological subtypes at a given stage at diagnosis. Furthermore, clinical guidelines indicate that the histological subtype is only an optional item for inclusion in pathology reports.[30] This probably explains why the primary histological subtypes of melanoma are often poorly specified, if at all, in pathology reports.[11,14] This in turn determines the high proportion of melanomas that are coded as 'malignant melanoma, not otherwise specified (NOS)' in cancer registry data.[13] In this global study, 43% of melanomas were registered as malignant melanoma, NOS. The proportion varied widely, and was higher in Asia, Central and South America, and Eastern Europe, as has been shown elsewhere.[13,31] However, our study demonstrates that the proportion of melanomas with poorly specified morphology has fallen in most countries over the last 15 years, which suggests that there have been improvements in pathological practice.[32]

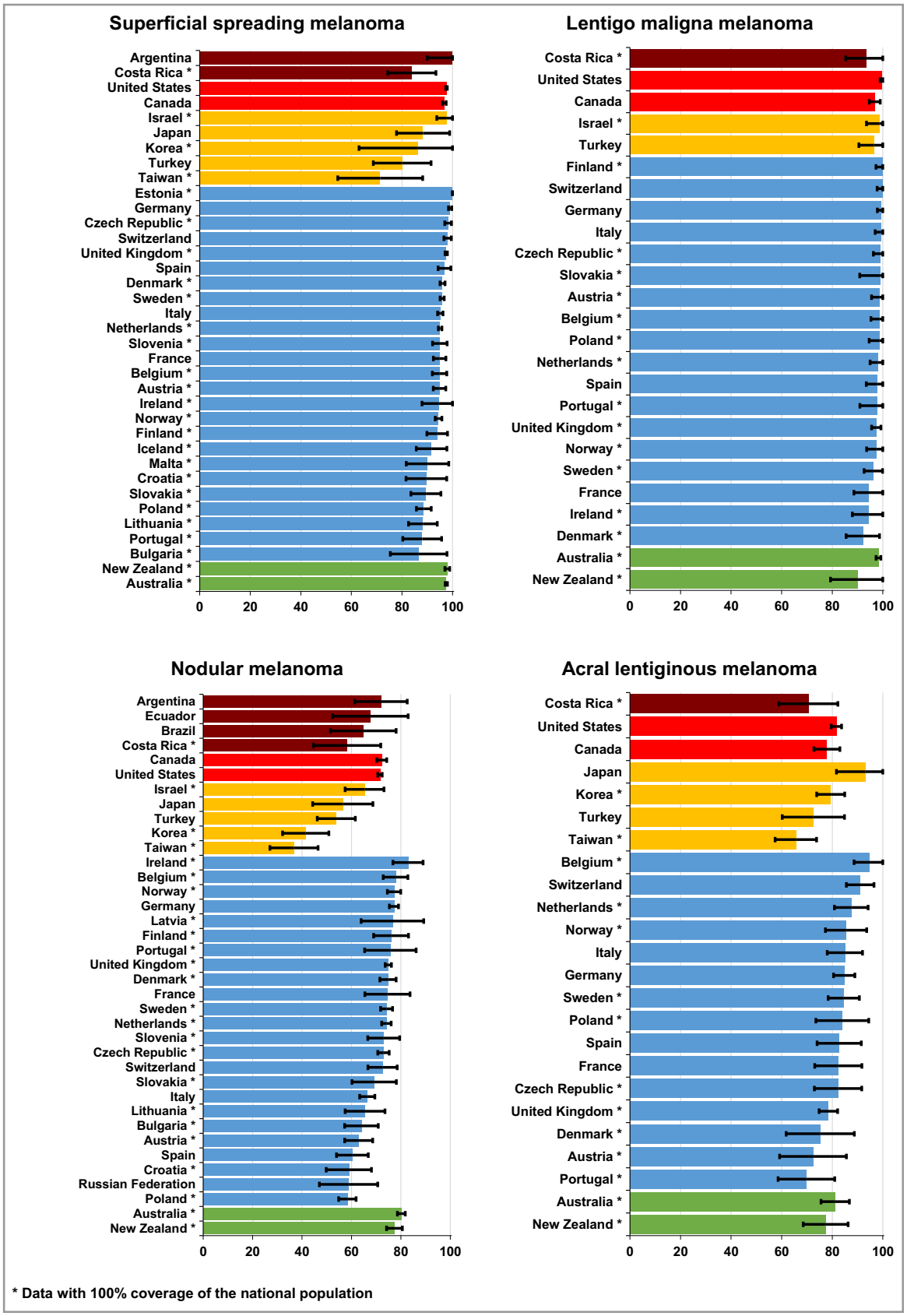

Figure 2 Age-standardized 5-year net survival for patients diagnosed with cutaneous melanoma during 2010–2014 by continent, country and morphology group

Table 5 Excess hazard ratio (EHR) of death in patients with malignant melanoma of the skin, by morphological type (reference category superficial spreading melanoma) in Germany, Spain and Norway

	Germany (Lower Saxony)			Spanish registries[a]			Norway[b]		
	n (%)	Model 1, EHR (95% CI)	Model 2, EHR (95% CI)	n (%)	Model 1, EHR (95% CI)	Model 2, HR (95% CI)	n (%)	Model 1, EHR (95% CI)	Model 2, EHR (95% CI)
Superficial spreading	9326 (58.9)	1.0	1.0	1642 (39.8)	1.0	1.0	8624 (54.0)	1.0	1.0
Lentigo maligna	1305 (8.2)	0.2 (0.0–35.1)	0.1 (0.0–26.9)	232 (5.6)	0.4 (0.0–17.2)	0.4 (0.1–2.1)	478 (3.0)	0.3 (0.1–6.4)	0.5 (0.2–1.4)
Nodular	1514 (9.6)	21.8 (14.7–32.3)	13.5 (9.6–18.9)	627 (15.2)	12.1 (8.1–18.1)	6.7 (4.8–9.3)	3234 (20.3)	6.7 (5.7–7.9)	4.1 (3.6–4.8)
Acral lentiginous	341 (2.2)	15.2 (9.0–25.5)	10.8 (6.8–17.1)	138 (3.4)	9.0 (5.2–15.5)	5.0 (3.1–8.1)	91 (0.6)	1.7 (0.5–5.1)	2.2 (1.0–4.9)
Malignant melanoma, NOS	2953 (18.7)	6.5 (4.3–9.9)	5.4 (3.8–7.6)	1178 (28.6)	4.2 (2.8–6.4)	2.9 (2.0–4.0)	3338 (20.9)	3.9 (3.3–4.7)	2.8 (2.4–3.3)
Other morphologies	385 (2.4)	8.6 (4.7–15.6)	6.5 (3.8–11.0)	307 (7.4)	5.6 (3.4–9.2)	3.7 (2.4–5.6)	201 (1.2)	4.5 (2.9–6.9)	2.4 (1.6–3.7)

NOS, not otherwise specified. EHR, excess hazard ratio. [a]Granada and Basque Country. [b]National coverage. Model 1 included only morphology. Model 2 included morphology, sex, age and stage at diagnosis.

Overall, superficial spreading melanoma was the most frequent of the specific morphologies, and the proportion of this morphological subtype has been increasing over time. This subtype is generally associated with an excellent prognosis in Europe, North America and Oceania, as has been shown in previous studies.[13,14,29,33] Several international studies have shown an increasing incidence of thinner melanomas (1 mm or less)[15,34–40] as a result of raised public awareness and earlier detection, especially for superficial spreading melanomas. The result is an increasing number of people with melanoma who are less likely to die as a result of their tumours. This phenomenon may help to explain the improvement in the already high 5-year net survival for superficial spreading melanoma.

Acral lentiginous melanoma accounted for less than 1% of the patients in Europe, North America and Oceania, but almost 6% of the patients in Asia and 7% in Central and South America. Very few studies have focused on survival from cutaneous melanoma in Asia and Central and South America, perhaps because the overall incidence is much lower than in fairer-skinned populations. In Singapore, acral lentiginous melanoma accounted for 16% of all cases diagnosed during 2008–2017.[41] In a study of 915 patients diagnosed with melanoma during 1997–2011 in Brazil, the acral subtype accounted for 7% of all cases and the 5-year cause-specific survival for this subtype was much lower (51%) than for superficial spreading melanoma (82%).[42] A study of 142 patients in China confirmed the poor prognosis for patients with acral lentiginous melanoma; the 5-year cause-specific survival was 53%.[43] By contrast, an analysis of 252 patients diagnosed in a single institution in Japan during 2001–2014 showed no difference between 5-year survival for acral and nonacral lentiginous subtypes (59% vs. 62% in men and 71% vs. 85% in women);[44] however, the numbers of patients were too small to derive definitive conclusions.

Our study found that age-standardized 5-year net survival for acral lentiginous melanoma was generally lower than for other morphological subtypes, with the only exception of nodular melanoma, and was in the range of 66–95% globally. The poorer prognosis for acral lentiginous melanoma, which usually develops on the palms, the sole of the foot or underneath the nails, is commonly ascribed to delayed diagnosis because these areas are not routinely examined by patients or primary care physicians.[45] Moreover, the proportion of the acral subtype is higher in black patients than in white patients;[46] but because the risk of melanoma in black populations is perceived to be low, the lack of secondary prevention is also considered a major cause of late diagnosis.[47,48]

Nodular melanoma had the poorest prognosis in all countries, as has been reported elsewhere.[49–51] In a study published over 40 years ago, a multivariable analysis of 339 patients diagnosed in a single institution in the USA during 1960–1977 found that the increased risk associated with nodular histology was confounded by an increase in thickness and ulceration; in other words, the higher risk of death was due to more advanced stage at diagnosis, and was not intrinsic to the morphological

subtype.[52] On the basis of this conclusion from a small study, the American Joint Committee on Cancer did not include histological subtype in the cutaneous melanoma staging system because it was not considered to be a significant prognostic factor.[53] However, 30 years later, a very large population-based study of 118 508 patients diagnosed in the USA with superficial spreading or nodular melanoma during 1973–2012 showed that morphology is in fact an independent predictor of survival.[29] After controlling for thickness, ulceration, mitotic index and stage at diagnosis, nodular subtype remained an independent risk factor for death from melanoma (hazard ratio 1.55, 95% CI 1.41–1.70). Another population-based study of 82 901 patients diagnosed in Germany during 1997–2013 showed that differences in 5-year survival by histological subtype were "only" partially explained by tumour size.[54]

Our population-based study confirms these findings. The multivariable analysis of data from four population-based registries with complete information on stage and morphology highlights a much higher excess risk of death for nodular or acral lentiginous melanoma than for superficial spreading melanoma, after controlling for major confounders. Sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes. The different magnitude of the excess hazard ratios in Germany, Spain and Norway may be due to the low baseline hazard for superficial spreading melanoma in Germany, where national skin cancer screening for people aged 35 years or more who have health insurance was introduced in 2008. This may have improved early detection of the generally slow-growing, less aggressive superficial spreading melanomas.[54]

Our study has also shown that while 5-year survival from cutaneous melanoma in Eastern Europe has been increasing in recent years, survival continues to lag behind the rest of Europe for each morphological subtype of melanoma. A study of seven common malignancies diagnosed in Europe during 2000–2007 found that late stage at diagnosis alone did not explain the lower survival for melanoma of the skin in Eastern Europe.[55] In the current study, data on stage at diagnosis in Eastern European countries were available only for Russia and Slovakia, where the proportion of metastatic disease (6% and 7%) was higher than in Norway (2%) and Denmark (3%) (data not shown). More detailed information on morphology would have helped in the investigation of the reasons for the persistent gap in survival.

The major limitation of our study was the high proportion of melanomas registered with poorly specified morphology, as this meant that the interpretation of net survival estimates for melanomas with specific morphological subtypes in all countries was limited. Information on stage at diagnosis was also limited; complete data could have contributed to the disentangling of the prognostic role of morphology at an international level. Additionally, we were not able to control for surgical margins, which are a relevant prognostic factor, as these data were not available.

Our study is the largest analysis to date of survival from cutaneous melanoma. It provides, for the first time, international comparisons of population-based survival for the main histological subtypes of melanoma from more than 50 countries. The higher frequency and poorer survival of nodular and acral lentiginous melanomas in Asia and in Central and South America suggest the need for health policies in these populations that are designed to improve public awareness, and especially to facilitate earlier diagnosis and prompt access to optimal treatment.

Funding sources

This project was supported by the American Cancer Society, Centers for Disease Control and Prevention, Swiss Re, Swiss Cancer Research Foundation, Swiss Cancer League, Institut National du Cancer, La Ligue Contre le Cancer, Rossy Family Foundation, The National Cancer Institute and the Susan G. Komen Foundation.

Conflicts of interest

The authors declare they have no conflicts of interest.

Data availability

These data are provided by more than 300 cancer registries worldwide. We hold the data in trust from each of the participating registries in order to perform the analyses agreed in the protocol. The protocol prohibits us from performing other analyses and from sharing the raw data with other parties, without express approval from the participating cancer registries.

Ethics statement

This study contains the results of secondary analysis of sensitive personal data, carried out with statutory approval from the Health Research Authority and ethical approval from the National Health Service Research Ethics Service.

References

1 van der Esch EP, Muir CS, Nectoux J *et al.* Temporal change in diagnostic criteria as a cause of the increase of malignant melanoma over time is unlikely. *Int J Cancer* 1991; **47**:483–90.
2 Coleman MP, Estève J, Damiecki P, Arslan A, Renard H. *Trends in Cancer Incidence and Mortality*. Lyon: International Agency for Research on Cancer, 1993.
3 Bray F, Colombet M, Mery L, Piñeros M, Znaor A *et al.* *Cancer Incidence in Five Continents*, vol. **XI**. Lyon: International Agency for Research on Cancer, 2017.
4 Chen YJ, Wu CY, Chen JT *et al.* Clinicopathologic analysis of malignant melanoma in Taiwan. *J Am Acad Dermatol* 1999; **41**:945–9.
5 Ishihara K, Saida T, Otsuka F, Yamazaki N, The prognosis statistical investigation committee of the Japanese Skin Cancer Society. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. *Int J Clin Oncol* 2008; **13**:33–41.
6 Allemani C, Matsuda T, Di Carlo V *et al.* Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**:1023–75.

7 Schoffer O, Schülein S, Arand G *et al.* Tumour stage distribution and survival of malignant melanoma in Germany 2002-2011. *BMC Cancer* 2016; **16**:936–48.

8 Rockberg J, Amelio JM, Taylor A *et al.* Epidemiology of cutaneous melanoma in Sweden. Stage-specific survival and rate of recurrence. *Int J Cancer* 2016; **139**:2722–9.

9 Xing Y, Chang GJ, Hu CY *et al.* Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer* 2010; **116**:2234–41.

10 Kemeny MM, Busch E, Stewart AK, Menck HR. Superior survival of young women with malignant melanoma. *Am J Surg* 1998; **175**:437–44.

11 Galceran J, Uhry Z, Marcos-Gragera R *et al.* Trends in net survival from skin malignant melanoma in six European Latin countries: Results from the SUDCAN population-based study. *Eur J Cancer Prev* 2017; **26**:S77–S84.

12 Enninga EAL, Moser JC, Weaver AL *et al.* Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992-2011. *Cancer Med* 2017; **6**:2203–12.

13 Crocetti E, Mallone S, Robsahm TE *et al.* Survival of patients with skin melanoma in Europe increases further: results of the EUROCARE-5 study. *Eur J Cancer* 2015; **51**:2179–90.

14 Pollack LA, Li J, Berkowitz Z *et al.* Melanoma survival in the United States, 1992 to 2005. *J Am Acad Dermatol* 2011; **65**:S78–86.

15 Downing A, Yu XQ, Newton-Bishop J, Forman D. Trends in prognostic factors and survival from cutaneous melanoma in Yorkshire, UK and New South Wales, Australia between 1993 and 2003. *Int J Cancer* 2008; **123**:861–6.

16 Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behaviour of primary human malignant melanomas of the skin. *Cancer Res* 1969; **29**:705–26.

17 Elder DE, Massi D, Scolyer RA, Willemze R. *WHO Classification of Skin Tumours*, 4th edn. Lyon: International Agency for Research on Cancer, 2018.

18 Ackerman AB, David KM. A unifying concept of malignant melanoma: biologic aspects. *Hum Pathol* 1986; **17**:438–40.

19 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L *et al. International Classification of Diseases for Oncology*, first revision of 3rd edn. Geneva: World Health Organization, 2013.

20 Pohar Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68**:113–20.

21 Clerc-Urmès I, Grzebyk M, Hedelin G. Net survival estimation with stns. *Stata J* 2014; **14**:87–102.

22 Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996; **78**:2004–10.

23 Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40**:2307–16.

24 United Nations Statistics Division. Methodology: standard countries or area codes for statistical use (M49). Available at: https://unstats.un.org/unsd/methodology/m49/ (last accessed 11 February 2022).

25 Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J* 2009; **9**:165–90.

26 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; **17**:1471–4.

27 Berrino F, Brown M, Moller C, Sobin L. *ENCR recommendation: Condensed TNM for Coding the Extent of Disease*. Lyon: Europen Network of Cancer Registries, 2002.

28 Young JL, Roffers SD, Ries LAG *et al. SEER Summary Staging Manual 2000: Codes and Coding Instructions*. Bethesda, MD: National Cancer Institute, 2001.

29 Lattanzi M, Lee Y, Simpson D *et al.* Primary melanoma histologic subtype: impact on survival and response to therapy. *J Natl Cancer Inst* 2019; **111**:180–8.

30 Swetter SM, Tsao H, Bichakjian CK *et al.* Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol* 2019; **80**:208–50.

31 de Vries E, Sierra M, Pineros M *et al.* The burden of cutaneous melanoma and status of preventive measures in Central and South America. *Cancer Epidemiol* 2016; **44**:100–9.

32 Barbarić J, Coebergh JW, Šekerija M. Completeness of data on malignant melanoma skin sites and morphology in the Croatian National Cancer Registry 2000–2014: an overview of recent progress. *Acta Dermatovenerol Croat* 2017; **25**:285–91.

33 Green AC, Baade P, Coory M, Aitken JF, Smithers M. Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *J Clin Oncol* 2012; **30**:1462–7.

34 Baade P, Meng X, Youlden D *et al.* Time trends and latitudinal differences in melanoma thickness distribution in Australia, 1990–2006. *Int J Cancer* 2012; **130**:170–8.

35 Montella A, Gavin A, Middleton R *et al.* Cutaneous melanoma mortality starting to change: a study of trends in Northern Ireland. *Eur J Cancer* 2009; **45**:2360–6.

36 Lyth J, Eriksson H, Hansson J *et al.* Trends in cutaneous malignant melanoma in Sweden 1997–2011: thinner tumours and improved survival among men. *Br J Dermatol* 2015; **172**:700–6.

37 Armstrong A, Powell C, Powell R *et al.* Are we seeing the effects of public awareness campaigns? A 10-year analysis of Breslow thickness at presentation of malignant melanoma in the South West of England. *J Plast Reconstr Aesthet Surg* 2014; **67**:324–30.

38 Sacchetto L, Zanetti R, Comber H *et al.* Trends in incidence of thick, thin and *in situ* melanoma in Europe. *Eur J Cancer* 2018; **92**:108–18.

39 Shaikh WR, Dusza SW, Weinstock MA *et al.* Melanoma thickness and survival trends in the United States, 1989 to 2009. *J Natl Cancer Inst* 2016; **108**:djv294.

40 Rubió-Casadevall J, Puig-Vives M, Puigdemont M *et al.* Patterns of increased incidence and survival of cutaneous melanoma in Girona (Spain) 1994–2013: a population-based study. *Clin Transl Oncol* 2018; **20**:1617–25.

41 Singapore Cancer Registry. *50 Years of Cancer Registration (1968–2017)*. Singapore, 2019.

42 Vazquez V L, Silva TB, Vieira MA *et al.* Melanoma characteristics in Brazil: demographics, treatment, and survival analysis. *BMC Res Notes* 2015; **8**:4.

43 Lv J, Dai B, Kong Y *et al.* Acral melanoma in Chinese: a clinicopathological and prognostic study of 142 cases. *Sci Rep* 2016; **6**:31432.

44 Wada M, Ito T, Tsuji G *et al.* Acral lentiginous melanoma versus other melanoma: a single-center analysis in Japan. *J Dermatol* 2017; **44**:932–8.

45 Albreski D, Sloan SB. Melanoma of the feet: misdiagnosed and misunderstood. *Clin Dermatol* 2009; **27**:556–63.

46 Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986–2005. *Arch Dermatol* 2009; **145**: 427–34.

47 Kundu RV, Kamaria M, Ortiz S *et al.* Effectiveness of a knowledge-based intervention for melanoma among those with ethnic skin. *J Am Acad Dermatol* 2010; **62**:777–84.

48 Byrd KM, Wilson DC, Hoyler SS, Peck GL. Advanced presentation of melanoma in African Americans. *J Am Acad Dermatol* 2004; **50**:21–4.

49 Mahendraraj K, Sidhu K, Lau CS *et al.* Malignant melanoma in African–Americans: a population-based clinical outcomes study involving 1106 African–American patients from the Surveillance, Epidemiology, and End Results (SEER) Database (1988–2011). *Medicine (Baltimore)* 2017; **96**:e6258.

50 Shaikh WR, Xiong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. *Arch Dermatol* 2012; **148**:30–6.
51 Mar V, Roberts H, Wolfe R *et al.* Nodular melanoma: a distinct clinical entity and the largest contributor to melanoma deaths in Victoria, Australia. *J Am Acad Dermatol* 2013; **68**:568–75.
52 Balch CM, Murad TM, Soong SJ *et al.* A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Ann Surg* 1978; **188**:732–42.
53 Balch CM, Buzaid AC, Soong SJ *et al.* New TNM melanoma staging system: linking biology and natural history to clinical outcomes. *Semin Surg Oncol* 2003; **21**:43–52.
54 Brunssen A, Jansen L, Eisemann N *et al.* A population-based registry study on relative survival from melanoma in Germany stratified by tumor thickness for each histologic subtype. *J Am Acad Dermatol* 2019; **80**:938–46.
55 Minicozzi P, Walsh PM, Sánchez M-J *et al.* Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? *Eur J Cancer* 2018; **93**:127–37.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 CONCORD Working Group.

Table S1 Malignant melanoma of the skin: distribution by morphology group, country and calendar period of diagnosis.