The epidemiology of multiple primary melanomas in Australia

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A thesis submitted to fulfil requirements for the degree of Doctor of Philosophy

Faculty of Medicine and Health
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Statement of originality

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

This thesis has not been submitted for any degree or other purposes.

Yuan Ni

Acknowledgements

This PhD journey as an international student residing over 8,000 kilometres from my hometown has been an unforgettable adventure and the support and warmth that I have received kept me going strong.

Firstly, I would like to express my gratitude to my PhD supervisors, **Associate Professor Serigne Lo**, and **Professor Anne Cust**. It is my privilege to be your PhD student. You both instilled in me the diligence, courage, confidence, and perseverance to undertake this degree. Thanks for sharing your knowledge and expertise in ways that illuminated my career path. Serigne, it has been a great honour to study under your mentorship. Thanks for answering my tons of questions and mentoring me to make progress to where I am today. I will remember Piccolo coffee and Thai lunch with our team at Melanoma Institute Australia (MIA) every Friday. Anne, I still remember our first meeting at Lifehouse, and how nervous I was. Thank you so much for seeing my potential and taking me on as a student at that time. Your choice genuinely changed my life. Words may not adequately express my tremendous appreciation from the bottom of my heart.

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Honestly, undertaking PhD research overseas during the COVID-19 period using a second language is genuinely tough. I would like to thank myself, who never considered giving up, no matter how hard it was.

COVID-19 Impact Statement

My PhD candidature was due to start in March 2020. Unfortunately, the COVID-19 pandemic struck worldwide, compelling me to remain in my home country, China, and postpone my acceptance of the PhD offer. Due to the uncertainty brought about by COVID-19 and the concurrent border closures during that period, my supervisors agreed for me to start my PhD research from July 2020 while residing overseas. Therefore, for the initial 18 months of my PhD candidacy, I was based in China and engaged with my supervisors through fortnightly online meetings, occasionally supplemented by unplanned meetings. In February 2022, I returned to Sydney and resumed work at on-campus with regular face to face meeting with supervisors and the research team.

The COVID-19 pandemic had a major impact on my PhD. The biggest challenge from this disruption was the difficulty in communicating over virtual meetings and email during the first 18 months, given my limited English speaking and written communication skills and statistical analysis skills at that time, which was particularly crucial at the beginning of a PhD candidature when additional instructions and guidance were necessary. Other challenges included needing to alter some of my original PhD research plans, social isolation due to working at home overseas, a reduction of research efficiencies and limited English-speaking opportunities in China. The border closure and lockdowns meant that I could not travel to Sydney and get access to on-campus facilities. I also had limited opportunities for communicating with colleagues and fellow PhD students. Transitioning my research entirely to an online mode proved challenging as a first-year PhD student. Consequently, these unforeseen circumstances led to delays in research progress and necessitated more time to complete the PhD (almost 4 years) than originally anticipated (3-3.5 years). I respectfully request that the PhD examiners take into consideration these unforeseen challenges posed by COVID-19 when examining the PhD thesis.

Thesis Abstract

Melanoma is a serious form of skin cancer and Australia (with New Zealand) has the highest incidence of melanoma in the world, and increasing rates among older generations. Early detection of melanoma is important as it is associated with a better prognosis. Overall survival rates after a diagnosis of melanoma are relatively high, which leads to many people living with a previous melanoma diagnosis. Compared to the general population, melanoma survivors are at a much higher risk of developing a subsequent primary melanoma and require ongoing skin surveillance. However, most epidemiological research has focused on the first melanoma diagnosis. The objective of my PhD was to contribute new insights to the understanding of the epidemiology of multiple primary melanomas in Australia. We aspire for these findings to be applicable to broader melanoma populations through replication and validation in further research.

This thesis comprises four quantitative studies that focused on investigating the survival rates, risk factors for occurrence, and incidence trends of multiple primary melanomas. The findings provide the most recent evidence regarding multiple primary melanomas. Chapter 2 evaluated absolute risk and potential risk factors of developing a second primary melanoma. The results indicated that male sex, older age, high naevus count and body site are risk factors associated with higher risk of second primary melanoma. Chapter 3 investigated risk factors of developing a second primary melanoma or other types of cancers after the initial melanoma diagnosis, indicating the most common second cancers were melanoma, followed by prostate cancer, breast cancer and colon cancer. Chapter 4 evaluated the trends in the incidence rate of second primary melanomas in Australia, finding out the incidence rates increased by 3 to 5-fold over three decades. Chapter 5 investigated whether there are survival variations between people diagnosed with single and multiple primary melanomas, and the result draws a conclusion that the number of melanomas is not an independent risk factor for prognosis.

The findings in my PhD provide important information for patients and health professionals regarding risk factors and survival associated with multiple primary melanomas, and will contribute to clinical practice guidelines for optimal skin surveillance following a first melanoma diagnosis.

List of publications included in the thesis

The publications which comprise this thesis are listed below.

1. **Y. Ni**, C.G. Watts, R. A. Scolyer, C. Madronio, B.K. Armstrong, R. L. Morton, S. W. Menzies, G. J. Mann, J. F. Thompson, S. N. Lo, and A. E. Cust (2023). "Risk of developing a second primary melanoma after a first primary melanoma in a population-based Australian cohort." Br J Dermatol. 188(6):814-816. doi: 10.1093/bjd/ljad076.

2. **Y. Ni**, C.G. Watts, R. A. Scolyer, C. Madronio, B.K. Armstrong, R. L. Morton, S. W. Menzies, G. J. Mann, J. F. Thompson, A. E. Cust, and S. N. Lo (2024). "Prognosis for people with multiple primary melanomas compared with a single primary melanoma." J Am Acad Dermatol. 90(1):170-174. doi: 10.1016/j.jaad.2023.08.089.

3. **Y. Ni**, C.G. Watts, A. H. R. Varey, A. E. Cust, and S. N. Lo. "Risk of developing another primary melanoma or other type of cancer after a first primary melanoma: An Australian population-based cohort study." The paper is currently under review by the American Journal of Epidemiology (impact factor 5.0).

4. **Y. Ni**, D. Espinoza, K. McLoughlin, S. N. Lo, and A. E. Cust. "Time trends in the incidence of multiple primary melanomas in Australia." The paper is currently under review by the Journal of Investigative Dermatology (impact factor 6.5).

Conference presentations based on the thesis chapter:

Results from my PhD have been presented at 11 national and international conferences, including 8 oral presentations and 3 poster presentations, as described below organised by chapter.

<u>Chapter2:</u>

1. **Y Ni**, SN Lo, AE Cust. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: A population-based Australian cohort. Oral presentation at the International Dermatology Epidemiology Association Meeting, 6-8 July 2022, Rotterdam, the Netherlands.

2. **Y Ni**, CG Watts, RA Scolyer, C Madronio, BK Armstrong, RL Morton, SW Menzies, GJ Mann, JF Thompson, AE Cust, SN Lo. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: A population-based Australian cohort. Poster presentation at the NSW Cancer Conference, 15-16 September 2022.

3. **Y Ni**, CG Watts, RA Scolyer, C Madronio, BK Armstrong, RL Morton, SW Menzies, GJ Mann, JF Thompson, AE Cust, SN Lo. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: an Australian population-based cohort. Poster presentation at the Australasian Melanoma Conference, 24-25 March 2023, Brisbane, Australia.

4. **Y Ni**, CG Watts, RA Scolyer, C Madronio, BK Armstrong, RL Morton, SW Menzies, GJ Mann, JF Thompson, AE Cust, SN Lo. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: an Australian population-based cohort. Oral presentation at the 2023 Research Retreat of Melanoma Institute Australia, 18 August 2023, North Sydney, Australia.

5. **Y Ni**, SN Lo, AE Cust. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: A population-based Australian cohort. Oral presentation at the Cancer Research Network Postgraduate Student Cancer Research Symposium, the University of Sydney, 16 November 2023.

6. **Y Ni**, SN Lo, AE Cust. Risk of developing a second primary melanoma following diagnosis of a first primary melanoma: A population-based Australian cohort. Oral presentation at the Early Career Researcher Cancer Epidemiology Conference, 23 November 2023, Sydney, Australia (virtual conference).

Chapter4:

7. **Y Ni**, SN Lo, AE Cust. Time trends in the incidence of multiple primary melanomas. Oral presentation at the 2024 Research Retreat of Melanoma Institute Australia, 27 September 2024, North Sydney, Australia.

8. **Y Ni**, SN Lo, AE Cust. Incidence and risk factors for second primary melanoma. Oral presentation at the Australasian Melanoma Conference, 25-26 October 2024, Sydney, Australia.

Chapter5:

9. **Y Ni**, SN Lo, AE Cust. Is Prognosis Worse for People with Multiple Versus Single Primary Melanoma? Oral presentation at the World Congress of Epidemiology, 3-6 September 2021, Melbourne, Australia (virtual conference).

10. **Y Ni**, SN Lo, AE Cust. Is Prognosis Worse for People with Multiple Versus Single Primary Melanoma? Oral presentation at the Sydney Cancer Conference, 9-10 September 2021.

11. **Y Ni**, SN Lo, AE Cust. Prognosis for people with multiple primary melanomas compared with a single primary melanoma. Poster presentation at the Faculty of Medicine and Health HDR Conference, the University of Sydney, 20 July 2022.

Authorship Attribution Statement

I, Yuan Ni (YN), carried out the research presented within this thesis during my PhD candidature from July 2020-April 2024 in the Daffodil Centre and Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney.

I undertook this research under the supervision of my supervisors, Associate Professor Serigne N Lo (SNL) and Professor Anne E Cust (AEC). I received financial support from the Melanoma Institute Australia (Postgraduate Research Scholarship, 2023-2024).

My contribution to the body of work presented in the thesis is demonstrated by my first authorship of four papers. For each of the research papers which have included in this thesis, I contributed to study design, then undertaking data analysis and writing and revising manuscripts. Specific contributions made by me, and all co-authors are detailed below for each chapter.

Chapter 1: Introduction

Yuan Ni (YN) wrote the chapter with input and feedback from Serigne N Lo (SNL) and Anne E Cust (AEC).

Chapter 2:

YN, SNL, and AEC designed the analysis. Caroline G Watts (CGW), Richard Scolyer (RS), Christine Madronio (CM), Bruce K Armstrong (BKA), Graham J Mann (GJM), John F Thompson (JFT), AEC and SNL collected and/or curated the data. YN undertook the data analysis under the supervision of SNL and AEC. YN drafted the first version of the manuscript. All authors edited, critically reviewed, and approved the final manuscript.

Chapter 3:

YN, SNL, AEC, CGW and Alex Varey (AV) designed the analysis. AEC and SNL collected the data. YN undertook the data analysis under the supervision of SNL and AEC. YN drafted the initial version of the manuscript. All authors edited, critically reviewed, and approved the final manuscript.

Chapter 4:

YN, SNL, and AEC, designed the analysis. AEC obtained funding, ethics approval and obtained access to the data. Biostatistician David Espinoza (DE) undertook the data analysis with ongoing communication and feedback from the other co-authors. Kirstie McLoughlin (KM) helped prepare the dataset and gave input into the analytical methodology. YN drafted the initial version of the manuscript. All authors edited, critically reviewed, and approved the final manuscript.

Chapter 5:

YN, SNL, and AEC designed the analysis. CGW, RS, CM, BKA, GJM, JFT, AEC and SNL collected and/or curated the data. YN undertook the data analysis under the supervision of SNL and AEC. YN drafted the first version of the manuscript. All authors critically reviewed and approved the final manuscript.

Chapter 6:

YN wrote the chapter with input and feedback from SNL and AEC.

In addition to the statements above, in the cases where I am not the corresponding author, permission to include the published materials in this thesis has been granted by the corresponding author.

Yuan Ni

April 2024

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Associate Professor Serigne Lo

April 2024

Professor Anne Cust

April 2024

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Chapter 1. Introduction

1. Background

1.1 Skin cancer

Skin cancer is a malignancy occurring from abnormal growth of skin cells. The three main types of skin cancer are melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Skin cancer in fair-skinned populations is mainly caused by ultraviolet (UV) radiation overexposure, responsible for 90-95% all skin cancers in countries such as Australia.[1,2] Skin cancer is a commonly diagnosed tumour in Australia, where more than two thirds of people will be diagnosed with any type of skin cancer in their lifetime.[3,4]

1.1.1 Non-Melanoma Skin Cancer (NMSC)

Keratinocyte cancers, also called non-melanoma skin cancers, are malignant tumours formed from keratinocytes and the most common cancers in Australia.[5] BCC composes approximately 70% of keratinocyte cancers.[3] It starts from the basal cells of the skin and mostly occurs at the body sites that are exposed to more UV radiation, such as head and neck.[6] BCC can manifest in younger populations, but it is more prevalent among people aged over 40 years. The other form of keratinocyte cancers is SCC, constituting approximately 30% of cases. SCC predominantly occurs in people aged over 50 years.[3] SCC begins from the squamous cells of the skin and tends to occur at the body parts which receive the most UV radiation.[6]

An Australian survey in 2002 showed the age-adjusted incidence rate was 1288 per 100,000 population for BCC and 593 per 100,000 population for SCC.[3] The incidence rate for keratinocyte cancers was highest in the group aged over 70 years, and men had a higher incidence rate than women.[3] Although keratinocyte cancers are the most diagnosed cancer in Australia, cancer registries in most states and territories except Tasmania do not collect data on their incidence apart from some rarer types of non-

melanoma skin cancer.[4] Because of the lack of routinely collected data, the incidence rate of keratinocyte cancers is uncertain and has not been updated regularly.[4] The latest estimates of keratinocyte cancer incidence are derived from the number on individuals who have utilised Medicare Australia, the publicly funded universal healthcare system in Australia.[7] There were 1,148,214 medical treatments for keratinocyte cancers covered by Medicare in 2021.[8] In 2022, keratinocyte cancer related mortality was predominately caused by SCCs (rather than BCCs), and there were 791 deaths from keratinocyte cancers in Australia.[9] Age-adjusted mortality from keratinocyte cancer has remained relatively stable over 1971 to 2021, increasing slightly from 1.9 to 2.1 deaths per 100,000 population.[9]

1.1.2 Melanoma

Melanoma is the most fatal type of skin cancer, because it is related to over 75% of mortality associated with skin cancer.[10] Melanoma develops from the unusual growth of melanocytes that produces melanin pigments to give skin its colour (Figure 1). Worldwide, the majority of melanomas are diagnosed in fair-skinned populations of European background, including in Australia, New Zealand, and European and North American countries.[11-13] However, in countries with predominantly darker-skinned populations, the acral subtype of cutaneous melanoma is the most common histological subtype.[14]

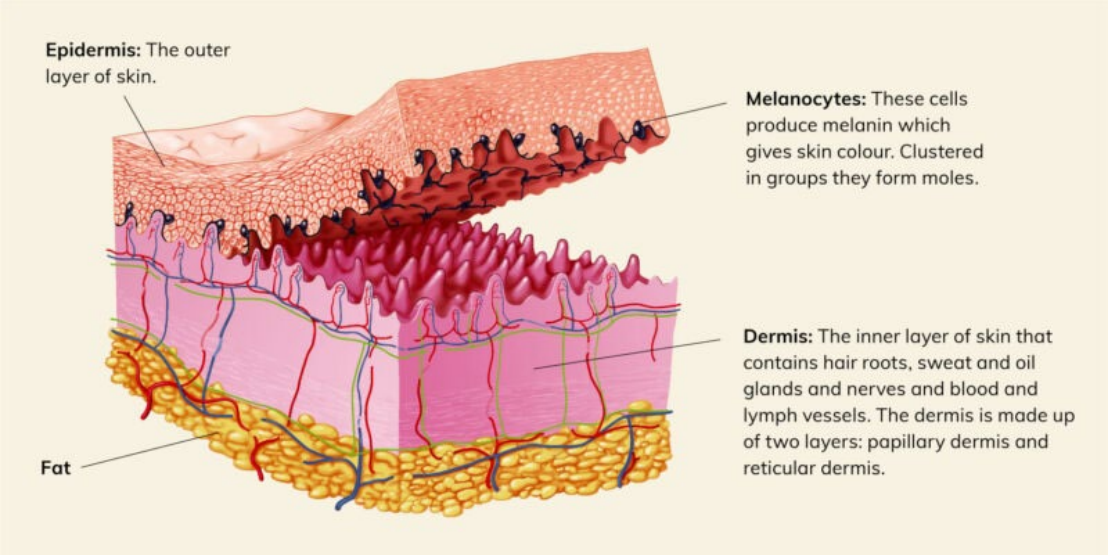

Figure 1. Skin layers.

Source: https://melanoma.org.au/about-melanoma/what-is-melanoma/

Australia (with New Zealand) has the highest age-standardised melanoma incidence rate in the world (36 cases per 100,000 person-years in 2020),[15] and the rate is nearly twice than the region of second highest melanoma incidence (Western Europe, 19 per 100,000 person-years in 2020).[15] Age-adjusted melanoma incidence in Australia has increased from 26.7 cases per 100,000 person-years in 1982 to 57.3 per 100,000 person-years in 2023,[9] with the rate over 16 times higher than the worldwide average incidence rate (3.4 per 100,000 person-years).[16] In Australia, the rising incidence has been identified in both males (from 27.6 to 68.9 per 100,000 person-years from 1982 to 2023) and females (from 26.3 to 47.1 per 100,000 person-years from 1982 to 2023),[9] while the growth in incidence among males is more steep. However, incidence trends over time have depended on age cohorts, with people aged under 30 years experiencing decreased incidence since 1997, stable incidence for people aged 30-60 and increasing rates for the older population, the differences predominantly attributed to the implementation of sun safety initiatives like Slip! Slop! Slap! targeted at younger generation since 1980s.[9,17] Compared to other malignancies, melanoma has a bigger impact on younger people, being the most common cancer affecting 20-39 year-old Australians,[9] and thus has substantial impacts on

working days and years-of-life.[18,19] The rising incidence and low mortality of melanoma have imposed a huge burden on healthcare systems.[20,21] The average treatment cost per individual newly diagnosed with melanoma (regardless of disease stages) in Australia was estimated $11,787 AUD in 2021. Cost varied from $644 AUD for in situ melanoma, to as high as $100,725 AUD for unresectable melanoma stage III/IV.[22] The estimated Australian healthcare costs for cutaneous melanoma were $201 million AUD in 2017, and this was higher after including presumptive melanoma later found to be benign lesions.[23] Melanoma prevention campaigns and other public health strategies have been shown to be cost-effective and provide substantial health benefits.[24,25]

1.2 Melanoma epidemiology

1.2.1 Melanoma mortality in Australia

It was estimated that 17,756 newly diagnosed melanoma cases and 1,440 Australians died from melanoma in 2022.[9] In contrast to an overall increasing trend of incidence rate, there has been a decline in the age-standardised melanoma mortality rate since 2017, dropping from 4.8 to 3.6 per 100,000 persons in 2023.[9] The risk of dying from melanoma began to decline from 2013.[9] In Queensland, data shows the mortality rate decreased 2% annually among men in the 40-59 age group, and the decline was more significant among people aged under 40 years, reaching 3% annually.[26] The reduction in melanoma mortality has been predominantly attributed to new treatments for melanoma, particularly immunotherapies, as well as melanoma prevention programs and increased awareness of early detection.[26]

1.2.2 Prognosis

Key factors that determine the prognosis of cutaneous melanoma include Breslow thickness and ulceration status as the two primary factors, as well as age, sex, body site of lesion, mitotic rate, regression and presence of sentinel lymph node metastases.[27,28] Breslow thickness is the measure of vertical distance between the upper level of the epidermis and the bottom level of the lesion. [29]

Ulceration refers to the absence of an intact epithelium overlying the melanoma,[30] and has been long-confirmed as a pathological factor associated with worse prognosis since 1978 from a large database study reporting its association with elevated risk for death and relapse.[31] Mitotic rate, an indicator of tumour cellular growth, is measured as number of mitoses per mm^2. [32] Higher mitotic rates have been recognised as a predictive factor for poor melanoma-specific prognosis.[32] The definition of regression is an immunological process that results in the partial or complete replacement of the lesion with vascular fibrous tissue.[33] Since melanoma regression was first documented in 1950s, there has been conflicting evidence on how the presence of regression impacts melanoma prognosis. [33]

Together, many of these factors form the American Joint Committee on Cancer (AJCC) staging system.[27] The stage of melanoma is described using the AJCC staging system, an internationally accepted system based on the information from over 17 thousand melanoma patients globally (Table 1.1).[34] According to the current AJCC staging system, the predictors of survival for patients with stages I to III are mitotic rate, Breslow thickness, presence of ulceration and metastatic lymph nodes.[35-37] The 8th edition of the AJCC cancer staging manual for melanoma showed the five-year melanoma-specific survival rates for people with melanoma at stages I, II, and III were 98% , 90% and 77%, respectively.[34] Serum lactate dehydrogenase level (a marker that is inversely associated with survival after cancer diagnosis[38]), the number of distant metastatic sites, and the neutrophil-to-lymphocyte ratio are predictors of prognosis among patients with metastatic disease (stage IV).[27,39 40] The five-year survival of stage IV patients was reported as 29.8%[41] but has been increasing with the availability of new treatments.

1.2.3 Melanoma subtypes

Melanoma is categorised into 9 different subtypes according to unique clinical, histopathological, genomic, and epidemiological characteristics.[14] Superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma are the four main subtypes of melanoma. Superficial spreading melanoma is normally diagnosed at body sites with less solar elastosis (a form of sun damage) such as the back and trunk of younger people, and usually carries mutations in $BRAF^{V600E}$.

Nodular melanoma is a fast-growing lesion presenting as a nodule.[42] Lentigo maligna melanoma is associated with solar elastosis, and arises at head and neck of older people,[14] and it possess *NRAS* or *NF1* mutations.[43,44] Acral lentiginous melanoma is the most common subtype in the Asian and darker-skinned populations. Desmoplastic melanoma is less common than the four subtypes mentioned above and tends to occur in sun-damaged body areas like the head and neck in older people. It is commonly more difficult to diagnose as it usually is skin-coloured or pink (i.e. lacks pigment)

Table 1.1 American Joint Committee on Cancer (AJCC) melanoma TMN staging classification for cutaneous melanoma (8th Edition).[45]

T	**Breslow thickness**	**Ulceration status**
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Melanoma in situ	
T1	≤1.0 mm	a: Without ulceration b: With ulceration
T2	>1.0-2.0 mm	a: Without ulceration b: With ulceration
T3	>2.0-4.0 mm	a: Without ulceration b: With ulceration
T4	>4.0 mm	a: Without ulceration b: With ulceration
N	**No. of metastatic nodes**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes cannot be assessed	No
N0	No reginal metastases detected	No
N1	1 tumour-involved node	a: No b: No c: Yes
N2	2-3 tumour-involved nodes	a: No b: No c: Yes
N3	4+ tumour-involved nodes, microsatellite metastases, or matted nodes, or in transit metastases/satellites with metastatic nodes	a: No b: No c: Yes
M	**Site**	**LDH level**[1]
M0	No distant metastasis	NA[2]
M1a	Distant skin, soft tissue or nonregional lymph node	Not elevated (M1a (0)) Elevated (M1a (1))
M1b	Lung metastasis	Not elevated l (M1b (0)) Elevated (M1b (1))
M1c	All non-CNS[3] visceral cites metastasis	Not elevated (M1c (0)) Elevated (M1c (1))
M1d	All CNS[3] distant metastasis	Not elevated (M1d (0)) Elevated (M1d (1))

[1] LDH, lactate dehydrogenase. [2]Not applicable. [3]CNS, central nervous system.

1.2.4 Risk factors

The main contributing risk factors to Australia experiencing the highest age-adjusted incidence rate of melanoma in the world are the accumulation of year-round high solar ultraviolet radiation,[46,47] and a high percentage of the population of European origin (e.g. with predominantly fair skin).[48,49] Red or fair hair, blue eye colour, poor ability to tan and a propensity to sunburn are also phenotypic factors that are related to increased risk.[49]

There is convincing evidence that UV exposure is an environmental risk factor for developing melanoma,[50,51] and it is estimated that over 90% of melanoma cases are caused by UV exposure in Australia.[2] Ultraviolet A (UVA) (wavelength: 320–400 nm) and ultraviolet B (UVB) (280–320 nm) are two main types of UV radiation affecting melanoma risk; UVA and UVB are able to reach the earth's surface, whereas ultraviolet C (UVC) (200–280 nm) is usually absorbed by the ozone layer.[52] The majority of UV radiation is UVA, which comprises more than 98% of UV radiation reaching the surface of the earth.[53] UVA causes skin ageing and tumorigenesis by the inducement of oxidative DNA damage, [54] and UVA-induced damage has been frequently observed in cutaneous melanoma.[52,55] UVB is associated with direct DNA damage and cell apoptosis by formatting cyclobutene pyrimidine dimers and 6 to 4 photoproducts.[52] Sunburn is the result of UVB-caused DNA damage and has been consistently associated with increased melanoma risk.[52,56] UVA and UVB are usually both generated by indoor tanning, with doses reported to be up to 12 times higher than that from sunlight.[57] Indoor tanning beds are a known risk factor for melanoma and keratinocyte cancers.[58,59]

Apart from UV exposure, other well-established significant risk factors for melanoma include family and personal history of melanoma, common and dysplastic naevi and certain germline mutations.[60-62]

Around 10% of melanomas occur in people who have a family history of the disease.[41] Familial melanomas usually refers to the diagnosis of over three melanomas among closely related individuals in a family.[63] Mutations in the *CDKN2A* and *CDK4* gene are rare but they are associated with up to 40% of familial cases,[64] and it is estimated that more than 50% of people who develop multiple primary

melanoma carry a mutation.[65] People who carry a *CDKN2A* mutation have a substantially increased risk for development of melanoma compared to the general population.[66,67] The onset of melanoma among *CDKN2A* mutation carriers occurs on average about 15 years earlier than general population.[68] In addition to gene inheritance, shared life patterns such as geographical location, UV radiation exposure, and sun-related behaviours among family members are also believed to influence melanoma incidence patterns in families.[63]

Common, low penetrant, genetic factors are also related to melanoma risk in the population. Melanocortin 1 receptor (*MC1R*) gene variants are the most well known of these genetic factors, and very common in Australia. They determine red hair colour and influence skin colour and as such are associated with moderately increased melanoma risk although this varies depending on the actual variant/s that are present.[69,70] There are many other low-penetrant genes contributing to melanoma risk, and the effects of these are often combined into a polygenic risk score reflecting a weighted summary score of an individual's genetic risk.[71] Polygenic risk scores are strongly associated with melanoma, similar in prediction to traditional risk variables.[71,72]

A personal history of non-melanoma skin cancer is strongly associated with increased risk of melanoma. The relative risk of diagnosing a melanoma among individuals diagnosed with squamous cell carcinomas or basal cell carcinoma was reported to range from 4 to 17 compared to those without a previous keratinocyte cancer.[61,73] A personal history of melanoma is associated with an approximately 10-fold increased risk of developing subsequent melanoma,[74] and individuals diagnosed with melanoma are recommended to have ongoing surveillance.[75,76]

Moles are considered both as markers of melanoma risk and as a precursor lesion to some melanomas,[41] as around 50% of melanomas develop from a change in a pre-existing naevus.[77] Moles are benign growths of melanocytes or naevus cells.[78] Common and dysplastic naevi are benign lesions but confer an increased risk for developing melanoma, with a higher number representing higher risk.

It is estimated that people with more than 100 atypical naevi (101-120 naevi) have a seven-fold risk for melanoma compared to people with very few moles (0-15 moles).[60]

1.3 Melanoma prevention

Melanoma prevention strategies are multilevel and primarily encompass both primary and secondary prevention. Primary prevention focuses on reducing excessive UV exposure[79] and modifying sun protection behaviours,[52] whereas secondary prevention focuses on detecting melanoma at an early stage as it is associated with a better prognosis.[52,80]

1.3.1 Primary Prevention

The occurrence of melanoma is attributed to the interactions of genetic factors and UV exposure.[79] Genetic testing and chemoprevention strategies are not widely implemented and are insufficient as population-wide prevention strategies.[79,81] Thus, melanoma prevention focuses predominantly on minimising exposure to UV and improving sun protection behaviours.

Common prevention strategies to reduce UV exposure include physical protection, topical protection and systemic protection.[82] Physical prevention includes using protective clothing (long-sleeved shirts, long pants, and wide-brimmed hats) and sunglasses to prevent or limit exposure from UV radiation[82] and decrease sunburns.[83] Physical UV prevention strategies such as shade structures and tailoring outdoor times are also recommended particularly for outdoor workers.[84] Applying sunscreen as a topical protection has been confirmed to lower the risk of melanoma.[85,86] It is recommended to use sunscreen that is broad-spectrum and water-resistant with a sun protection factor (SPF) 30+, applying 20 minutes before UV exposure, and reapplying every two hours (Figure 2).[87] Given the oxidative stress and reactive oxygen species mediated by UV radiation exposure,[88] systemic administration of antioxidants has also been proposed as a strategy for UV protection.[82]

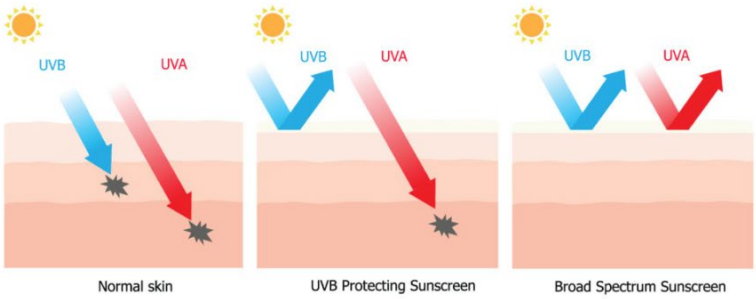

Figure 2. The effect of sunscreen in minimising skin exposure to UV radiation from sunlight.

Source: https://melanomapatients.org.au/preventing-melanoma/prevention/

1.3.2 Secondary Prevention

Early detection of melanoma is the main secondary prevention strategy, to ensure that melanoma is detected at a stage that is more easily treated and associated with a better prognosis. Secondary prevention may also include treatments to prevent disease progression and recurrence - strategies that aim to improve a patient's prognosis by reducing mortality and morbidity associated with a melanoma diagnosis.[27,50,89]

For some other cancers in Australia such as breast, bowel and cervical cancers, organised population screening programs exist in which asymptomatic people meeting the age and sex eligibility criteria are screened without consideration of other personal risk factors. [90] Even though melanoma is a common cancer in Australia, an organised population screening program does not exist[90] due to insufficient high-quality evidence of a reduction in melanoma-specific mortality;[91] instead opportunistic screening is in place as recommended by the Royal Australian College of General Practitioners (RACGP), Cancer Council Australia, and US Preventive Services Task Force.[92-96] Opportunistic screening is usually patient driven and sometimes clinician led and occurs predominantly in primary care in general practice and skin cancer clinics, but also in specialist dermatology settings.[97] Skin self-examination is also recommended for people at high risk of melanoma, as a pathway for individuals to identify suspicious lesions and bring them to the attention of a health professional for further evaluation. In some studies internationally, over 50% of melanoma are found through self-examination[98,99] and this may help to

detect melanoma at an early stage.[100] The RACGP recommends opportunistic screening for people with characteristics associated with high risk of melanoma, such as light skin colour, light hair colour, and atypical moles, and encourages people at high risk of melanoma to undergo self-examination regularly and clinical skin examinations at least annually.[95] Australian clinical practice guidelines recommend that very high risk individuals have a full body clinical skin examination using dermoscopy and photography every six months.[76]

1.4 Melanoma risk prediction models

Current clinical practice guidelines recommend that routine skin examinations be reserved for high risk individuals only.[101] Understanding an individual's personal melanoma risk could lead to more personalised skin screening and surveillances approaches,[45] facilitate detection of melanoma at an early stage and ensure that healthcare resources are more efficiently.[102] Reducing the frequency of skin checks for individuals at low-risk of melanoma may alleviate psychological burden[103] and spare them the anxiety associated with overtreatment and overdiagnosis.

A complex interaction among melanoma risk factors makes communicating melanoma risk to patients difficult.[104,105] Absolute risk prediction can be summarised and communicated as a probability value between 0 (no risk at all) to 100% (certain to develop melanoma).[106] Absolute risk can be communicated for different periods, for example as a remaining lifetime risk or as a 10-year risk. Relative risk can also be communicated, such as "50% higher risk than other people your age and sex", as can a risk category – for example higher than average, average risk or lower than average risk. Risk prediction models comprise a mathematical algorithm based on the combined effects of individual risk factors to estimate the likelihood of an individual experiencing a clinical outcome.[107] Risk prediction models are widely used in research and clinical practice to offer a more personalised management rather than a one-size-fits-all approach.[107] Using personalised prevention and management strategies based on risk prediction models can facilitate the planning of interventional trials and inform decision making processes.[104,108-110] Creating a new risk prediction model necessitates rigorous statistical

methods to ensure its accuracy and validity before translation into clinical practice.[111] The initial requirement for a predictive model is that it must undergo internal validation. Internal validation techniques involve applying procedures to the same dataset from which the prediction model was developed, evaluating its predictive performance, i.e. its ability to distinguish risk levels between individuals who will develop the clinical outcome of interest and those who won't. However, such approaches are prone to yielding optimistic results and may lead to overfitting.[112] The second requirement involves external validation, which aims to assess the predictive model's performance when applied to independent datasets not involved in the model's development to ensure that it is accurate and generalisable to other settings.[113,114]

Given the insufficient evidence of the net benefits for a population-based melanoma screening program, targeted screening program for people at higher risk of melanoma diagnosis may be more feasible and cost-effective and is currently the subject of further research.[102] Risk prediction models for melanoma can assist in identifying a cohort of individuals at high risk of developing melanoma that may be suitable for targeted screening.[115] Communication of personalised risk estimates from a risk prediction model might also encourage people identified as high risk to increase preventative behaviours such as sun protection or skin examinations.[116-119]

1.5 Melanoma treatment

Most melanomas that are diagnosed at an early stage can be treated and cured solely with surgery (wide local excision of skin and subcutaneous tissues around the melanoma).[36,76,120] For melanomas diagnosed at later stages or at a high risk of recurrence, other treatments such as radiation therapy, targeted therapy, and immunotherapy may be required.[14] A sentinel lymph node biopsy is recommended for melanomas above a certain thickness or with a higher risk of recurrence, to check whether melanoma has spread to lymph nodes (stage III melanoma).[6] Advanced melanoma (stage IV) refers to melanoma that has metastasized to distant lymph nodes or other organs and tissues.[6] Immunotherapy enables the patients' immune system to recognise and attack cancer cells.[121] Targeted

therapy targets specific molecules in cancer cells to stop its growth; examples include BRAF inhibitors and MEK inhibitors.[121] Radiation therapy aims to kill or damage melanoma cells using radiation. In some cases, it is also used to prevent recurrence of melanoma after surgery or to relieve pain caused by advanced melanoma.[6]

1.6 Definition of multiple primary melanomas

Multiple primary melanomas are defined as that two or more melanomas occur at the same person. The phenomenon that individuals may develop multiple primary melanomas is not new and already in 1952 Pack described the occurrence of more than one primary melanoma in a single person. [122] From the perspective of epidemiology, lesions presented at different body sites and/or different histological codes are considered multiple primaries. The criteria of multiple primary cancers have changed over time, and the current understandings of multiple primary cancers are based on rules provided by the Surveillance, Epidemiology, and End Results Program (SEER), mainly used in North American countries or the International Agency for Research on Cancer (IARC), more internationally used criteria.[123] In this PhD thesis, we defined multiple primary melanomas as the people with new primary melanoma diagnosis after three months of first primary melanoma diagnosis.

Early detection of melanoma is associated with better survival rates,[124] and the prevalence of melanoma survivors is projected to increase.[125] Yet, melanoma survivors face an average 10-fold increased risk of developing another primary melanoma compared to the general population, regardless of the invasiveness of the initial melanoma, putting them at an increased risk of subsequent primary malignancies, especially melanomas.[125,126] The incidence of multiple primary melanomas is reported to be in the range of 1.1-20.4%. [127,128] A literature review showed that trunk was the most common anatomical site, and superficial spreading melanoma subtype in both first and second primary melanoma.[129] In terms of Breslow thickness, subsequent melanomas tend to be thinner than first primary melanoma. The mean number of primary melanomas is reported to be in

the range of 2.1-2.8, and the highest number of subsequent melanomas was documented in the US. [130]

1.7 Risk of multiple primary melanomas

In a recent comprehensive meta-analysis that considered all risk factors associated with the development of subsequent primary melanoma, Smith et al showed that an individual's risk depends on independent risk factors including *CDKN2A* mutation, high naevus count, increasing age, atypical naevus, moderate naevus count, male sex, a family history of melanoma, lighter skin, initial head or neck lesions, inadequate sun protection, lentigo maligna subtype and other subtypes.[125] For people who developed a second primary melanoma in an Australian population-based study, the median time to diagnosis between the first and second melanoma was 3.7 years, and the time interval declined with each new primary melanoma, decreasing to 0.7 years after the sixth melanoma. [103]

1.8 Risk of multiple primary cancers

Melanoma patients also have increased risk of cancers other than skin cancer. A previous meta-analysis found the overall risk (provided as a standardised incidence ratio, similar to relative risk) of developing a second primary cancer among melanoma survivors was 1.5 (95% CI 1.3–1.9) including cancers at other sites including soft issue, non-melanoma skin cancer, prostate, female breast, colon, and kidney.[131] An increased risk of other primary cancers are attributed to the simultaneous occurrence of different risk factors, including genetic risk factors.[131]

1.9 Thesis outline

Rationale

Australian and international clinical practice guidelines lack sufficient information concerning optimal screening and surveillance for people with a single or multiple primary melanoma.[132] Most guidelines and AJCC staging criteria are also based on people with single primary melanoma, without considering

the potential impacts of subsequent primary melanomas and other cancer diagnoses.[133] Compared to knowledge about single primary melanoma, relatively little is known about the incidence and risk factors for multiple primary melanoma and its impact on prognosis and risk of other cancers.

Aim and objectives

The aim of this PhD thesis was to increase knowledge about the epidemiology of multiple primary melanomas, to inform education, prevention, and clinical management particularly in Australia. The specific objectives were to:

(1) Describe the characteristics and prognosis (overall survival and melanoma-specific survival) of people with single and multiple primary melanomas.
(2) Investigate risk factors for development of a second primary melanoma.
(3) Examine the incidence and risk of developing a second primary melanoma or other type of cancer after a first primary melanoma diagnosis.
(4) Examine the incidence trends of multiple primary melanomas over time.

To address these objectives, I analysed population-based Australian data.

Thesis outline

Chapter 1 is an introduction to the thesis and provides an overview of skin cancer, specifically focused on melanoma. It covers various aspects including the epidemiology of melanoma including prevention and treatment strategies and risk factors.

Chapter 2 is entitled "*Risk of second primary in situ and invasive melanoma in an NSW population-based cohort:2006-2018*". This chapter used data from the Melanoma Patterns of Care study to estimate absolute risk and risk factors for developing a second primary melanoma. The results indicated that male sex, older age, high naevus count and body site are risk factors associated with risk of second primary melanoma. Patients with these factors could be targeted for additional surveillance

or preventative strategies following a first melanoma diagnosis. This manuscript was published in the *British Journal of Dermatology*.

Chapter 3 is entitled "*Absolute Risk of Developing a Second Primary Cancer After a First Primary invasive or in situ Melanoma: An Australian Population-Based Cohort Study*". This chapter used a NSW population-based cohort from the Enduring Cancer Data Linkage (CanDle) Initiative. The incidence of a second primary melanoma or other type of second primary cancer (not melanoma) was depicted graphically and numerically. I also investigated risk factors associated with the development of second primary cancers. The findings showed that the most commonly diagnosed second cancers were melanoma (either invasive or in situ), followed by prostate cancer, breast cancer and colon cancer.

Chapter 4 is entitled "*Time trends in the incidence of multiple primary melanomas in Australia*". This chapter used data from seven Australian cancer registries to investigate time trends in the incidence of subsequent primary melanoma. The results revealed a rising incidence of subsequent primary melanoma since 1982 for all demographic groups, although males aged over 55 years experienced the highest incidence. The increasing trend in subsequent primary melanoma incidence is reflective of the rising incidence pattern of first primary melanomas in Australia.

Chapter 5 is entitled "*Factors associated with 10-year overall and melanoma-specific mortality for people with multiple primary melanomas compared with a single primary melanoma*". This chapter used data from the Melanoma Patterns of Care study, based on cancer registry records and questionnaires obtained from health professionals who managed the care of all patients diagnosed with melanoma and notified to the NSW cancer registry between 23 October 2006 and 22 October 2007. This study aimed to compare the survival for patients diagnosed with a single versus multiple primary melanomas.

The results showed similar melanoma-specific mortality rates for patients diagnosed with a single primary melanoma and those diagnosed with multiple primary melanomas. The analysis revealed no statistically significant differences with or without the inclusion of potential confounding factors such

as sex, age and other histopathological parameters. This manuscript was published in the *Journal of the American Academy of Dermatology*.

Chapter 6 presents a discussion of the key findings from the thesis, describes the strengths and limitations, future directions and conclusions.

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Chapter 2: Risk of second primary in situ and invasive melanoma in an NSW population-based cohort:2006-2018

People diagnosed with first primary melanoma are at an elevated risk of developing subsequent primary melanomas compared to the general population. This chapter presents the findings from an analysis that examined risk factors and absolute risk of developing a second primary melanoma after a first primary melanoma. It contributes to evidence on the associations between the development of subsequent primary melanomas with demographic, histopathological and phenotypic factors and can be used to inform melanoma patients and clinicians regarding the ongoing risk of developing a second primary melanomas. The manuscript was published in the British Journal of Dermatology (BJD) as a research letter.

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Risk of developing a second primary melanoma after a first primary melanoma in a population-based Australian cohort

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Dear Editor, People diagnosed with a primary melanoma have a higher risk of developing subsequent primary melanomas compared with the general population; however, individual risk varies substantially.[1] A better understanding of the risk factors and absolute risk of developing a subsequent primary melanoma among individuals with a previous melanoma is important to guide follow-up recommendations for skin surveillance.[2] Using a population-based cohort with long follow-up, we aimed to identify risk factors and absolute risk for developing a second primary melanoma.

The Melanoma Patterns of Care study is a population-based observational study of clinicians' reported management of patients diagnosed with a primary invasive or (for a subset) *in situ* melanoma between October 2006 and October 2007 (baseline) conducted in New South Wales (NSW), Australia. Clinical and follow-up information, including subsequent primary melanomas and death, were collated using data linkage with cancer and death registries up to 2018. For this analysis, we excluded patients with a history of melanoma prior to baseline. Follow-up for each participant was calculated from the diagnosis of first melanoma until development of a second melanoma, death, or the end of 2018 (mean follow-up 9.5 years, range 0–14). Comprehensive details on the study design, methods and ethics approval have been published elsewhere.[3] Owing to ethical restriction, the data that support the findings of this study are not available publicly (interested people may contact A.E.C. for potential collaborations). The NSW Population & Health Services Research Ethics Committee approved this study (AU RED Reference: HREC/17/CIPHS/40; Cancer Institute NSW Reference: 2017/HRE1004).

A cohort of 3508 patients (3108 with a first invasive melanoma and 400 with a first *in situ* melanoma) was analysed. Cox regression models were used to evaluate potential risk factors associated with the development of a second primary invasive or *in situ* melanoma. Multivariable models included all factors with P-values < 0.2 from the univariable analyses. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) were reported.

During follow-up, 579 patients (16.5%) developed a second primary melanoma (294 *in situ*, 285 invasive). The median interval between diagnosis of a first and second melanoma was 3.0 years (interquartile range 0.7–5.7). The mean absolute risk of developing a second primary melanoma after baseline was 4.6% (SD 20.9%) within 1 year, 6.6% (SD 24.9%) within 2 years, 11.3% (SD 31.6%) within 5 years and 16.4% (SD 37.1%) within 10 years. Of the patients diagnosed with a second primary melanoma within 10 years, 27.7% were diagnosed within 1 year, 40.7% within 1.1–5.0 years and 31.6% within 5.1–10.0 years.

Risk factors for developing a second primary melanoma are shown in Table 1. In a multivariable model, factors associated with higher risk of developing a second primary melanoma were male sex, older age, high naevus count and body site. Factors that were not found in this study to be independently associated with risk of developing a second primary melanoma included socioeconomic status (based on location of residence), geographical location, Breslow thickness, melanoma subtype, ulceration, regression and mitotic rate. There was no statistically significant interaction between body site and melanoma subtype ($P = 0.46$).

Our findings of older age, male sex and high naevus count as risk factors for subsequent melanomas are consistent with previous studies.[1,2,4] Breslow thickness was not related to risk of developing a second melanoma, which is also similar to previous studies.[1,5] Although family history of melanoma in a blood relative was a risk factor, the statistical significance seems to be driven by the risk difference between people

Table 1 Cox proportional hazard model estimates of risk of developing a second primary melanoma after diagnosis of a first primary melanoma

Characteristic	*n* (%)	Univariable		Multivariable	
		HR (95% CI)	*P*-values	HR (95% CI)	*P*-values
Sex					
Female	1386 (39.5)	1.00 (Ref.)	< 0.001	1.00 (Ref.)	< 0.001
Male	2122 (60.5)	1.73 (1.45–2.07)		1.62 (1.34–1.95)	
Age (5-year unit)					
Age	3508 (100.0)	1.13 (1.10–1.17)	< 0.001	1.13 (1.09–1.16)	< 0.001
Socioeconomic status[a]					
Quintile 1	304 (8.7)	1.00 (Ref.)	0.236	N/A	N/A
Quintile 2	534 (15.2)	0.95 (0.66–1.36)			
Quintile 3	1101 (31.4)	1.07 (0.77–1.47)			
Quintile 4	661 (18.8)	0.91 (0.64–1.29)			
Quintile 5	908 (25.9)	1.18 (0.86–1.64)			
Geographical location[b]					
Major cities	1480 (42.2)	1.00 (Ref.)	0.534	N/A	N/A
Inner regional	1426 (40.6)	0.91 (0.76–1.08)			
Outer regional	574 (16.4)	0.85 (0.67–1.09)			
Remote	28 (0.8)	1.04 (0.43–2.51)			
Family history					
Absent	1623 (46.3)	1.00 (Ref.)	< 0.001	1.00 (Ref.)	0.007
Present	192 (5.5)	1.15 (0.80–1.66)		1.38 (0.95–2.00)	
Unknown	1693 (48.2)	1.36 (1.15–1.61)		1.39 (1.12–1.73)	
High naevus count					
Absent	1538 (43.8)	1.00 (Ref.)	0.024	1.00 (Ref.)	0.006
Present	467 (13.3)	1.71 (1.42–2.04)		1.47 (1.15–1.87)	
Unknown	1503 (42.9)	1.29 (1.11–1.48)		1.02 (0.81–1.27)	
Breslow thickness (mm)					
In situ (0)	398 (11.3)	1.00 (Ref.)	0.262	N/A	N/A
0.1–0.8	1588 (45.3)	1.21 (0.92–1.58)			
0.9–1.0	231 (6.6)	0.91 (0.60–1.39)			
1.1–2.0	574 (16.4)	1.13 (0.82–1.55)			
2.1–4.0	370 (10.5)	1.15 (0.80–1.65)			
> 4.1	231 (6.6)	1.16 (0.74–1.83)			
Missing	116 (3.3)	0.42 (0.15–1.14)			
Body site					
Head and neck	690 (19.7)	1.00 (Ref.)	0.055	1.00 (Ref.)	0.019
Trunk	1196 (34.1)	1.18 (0.94–1.49)		1.32 (1.03–1.70)	
Upper limbs	864 (24.6)	1.14 (0.89–1.46)		1.45 (1.11–1.88)	
Lower limbs	652 (18.6)	0.91 (0.69–1.20)		1.30 (0.97–1.75)	
Unknown	106 (3.0)	0.37 (0.12–1.16)		0.40 (0.12–1.27)	
Melanoma subtype					
SSM	1634 (46.6)	1.00 (Ref.)	0.009	1.00 (Ref.)	0.165
NLM	440 (12.5)	1.02 (0.77–1.35)		0.98 (0.74–1.31)	
ALM	458 (13.1)	1.48 (1.18–1.86)		1.28 (1.00–1.64)	
Other	218 (6.2)	0.98 (0.68–1.42)		0.89 (0.61–1.29)	
Unknown	758 (21.6)	0.97 (0.78–1.21)		0.92 (0.73–1.16)	
Ulceration					
Absent	2365 (67.4)	1.00 (Ref.)	0.912	N/A	N/A
Present	403 (11.5)	1.06 (0.81–1.40)			
Missing	740 (21.1)	1.01 (0.82–1.24)			
Regression					
Absent	1178 (33.6)	1.00 (Ref.)	0.005	1.00 (Ref.)	0.193
Present	1217 (34.7)	1.40 (1.14–1.71)		1.20 (0.97–1.47)	
Missing	1113 (31.7)	1.22 (0.99–1.51)		1.19 (0.95–1.49)	
Mitotic rate (per mm^2)					
< 1	1022 (29.2)	1.00 (Ref.)	0.203	N/A	N/A
1–2	664 (18.9)	0.86 (0.67–1.11)			
3–10	524 (14.9)	1.02 (0.78–1.33)			
> 10	140 (4.0)	1.05 (0.65–1.71)			
Missing	1158 (33.0)	1.16 (0.95–1.41)			

ALM, acral lentiginous melanoma; CI, confidence interval; HR, hazard ratio; N/A, not applicable; NLM, nodular melanoma; SSM, superficial spreading melanoma. Missing/unknown categories were included for some variables to keep the sample size consistent between models. *P*-values are Wald type statistics derived from multivariable Cox regression. [a]Socioeconomic status: quintile 1 (most disadvantaged), quintile 5 (least disadvantaged). [b]Geographical location is based on a remoteness area variable that classifies people as living in rural or urban areas based on their residential postcode.

with unknown family history and those without family history. In a previous population-based study from NSW that recruited patients between 2000 and 2003,[1] first melanoma diagnosis on the head or neck (generally associated with high cumulative sun exposure)[5] or the trunk was associated with higher risk of a second melanoma, whereas our study found that the trunk and upper limbs were associated with higher risk. While the previous NSW study identified differences in risk by melanoma subtype, our study did not find subtype to be an independent risk factor for second primary melanoma.[1] Our estimates of absolute risk of developing a second primary invasive or *in situ* melanoma (4.6%, 11.3% and 16.4% after 1, 5 and 10 years, respectively) in this study are higher than those in the previous NSW study (3.5%, 8.0% and 13.1%, respectively) and in a meta-analysis by van der Leest *et al.*[6] (2.4%, 3.5% and 5.3%, respectively) and may reflect increases over time in opportunistic skin checks[7] and melanoma incidence, particularly melanoma *in situ* and in older age groups.[8] The median time to diagnosis of a second primary melanoma was also slightly shorter in this study (3.0 vs. 3.7 years).[1] Our study included the following limitations: not all known risk factors were measured, e.g. hair colour,[1,4] dysplastic naevi[4] and genetic factors;[1] risk factors were recorded at one time-point only; and there were substantial missing data for some variables. Strengths of our study include the comprehensive set of histopathological and sociodemographic variables analysed, large sample size, population-based design and long follow-up. While all people who develop a melanoma are at higher risk of a new primary melanoma compared with the general population, patients with melanoma who have characteristics such as male sex, older age, high naevus count, or melanoma on the trunk or upper limbs have a substantially higher risk of subsequent melanoma and should be more intensively monitored.

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Supporting Information

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

File S1 Full list of affiliations.

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Chapter 3: Absolute Risk of Developing a Second Primary Cancer After a First Primary invasive or in situ Melanoma: An Australian Population-Based Cohort Study

This chapter reports the findings from an analysis that identified risk of developing a second primary melanoma and other types of second primary cancers after a first primary melanoma. This chapter emphasises that history of melanoma is a risk factor for developing second malignancies, and people diagnosed with melanomas need to be aware of the risk of subsequent malignancies during follow-up. The manuscript is currently under review by the American Journal of Epidemiology. Supplementary materials for this publication are in Appendix D.

Chapter 3 is formatted as an original research paper:

Ni Y, Watts CG, Varey AHR, Cust AE, and Lo SN. "Absolute Risk of Developing a Second Primary Cancer After a First Primary invasive or in situ Melanoma: An Australian Population-Based Cohort Study."

Absolute Risk of Developing a Second Primary Cancer After a First Primary invasive or in situ Melanoma: An Australian Population-Based Cohort Study

Abstract

***Background**:* Understanding the risk of developing a second primary cancer is important to guide patient surveillance and education. We aimed to examine cumulative incidence and factors associated with development of a second primary cancer (melanoma versus other) after diagnosis of a first primary melanoma.

***Methods**:* We analysed a population-based study cohort of 154,695 people diagnosed with a first primary invasive or in situ melanoma in the state of New South Wales, Australia, between 1982-2019. The cohort was followed for future cancer incidence and vital status for a median of 7.0 years. We used Fine-Gray regression models to account for competing risks and death.

***Results**:* After a first primary melanoma, 23.7% developed a second primary cancer, including 12.7% who developed a second primary invasive or in situ melanoma (mean 5-year risk: 7.6%). The next most common second primary cancer types were prostate, breast and colon cancers, with mean 5-year risks after the initial melanoma diagnosis of 1.6% (5.0% male-specific incidence), 0.7% (2.8% female-specific incidence), and 0.6%, respectively. People whose first primary melanoma was in situ had a similar risk of other types of second cancers (10-year risk: 10.1%) compared to those whose first primary melanoma was invasive (10-year risk: 10.2%) but a higher incidence of a second primary melanoma (14.1% and 11.3% at 10-years, respectively).

***Conclusions**:* The most common second primary cancer to be diagnosed among people with a first primary melanoma is another primary melanoma (invasive or in situ), followed by prostate cancer, breast cancer and colon cancer. Our study demonstrated a first primary melanoma diagnosis is associated with developing subsequent cancers. For people with a first primary melanoma, the findings will help to inform them not only about melanoma recurrence but also the risk of being diagnosed with other types of cancers.

Introduction

The rising incidence of cutaneous melanoma in fair-skinned populations of European descent is well-documented.[15,47] Although most people who develop a melanoma have a very good prognosis,[27] they have a substantially elevated risk of developing subsequent primary melanoma.[125,134,135] A higher risk of other types of second primary cancers has also been reported, including higher risks of developing soft tissue sarcoma, non-Hodgkin lymphoma (NHL), kidney, prostate, and breast cancers.[131,136-141] A better understanding of risk of subsequent primary melanoma and other types of cancers is important to guide patient surveillance and education.[142]

Most studies that have assessed risk of subsequent melanoma and other malignancies have applied a cause-specific approach using Cox regression models, censoring death but ignoring the development of other types of cancers. Previous population-based studies have typically reported standardised incidence ratios (SIR) to describe associations between the first and second malignancies, however few studies have reported absolute risks, which can be easier for patients to understand. [136,143,144] Here, we address these limitations in a study that aimed to investigate the absolute risk of developing a second primary melanoma or other types of

cancer (e.g. breast, prostate, colorectal, lung, other) while accounting for competing risks of death and development of different types of second primary cancers. We also examined demographic and histopathological risk factors associated with a development of a second primary melanoma.

Methods

Study population

We used data from the Enduring Cancer Data Linkage (CanDLe), a linked cancer dataset led by the Cancer Institute NSW and supported by the NSW Ministry of Health. Our study analysis protocol was approved by the NSW Population & Health Services Research Ethics Committee. The CanDLe cohort includes people diagnosed with cancer in NSW identified via the NSW Cancer Registry, linked with the NSW Registry of Births Deaths and Marriages Death Registrations and the Cause of Death Unit Record File held by the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence. Data linkage was conducted by the Centre for Health Record Linkage. Our analysis dataset consisted of people aged 18 years or more with a diagnosis of in situ or invasive primary melanoma between 1982 until 2019 and without a recorded personal history of another cancer (except non-melanoma skin cancer) at the date of the first melanoma diagnosis. Data for in situ melanomas were only available since 2002. People aged under 18 years is not in the scope of analysis according to analysis protocol.

Exposure and outcome variables

People diagnosed with a first primary melanoma in the NSW Cancer Registry were identified by ICD-O-3 codes along with behaviour codes (in situ, invasive). The data collected at the

time of the first primary diagnosis included socio-demographic variables (sex, age, residence-based socio-economic status using the Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD)[145]), and histopathological features (body site, histological subtype, and Breslow thickness). During the follow-up period in the registry database, information on subsequent primary cancers (ICD-O-3 codes, date of diagnosis) and vital status (if died and date of death) were also collected. Common non-melanoma skin cancers were not included as they were not routinely recorded in the cancer registry. Some people may occur multiple first primary melanomas on the same day, however, we only selected one primary melanoma as the index lesion for first primary melanoma.

Statistical Analysis

Socio-demographic variables and histopathological features from the first primary melanoma were summarised for the entire cohort and also stratified by the outcome status at the end of the follow-up period, i.e. by type of second cancer that an individual developed (melanoma, colon, breast, prostate, lung, other), died (before developing a second primary cancer), or single primary melanoma (did not die nor develop a second primary cancer). Differences between groups were assessed using the Wilcoxon rank test for continuous variables and chi-square tests for categorical variables.

The main outcome of interest in this analysis was the time to second primary cancer, including second primary melanoma and other types of cancer. For melanoma, we analysed invasive and in situ melanomas combined and separately. Overall survival (OS), Melanoma-specific survival (MSS) and Cancer-specific survival (CSS) for the entire cohort were considered as secondary outcomes. Follow-up time was calculated from the date of the first primary

melanoma diagnosis until the date of the second primary cancer (melanoma or other type), or the date of death, or December 31, 2019, whichever occurred first.

The standard approach to survival analysis for cancer risk is based on cause-specific methods that focus on one event of interest while treating other events as independent censoring. For example, when the outcome of interest is second primary melanoma, occurrences of second other cancer types are disregarded, and individuals who died before developing a second primary are censored.[146,147] These intermediate cancers may influence survival outcomes, and their omission could lead to biased analyses. Moreover, since death precludes the occurrence of a second primary melanoma, standard analyses employing Kaplan-Meier methods and Cox proportional hazard models may yield biased results particularly for older individuals,[147] as the proportion of individuals who died without experiencing a second cancer is >10%. To minimise this bias, we used competing risk methods, which considered different types of second primary cancers and death as competing events.

Cumulative incidence function curves were used to graphically describe the incidence of second primary cancers, separately for melanoma and other cancer types, and presented for the whole cohort as well as stratified by invasiveness of the first melanoma, sex, and age. The cumulative incidence rates for each outcome at 10-years and 20-years were derived from the cumulative incidence function and accounted for competing events. Subgroup analysis of the cumulative incidence of second melanoma compared to other second cancers was performed using the following calendar year periods: 1982-1991, 1992-2001, 2002-2011, and 2012-2019. This analysis aimed to investigate potential melanoma overdiagnosis in individuals with a first primary melanoma.

Sociodemographic and histopathological factors from the first primary melanoma were examined for associations with the development of a second primary melanoma using Fine-Gray hazard models;[148] these results were not presented for development of other second primary cancer types as histopathological factors were less relevant to risk of other types of second cancers. Fine-Gray subdistribution hazard models describe as a cumulative incidence function model, which considered competing events.[149] Univariable and multivariable subdistribution hazard ratios and 95% confidence intervals (CIs) for risk of a second primary melanoma were derived for the whole cohort and also separately for those who had in situ melanoma as the first primary cancer All available variables were considered a potential confounder and included in both the univariable and multivariable models. A single imputation method was applied for the missing variable by creating an "unknown" category for missing cases.[150] Absolute risks of second primary melanoma and other types of cancers were calculated from standard Cox proportional hazards models. The figures were drawn using R version 4.2.3 (R Core Team, Vienna, Austria) and the Fine-Gray regression models were performed using SAS 9.4 (SAS Institute Inc). All statistical tests were two-sided with a p-value <0.05 considered statistically significant.

Results

Study cohort

A total of 154,695 people with a diagnosis of single primary melanoma were included in the analysis dataset (Table 1). The median age at diagnosis of the first melanoma was 62 years (interquartile range: 50-73) and 56.1% were male. Some differences in patient characteristics between calendar year periods were observed. The proportion of males with a first primary

melanoma was higher across all diagnosis year groups. The mean age increased as the diagnosis periods advanced. Additionally, the mean Breslow thickness was thinner in patients diagnosed in more recent periods (Table S1). A total of 36,590 (23.7%) individuals developed a second primary cancer over the median 7 years of follow-up, including 12.7% who developed a second primary invasive or in situ melanoma. Of the 36,590 second primary cancers, 19,708 (53.9%) were melanoma, 4,380 (12.0%) prostate cancer, 1,933 (5.3%) breast cancer, 1658 (4.5%) colon cancer, and 1461 (4.0%) lung cancer and 7,450 (20.4%) other types of cancers. Additionally, 20,058 individuals (13.0%) died before experiencing a second primary cancer.

Cumulative incidence

The mean absolute risk of developing a second primary invasive or in situ melanoma within 5-years was 7.6% (95%CI 7.5%-7.8%), of which 4.1% (95%CI 4.0%-4.2%) for a second primary in situ melanoma and 3.5% (95%CI 3.4%-3.6%) for a second primary invasive melanoma. The next most common second primary cancer types were prostate, breast and colon cancers, with mean 5-year risks after the initial melanoma diagnosis of 1.6% (95% CI 1.5%-1.7%; 5.0% male-specific incidence), 0.7% (95% CI 0.6%-0.7%; 2.8% female-specific incidence), 0.6% (95% CI 0.5%-0.7%), respectively.

Cumulative incidences curves of second primary cancer are displayed in the Figures, showing cumulative risk of developing a second primary melanoma (invasive melanoma and in situ melanoma presented combined and separately) and second primary cancers that were other cancer types (combined as one group). Figure 1 shows that after an initial diagnosis of invasive or in situ melanoma, an individual has, on average, a higher risk of developing a second primary melanoma (12.0% at 10 years and 18.0% at 20 years) than a different type of cancer primary diagnosis (8.4% at 10 years and 13.6% at 20 years). This pattern was the

same for males (Figure S1) and females (Figure S2) although males had overall higher second cancer incidence than females. However, the pattern differed when stratified by age (Figures S3 to S7), with the risk of a second melanoma almost double the risk of other types of second cancers at younger ages <50 years (Figures S3 and S4), the incidence gap for second primary melanoma and other types of cancers narrowing at ages 50-74 years (Figures S5 and S6) and eventually reversed in those aged ≥75 years (Figure S7). The 20-year absolute incidence of a second cancer as melanoma (invasive or in situ) was 5.7% in individuals aged 18-24 years, 12.7% in those aged 25-49 years, 21.5% in those aged 50-64 years, 21.9% in individuals aged 65-74 years, and 15.3% in those aged 75 years and older (Figures S3-S7).

After a first primary invasive or in situ melanoma, there was a slightly higher risk of developing a second in situ melanoma (6.4% at 10-years) than a second invasive melanoma (5.6% at 10 years) (Figure 1). The higher incidence of second primary in situ melanoma than second primary invasive melanoma was more accentuated for females (Figure S2) and at ages 50-74 years (Figures S5 and S6) but a second primary invasive melanoma was more common than a second primary in situ melanoma in the oldest age-group ≥75 years (Figure S7).

When comparing second primary cancer incidence for people whose first primary melanoma was in situ (Figure 3) versus invasive (Figure 2), we found a similar cumulative incidence of other (non-melanoma) types of second cancers (8.6% and 8.4% at 10-years, respectively) but a higher incidence of a second primary melanoma (14.1% and 11.3% at 10-years, respectively). This difference in second primary melanoma incidence was because individuals whose first primary melanoma was in situ were more likely to develop a second primary in situ melanoma (8.9% at 10-years) than those whose first primary melanoma was invasive (5.1% at 10-years). Conversely, cumulative incidence of a second primary invasive

melanoma was slightly higher for those whose first primary melanoma was invasive (6.1% at 10-years) than those whose first primary melanoma was in situ (5.2% at 10-years).

The subgroup analysis by calendar year period showed that the incidence of second melanoma was lower than the incidence of other second cancers in people diagnosed with a first primary melanoma during 1982-1991 (Figure 4 A). The incidences of second melanoma and other second cancers were similar during the period 1992-2001 (Figure 4 B). However, after 2002, the incidence of second primary melanoma was significantly higher than that of other second cancers (Figures 4 C-D). Similar pattern was observed when focusing on patients diagnosed with first invasive melanoma (Figures 5 A-D) or first in situ melanoma (Figures S8-9 for the period 2002-2011 and 2012-2019 where in situ data were recorded in the registry database). Furthermore, among people who experienced a second cancer, the proportion of melanoma cases tended to increase over time, in contrast to other types of cancer, which appeared to remain relatively stable across the years when the primary melanoma was diagnosed (Table S1).

Secondary outcomes

The overall survival rates were 81.4% (95% CI 81.2% – 81.6%) and 69.8% (95% CI 69.5%- 70.2%) at 10- and 20-year respectively (Figure S10). Whilst for MSS and CSS, the 20-year rates were 99.9% (95% CI 99.9% – 99.9%) and 85.3% (95% CI 85.1%– 85.6%) respectively (Figures S11 and S12).

Fine-Gray regression models

In both the univariable and multivariable analyses, older age, male sex, lentigo maligna melanoma subtype, and higher socioeconomic status, were associated with a higher risk of developing second primary melanoma (Table 2). Conversely, individuals whose first melanoma was an acral lentiginous subtype, or located on their head and neck or lower limbs, or with Breslow thickness >2.0, had a lower risk of developing second primary melanoma. Results were similar when the analysis was restricted to those whose first

primary melanoma diagnosis was in situ, although body site and melanoma subtype were no longer statistically significant in the multivariable model.

Discussion

People who have been diagnosed with a first primary cancer are often concerned about their risk of developing subsequent primary cancers.[151] This is particularly relevant for people diagnosed with melanoma, because of high (>90%) survival rates and many of them are younger than is typical for most cancers and so they have a long time to develop another primary cancer.[152] Our study showed that nearly a quarter (23.7%) of individuals who had a first primary melanoma were diagnosed with a second primary cancer over a median follow-up of 7 years, and just over half of these second primary cancers were melanomas. The next most common cancers were prostate, breast, colon, and lung cancers. Population subgroups at higher risk of second cancers included males and those aged 65-74 years. People at younger ages had a lower 10-year risk of second primary cancers but melanomas represented a larger fraction of those second cancers.

It is well known that people who are diagnosed with a first primary melanoma have a substantially elevated risk of developing subsequent primary melanomas. [27]The 5-year cumulative risk of developing a second primary melanoma was 7.6% in our study, which is similar to previous research from the U.S. including the Surveillance, Epidemiology and End Results (SEER) database that reported 8.0%,[153] and Hwa et al who reported 8.7%,[154] but higher than a U.S. study by Jones et al (5.6%),[155] a meta-analysis (3.5%),[156] and a Dutch study (3.7%).[157] The risks reported in our study would have been higher if we had not accounted for the competing risks of other second cancers and deaths. To the best of our knowledge, other studies that assessed the risk of second primary melanoma did not account for competing risks of other types of cancers and death.

An Italian study found the most frequent other cancer types of second primary cancer after a first primary melanoma were breast, prostate and lung cancers.[158] A U.S. study using SEER data showed that prostate, breast and lung cancers were most common other cancer types after melanoma.[159] In our study, colon cancer was more common than lung cancer as a second cancer. Australia has organised screening programs in place for breast and colon cancers, opportunistic screening for prostate cancer, and a lung cancer screening program targeting high-risk individuals will soon be established.

We found that overall, cumulative incidence of second primary in situ melanoma was higher than cumulative incidence of second primary invasive melanoma, which is consistent with previous studies[140,160-162] and likely reflects increased skin surveillance following an initial melanoma diagnosis. We also observed that it was more common for people diagnosed with a first in situ melanoma to develop a second primary melanoma – in particular, a second in situ melanoma. This is consistent with other reports in the U.S.[163] and Queensland, Australia,[127] that found having in situ melanomas in a cohort enhanced the risk of subsequent primary melanomas. In situ melanomas are more commonly diagnosed in people having routine skin checks,[97] and the higher incidence of in situ melanoma would also reflect increased overdiagnosis, i.e. diagnosis of melanomas that would not have caused any harm if left undetected and untreated.[164,165]

Several sociodemographic and histopathological risk factors from the first primary melanoma were associated with risk of a second primary melanoma, including age, sex, melanoma subtype, socioeconomic status, and Breslow thickness. Our findings, except for Breslow thickness, are consistent with the previous literature.[125,166] Lentigo maligna melanoma was associated with higher risk; this subtype is related to high cumulative

ultraviolet radiation (UV) exposure,[167,168] and another study showed higher risk associated with UV exposure.[169] A previous Australian study[103] and an analysis of U.S. SEER data[140] found that melanoma on the head and neck region, which is generally associated with higher sun exposure than other body sites,[168] was associated with elevated risk of second primary melanoma, although we did not observe this finding in this study. A meta-analysis showed that melanoma was more likely to occur among people with high socio-economic status,[166] and similar observations have been made for prostate and breast cancers.[170,171] These associations may be linked to education including awareness of early signs of cancer, access to healthcare, or participation in screening.[172,173]

Strengths of our study include the availability of a large population-based cohort and use of competing risk statistical methods. Previous research has demonstrated that Fine and Gray hazard models, used in our study, are less prone to overestimating coefficients[174] and better at predicting individual risks when compared to Cox proportional hazard models in the presence of competing events.[175]

The study has some limitations mostly related to the registry-based data analysed. Some known risk factors for developing second primary melanoma were not available, including phenotypic factors (e.g. hair colour, naevus count), UV exposure, and family history of melanoma.[127,169,176,177] We also did not have risk factor data for the other types of second cancers. The treatment (chemotherapy or radiotherapy) and immigration data were also not available to us, these factors may have effects on the estimates of risk of developing second primary melanoma and other cancer. Biological factors, lifestyle factors, an elevated awareness of early detection and participation in screening may all be factors that might explain increased incidence of a second cancer. Another potential factor is surveillance bias, related to more

frequent or intensive medical examinations over the follow-up period. For example, people with high UV exposure may be more likely to get skin checks because of sun-damaged skin and perceived risk, increasing the chance of overdiagnosis of melanoma.[178] The high proportion of in situ or thin melanoma in cohort may be partly attributed to overdiagnosis.

Other studies have reported lower cumulative incidence rates, for instance, the 5-year cumulative incidence rate of second melanoma was 3.7% in the Netherlands. [177] However, the 5-year cumulative incidence rate of 7.6% in this study was similar to the 8% reported in SEER data.[179] The results of comparing cumulative risk of second primary melanoma among different cohorts may be constrained by which confounding factors are included and whether competing risks were accounted for.

Another limitation of this analysis is the absence of cancer incidence data for individuals without any cancer history, which prevents quantifying the magnitude of risk difference between the first cancer and subsequent cancers following the first primary melanoma. However, recent NSW statistics showed the most common incident cancers in the state are prostate, breast, melanoma, lung and bowel.[180]

In conclusion, in this Australian cohort, we found that the most common second primary cancer to be diagnosed after a first primary melanoma was another primary melanoma, followed by prostate cancer, breast cancer and colon cancer. This information, including specific absolute cancer risks and risk factors for second primary melanoma, have implications for patient surveillance and education, and the development of follow-up guidelines.

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Table 1. Characteristics of patients at the time of their first primary melanoma, stratified by the outcome status at the end of the follow-up period, being either development of a second primary cancer, died, or single primary melanoma

			Second Cancer							
Characteristic	Whole cohort (N = 154695)	One melanoma only (N = 98047)	Melanoma (N = 19708)	Prostate (N = 4380)	Breast (N = 1933)	Colon (N = 1658)	Lung (N = 1461)	Other cancers (N = 7450)	Died (N = 20058)	P-value
Sex										
Male	86836 (100%)	50512 (58.2%)	12679 (14.6%)	4380 (5.0%)	30 (<0.1%)	971 (1.1%)	944 (1.1%)	4664 (5.4%)	12656 (14.6%)	<.001
Female	67859 (100%)	47535 (70.0%)	7029 (10.4%)	0 (0.0%)	1903 (2.8%)	687 (1.0%)	517 (0.8%)	2786 (4.2%)	7402 (10.9%)	
Age at first melanoma diagnosis (years)										
18-24	1915 (100%)	1666 (87.0%)	100 (5.2%)	0 (0.0%)	12 (0.6%)	1 (<0.1%)	1 (<0.1%)	24 (1.3%)	111 (5.8%)	<.001
25-49	34470 (100%)	27490 (79.8%)	3294 (9.6%)	341 (1.0%)	452 (1.3%)	124 (0.4%)	128 (0.4%)	813 (2.4%)	1828 (5.3%)	
50-64	48712 (100%)	32863 (67.5%)	6826 (14.0%)	1689 (3.5%)	727 (1.5%)	439 (0.9%)	433 (0.9%)	2218 (4.6%)	3517 (7.2%)	
65-74	36876 (100%)	21141 (57.3%)	5520 (15.0%)	1507 (4.0%)	446 (1.2%)	564 (1.5%)	493 (1.3%)	2272 (6.2%)	4933 (13.4%)	
>75	32722 (100%)	14887 (45.5%)	3968 (12.1%)	843 (2.6%)	296 (0.9%)	530 (1.6%)	406 (1.2%)	2123 (6.5%)	9669 (29.5%)	
Remoteness of residence										
Not available	27885 (100%)	9888 (35.5%)	4193 (15.0%)	1306 (4.7%)	594 (2.1%)	541 (1.9%)	507 (1.8%)	2304 (8.3%)	8552 (30.7%)	<.001
Major Cities	81284 (100%)	56666 (69.7%)	10141 (12.5%)	1956 (2.4%)	868 (1.1%)	703 (0.9%)	569 (0.7%)	3308 (4.1%)	7073 (8.7%)	
Inner Regional	35305 (100%)	24422 (69.2%)	4250 (12.0%)	846 (2.4%)	355 (1.0%)	334 (0.9%)	291 (0.8%)	1419 (4.0%)	3388 (9.6%)	
Outer Regional	9629 (100%)	6649 (69.1%)	1075 (11.2%)	253 (2.6%)	109 (1.1%)	76 (0.8%)	85 (0.9%)	399 (4.1%)	983 (10.2%)	
Remote/very remote	592 (100%)	422 (71.3%)	49 (8.3%)	19 (3.2%)	7 (1.2%)	4 (0.7%)	9 (1.5%)	20 (3.4%)	62 (10.5%)	
Socioeconomic advantage and disadvantage										
Not available	25767 (100%)	9099 (35.3%)	3833 (14.9%)	1183 (4.6%)	554 (2.2%)	503 (2.0%)	464 (1.8%)	2129 (8.3%)	8002 (31.1%)	<.001
quintile1 (most disadvantaged)	25727 (100%)	16741 (65.1%)	2913 (11.3%)	606 (2.4%)	291 (1.1%)	271 (1.1%)	289 (1.1%)	1240 (4.8%)	3376 (13.1%)	
quintile2	25125 (100%)	17171 (68.3%)	3034 (12.1%)	598 (2.4%)	239 (1.0%)	229 (0.9%)	205 (0.8%)	1069 (4.3%)	2580 (10.3%)	
quintile3	24451 (100%)	17135 (70.1%)	2941 (12.0%)	534 (2.2%)	276 (1.1%)	205 (0.8%)	199 (0.8%)	974 (4.0%)	2187 (8.9%)	
quintile4	25256 (100%)	17819 (70.6%)	3135 (12.4%)	655 (25.9%)	278 (1.1%)	217 (0.9%)	154 (0.6%)	977 (4.0%)	2021 (8.3%)	
quintile5 (least disadvantaged)	28369 (100%)	20082 (70.8%)	3852 (13.6%)	804 (2.8%)	295 (1.0%)	233 (0.8%)	150 (0.5%)	1061 (3.7%)	1892 (6.7%)	
Breslow thickness (mm)										

Characteristic	Whole cohort (N = 154695)	One melanoma only (N = 98047)	Second Cancer: Melanoma (N = 19708)	Prostate (N = 4380)	Breast (N = 1933)	Colon (N = 1658)	Lung (N = 1461)	Other cancers (N = 7450)	Died (N = 20058)	P-value
Mean, SD	0.8 (1.9)	0.6 (1.4)	0.7 (1.5)	0.8 (1.4)	0.8 (1.6)	0.9 (1.5)	1.1 (2.0)	1.0 (1.8)	2.2 (3.5)	<.001
1st 2nd 3rd quartile	0.0 0.3 0.8	0.0 0.2 0.6	0.0 0.4 0.8	0.0 0.4 0.8	0.0 0.4 0.8	0.0 0.5 1.1	0.0 0.5 1.2	0.0 0.5 1.0	0.4 1.1 3.0	
Breslow thickness category (mm)										
In situ (0)	61971 (100%)	47312 (76.3%)	7265 (11.7%)	1451 (2.3%)	611 (1.0%)	473 (0.8%)	377 (0.6%)	2122 (3.4%)	2360 (3.8%)	<.001
0.1-0.8	46161 (100%)	29050 (62.9%)	6790 (14.7%)	1599 (3.5%)	720 (1.6%)	583 (1.3%)	502 (1.1%)	2617 (5.7%)	4300 (9.3%)	
0.9-1.0	7441 (100%)	4409 (59.3%)	1085 (14.6%)	274 (3.7%)	108 (1.5%)	107 (1.4%)	82 (1.1%)	426 (5.7%)	950 (12.8%)	
1.1-2.0	15059 (100%)	8201 (54.5%)	2132 (14.2%)	464 (3.1%)	223 (1.5%)	200 (1.3%)	184 (1.2%)	894 (5.9%)	2761 (18.3%)	
2.1-4.0	9519 (100%)	3994 (26.5%)	1243 (8.3%)	241 (2.5%)	114 (1.2%)	141 (1.5%)	142 (1.5%)	629 (6.6%)	3015 (31.7%)	
>4.1	6552 (100%)	2283 (34.8%)	610 (9.3%)	157 (2.4%)	62 (0.9%)	79 (1.2%)	91 (1.4%)	370 (5.6%)	2900 (44.3%)	
Unknown	7992 (100%)	2798 (35.0%)	583 (7.3%)	194 (2.4%)	95 (1.2%)	75 (0.9%)	83 (1.0%)	392 (4.9%)	3772 (47.2%)	

1 The index of relative socioeconomic advantage and disadvantage (IRSAD), based on postcode of residence. Data were not available prior to 1998.

Table 2. Fine-Gray regression model estimates of risk of developing a second primary invasive or in situ melanoma after diagnosis of a first primary melanoma, in relation to different risk factors

Characteristic	N (%)[1]	Risk of second primary melanoma (full cohort – invasive and in situ) N=154695				Risk of second primary melanoma (subset - first melanoma was in situ)[2] N=61971			
		Univariable		Multivariable		Univariable		Multivariable	
		SHR (95%CI)	P-value	SHR (95%CI)	P-value	SHR (95%CI)	P-value	SHR (95%)	P-value
Age-10 year	154695	1.06 (1.05-1.06)	<0.01	1.06(1.05-1.06)	<0.01	1.06 (1.05-1.06)	<0.01	1.07 (1.06-1.08)	<0.01
Sex									
Males	86836(56.1)	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
Females	67859(43.9)	0.68 (0.66-0.70)		0.69 (0.67- 0.72)		0.68 (0.66-0.70)		0.68 (0.65-0.72)	
Socioeconomic status[2]									
Quintile 1	25727(16.6)	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
Quintile 2	25125(16.2)	1.09 (1.04-1.15)		1.10 (1.03-1.18)		0.70 (0.43-1.13)		1.05 (0.97-1.13)	
Quintile 3	24451(15.8)	1.11 (1.05-1.16)		1.15 (1.08-1.23)		1.06 (0.98-1.14)		1.08 (0.99-1.17)	
Quintile 4	25256(16.4)	1.14 (1.08-1.19)		1.20 (1.12-1.29)		1.08 (0.99-1.16)		1.09 (1.01-1.18)	
Quintile 5	28369(18.3)	1.25 (1.19-1.31)		1.29 (1.21-1.39)		1.20 (1.12-1.29)		1.22 (1.13-1.32)	
Not available	25767(16.7)	0.82 (0.78-0.86)		1.03 (0.93-1.14)		0.82 (0.78-0.86)		0.61 (0.35-1.05)	
Geographical location									
Major cities	81284(52.5)	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	0.02
Inner regional	35305(22.8)	0.95 (0.92-0.99)		1.01 (0.97-1.05)		0.94 (0.89-0.99)		0.99 (0.94- 1.06)	
Outer regional	9629(6.2)	0.88 (0.82-0.93)		0.96 (0.90-1.03)		0.80 (0.73-0.89)		0.90 (0.81- 0.99)	
Remote/very remote	592(0.4)	0.61 (0.46-0.81)		0.67 (0.51-0.89)		0.48 (0.30-0.76)		0.57 (0.37-0.87)	
Unknown	27885(18.1)	0.72 (0.70-0.75)		0.87 (0.79-0.95)		1.53 (0.46-5.06)		1.63 (0.45-5.91)	
Breslow thickness (mm)			<0.01		<0.01				
In situ (0)	61971(40.1)	1.11 (1.07-1.15)		0.97 (0.93-1.00)		N/A		N/A	
0.1-0.8	46161(29.8)	1.00		1.00					
0.9-1.0	7441(4.8)	0.98 (0.92-1.04)		0.99 (0.93-1.06)					
1.1-2.0	15059(9.7)	0.97 (0.93-1.02)		0.97 (0.92-1.02)					
2.1-4.0	9519(6.2)	0.94 (0.88-0.99)		0.88 (0.82-0.95)					
>4.1	6552(4.2)	0.70 (0.64-0.76)		0.63 (0.57-0.70)					
Unknown	7992(5.2)	0.49 (0.45-0.53)		0.57 (0.52-0.64)					
Body site									
Trunk	52478(34.2)	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	0.02
Head and neck	32592(21.2)	0.97 (0.93-1.00)		0.90 (0.87-0.94)		0.97 (0.91-1.02)		0.91 (0.86-0.97)	
Upper limb and shoulder	36904(24.1)	0.93 (0.89-0.96)		0.98 (0.94-1.02)		0.94 (0.89-1.00)		0.99 (0.94-1.06)	
Lower limb and hip	27174(17.7)	0.78 (0.75-0.82)		0.94 (0.90-0.99)		0.79 (0.73-0.86)		0.94 (0.87-1.02)	
Other	5547(2.8)	0.35 (0.31-0.40)		0.50 (0.43-0.58)		0.80 (0.58-1.10)		0.82 (0.60-1.13)	
Melanoma subtype									
SSM	51312(33.2)	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	0.74
DM	1748(1.1)	1.05 (0.92-1.19)		1.15 (1.00-1.31)		N/A		N/A	
LMM	28731(18.6)	1.27 (1.22-1.32)		1.11 (1.06-1.17)		1.14 (1.06-1.22)		1.01(0.94-1.09)	
NM	10927(7.1)	0.87 (0.82-0.92)		0.93 (0.87-1.00)		N/A		N/A	
ALM	864(0.5)	0.63 (0.49-0.81)		0.67 (0.52-0.86)		1.07(0.70-1.63)		1.05(0.68-1.61)	
Other	61113(39.5)	0.97 (0.93-0.99)		1.03 (0.99-1.06)		1.01(0.94-1.08)		0.98(0.92-1.05)	

Footnote Table 2: CI, confidence interval; SHR, subdistribution hazard ratio; SSM, superficial spreading melanoma; DM, desmoplastic melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma.

1. Number and percentage based on the full cohort.
2. Data for in situ melanomas were not systematically collected at the NSW cancer registry before 2002, so follow-up time for this subset is reduced (based on a mean of 7 years).
3. Socioeconomic status is based on postcode of residence using the index of relative socioeconomic advantage and disadvantage (IRSAD). Quintile 1 represents the most disadvantaged status and Quintile5 represents the least disadvantaged status. Data are not available prior to 1998.

Figure 1. Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive or in situ melanoma

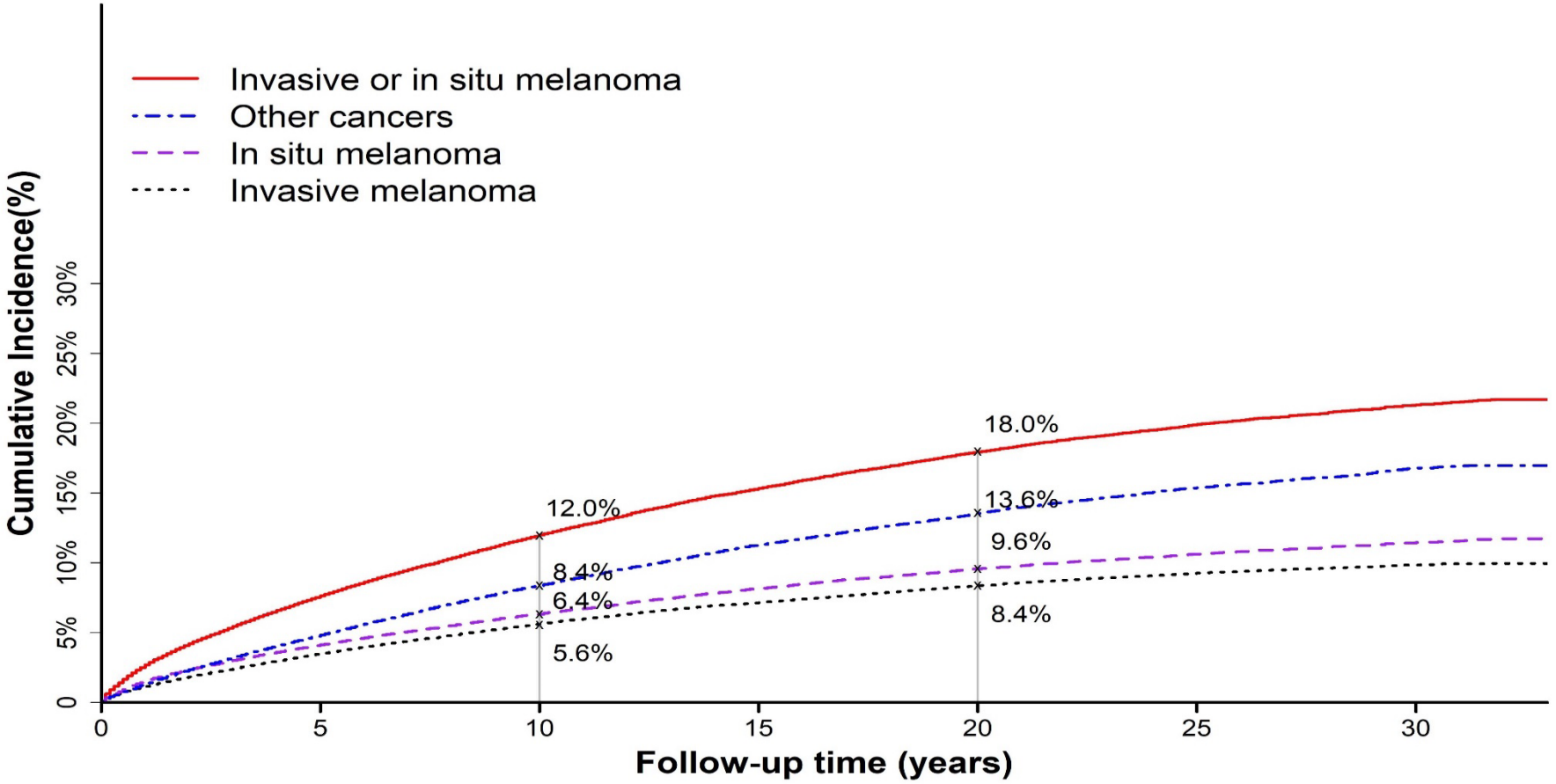


Figure 2. Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive melanoma

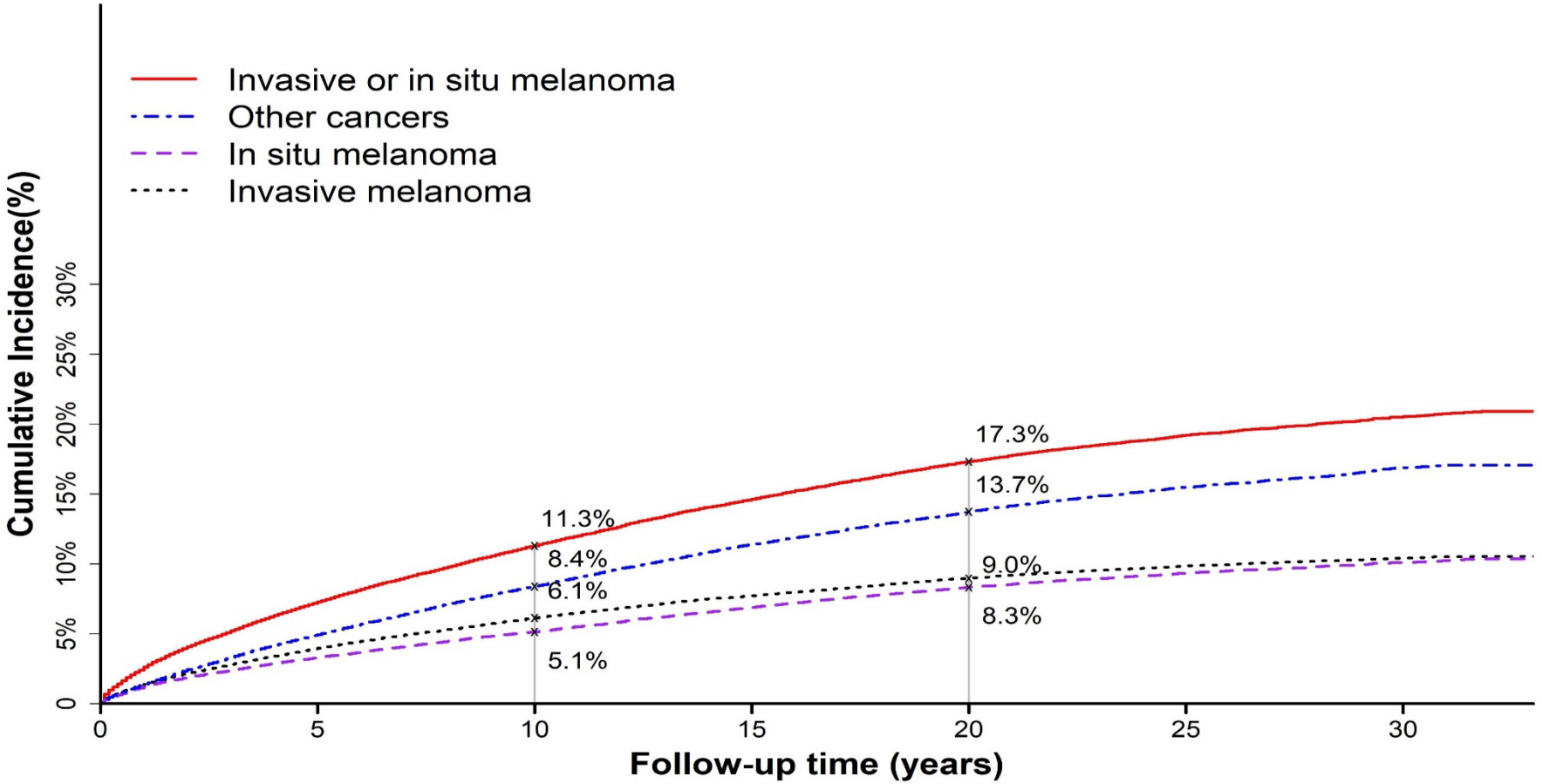


Figure 3. Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary in situ melanoma

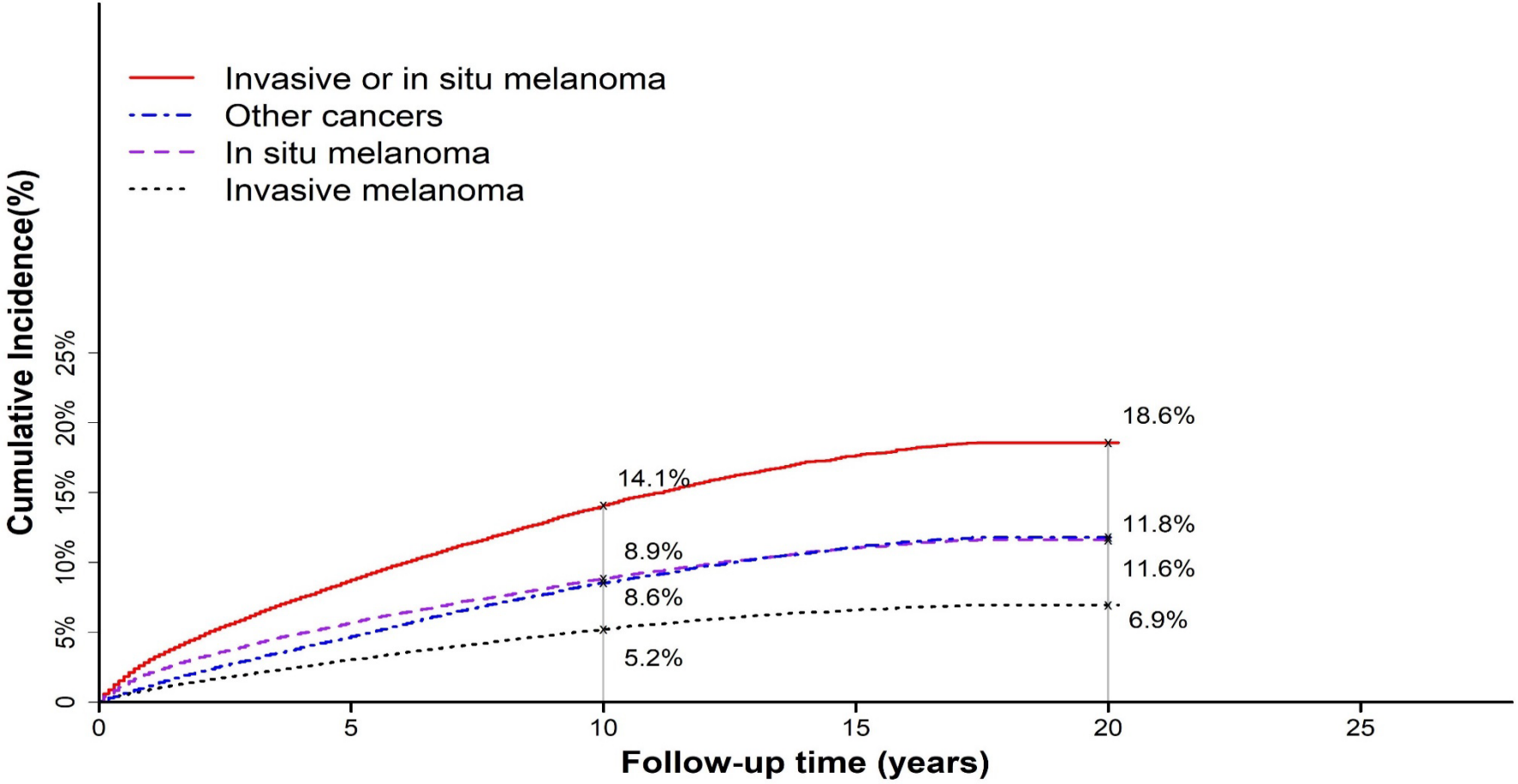


Figure 4 (A). Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive or in situ melanoma diagnosed during the period 1982-1991

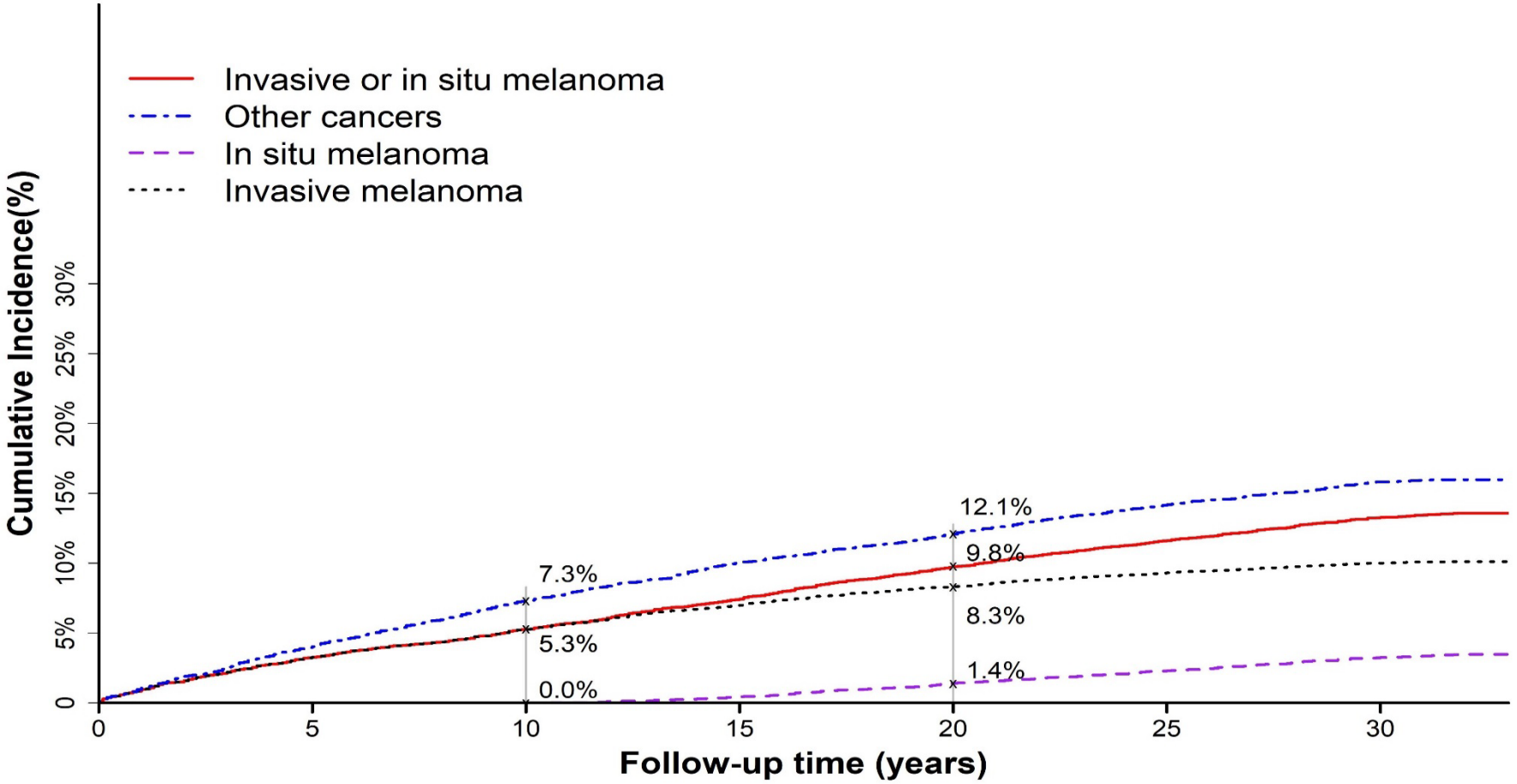


Figure 4 (B). Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive or in situ melanoma diagnosed during the period 1992-2001

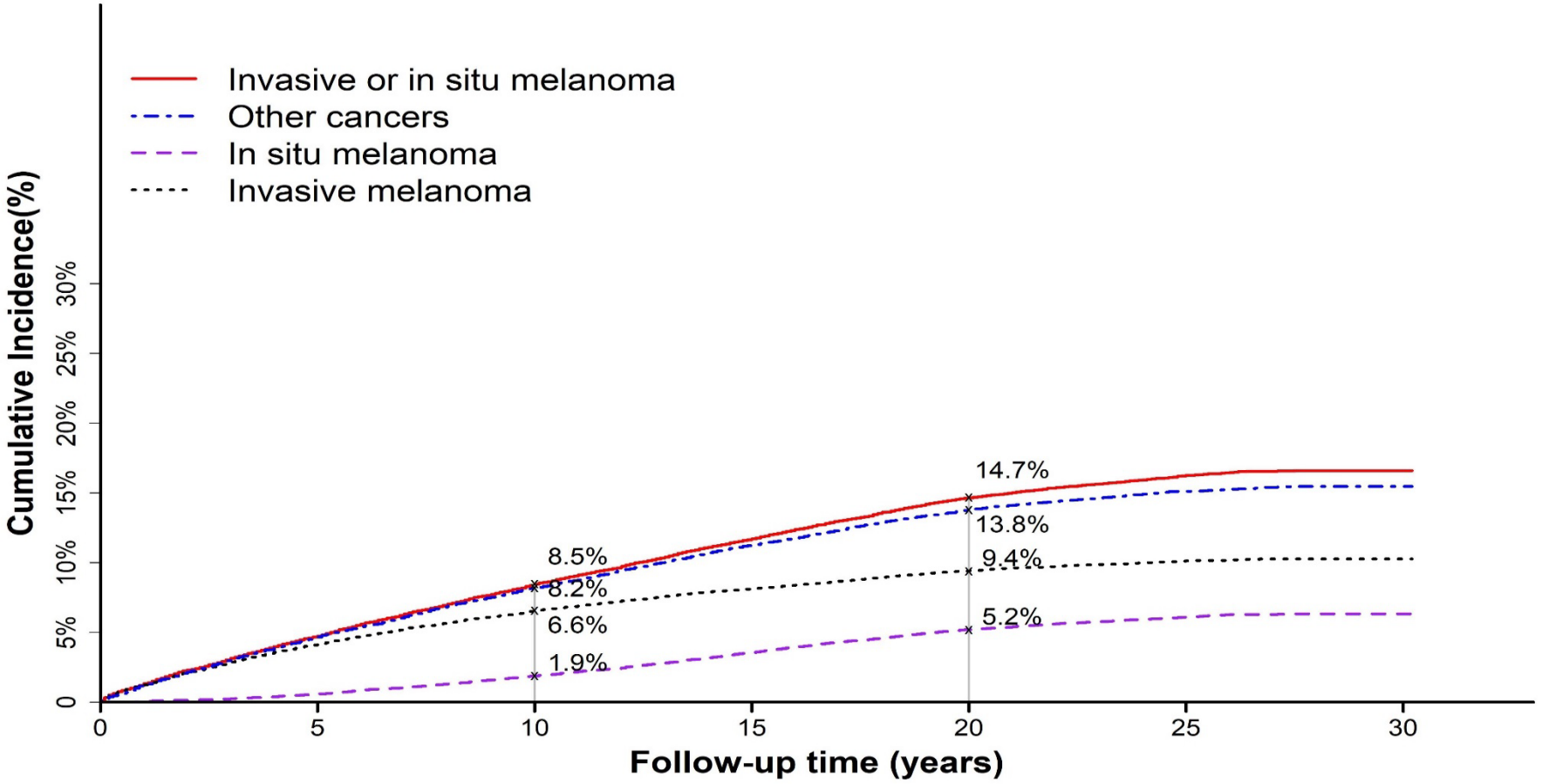


Figure 4 (C). Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive or in situ melanoma diagnosed during the period 2002-2011

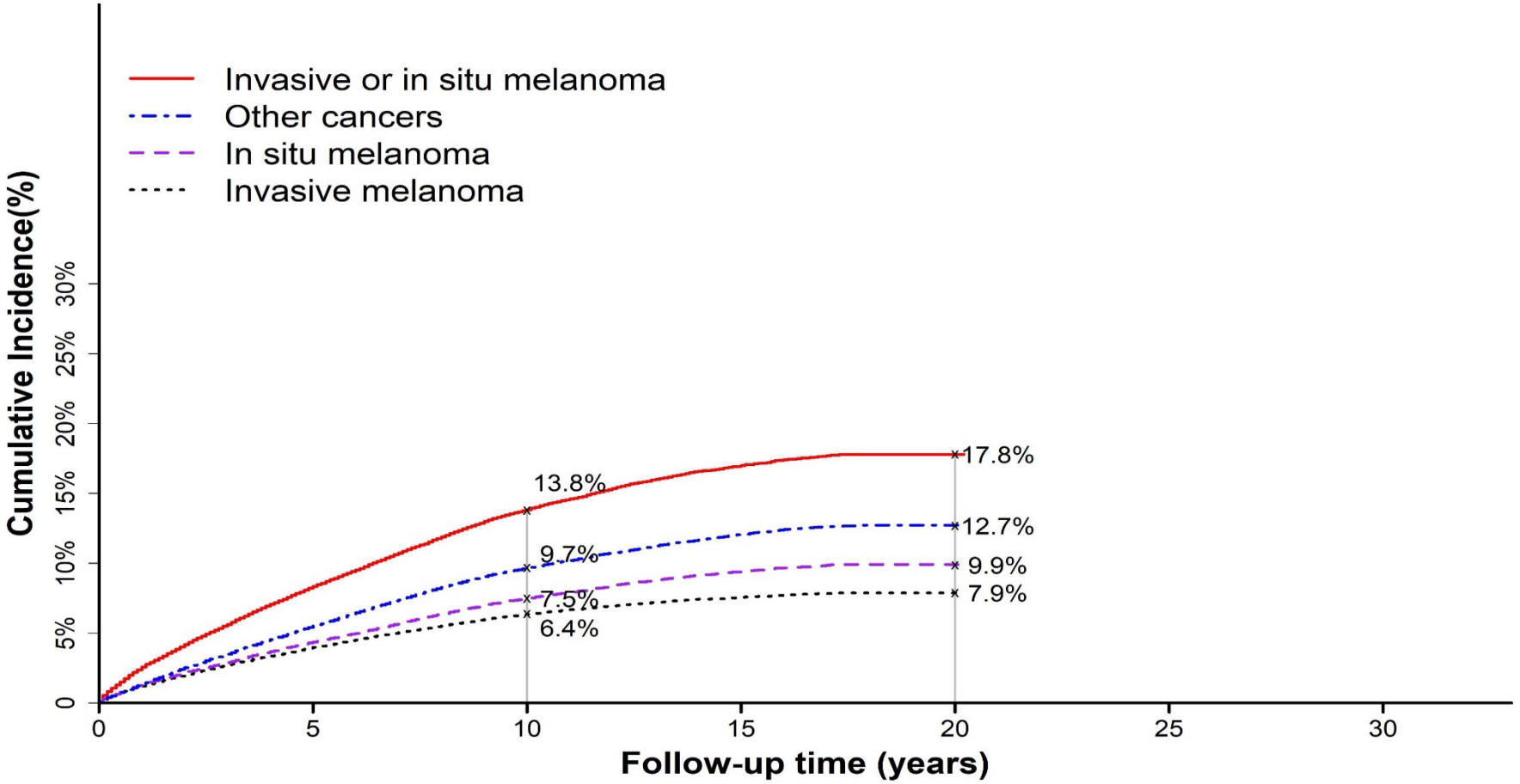


Figure 4 (D). Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive or in situ melanoma diagnosed during the period 2012-2019

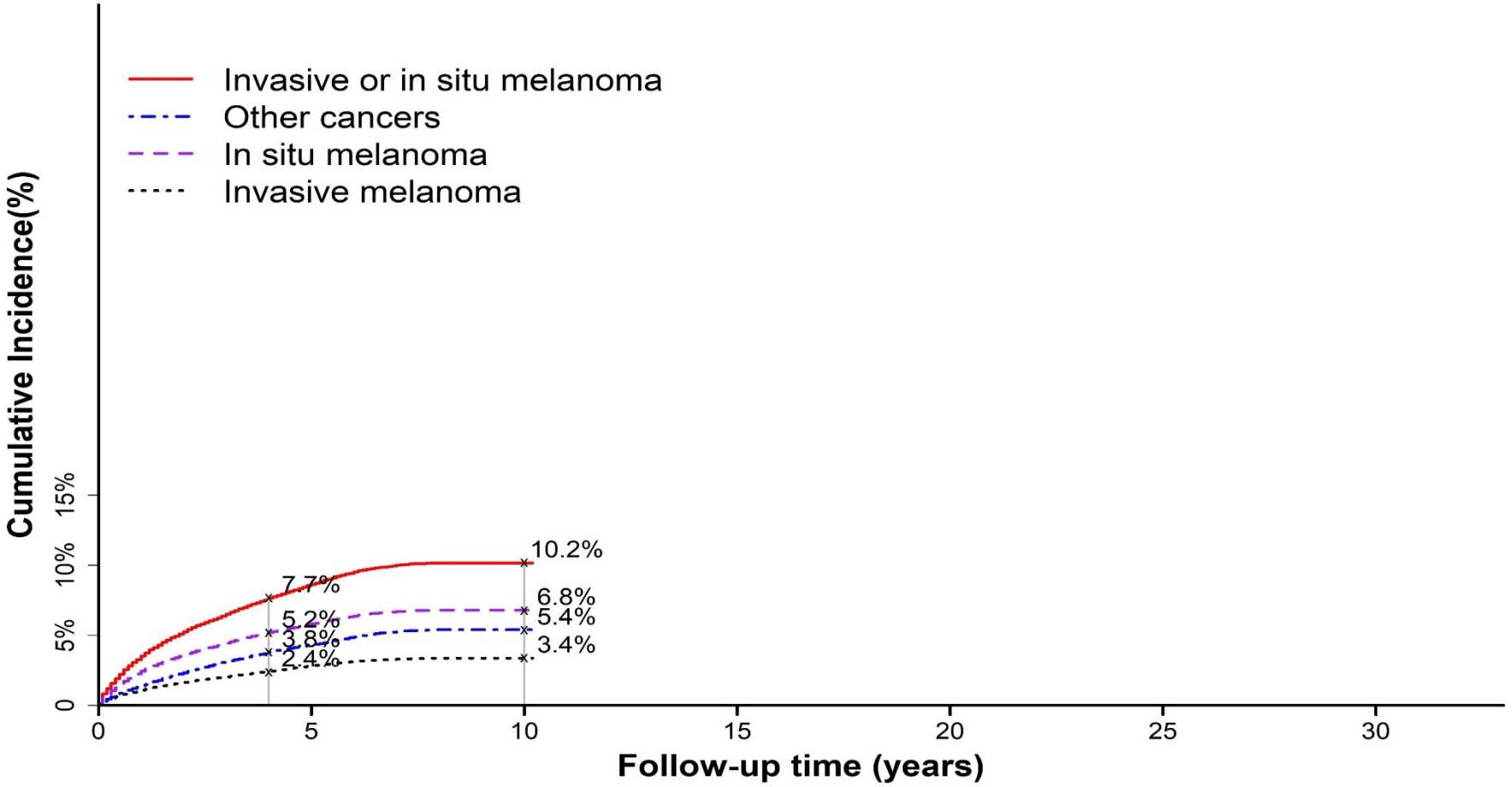


Figure 5 (A). Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary invasive melanoma diagnosed during the period 1982-1991

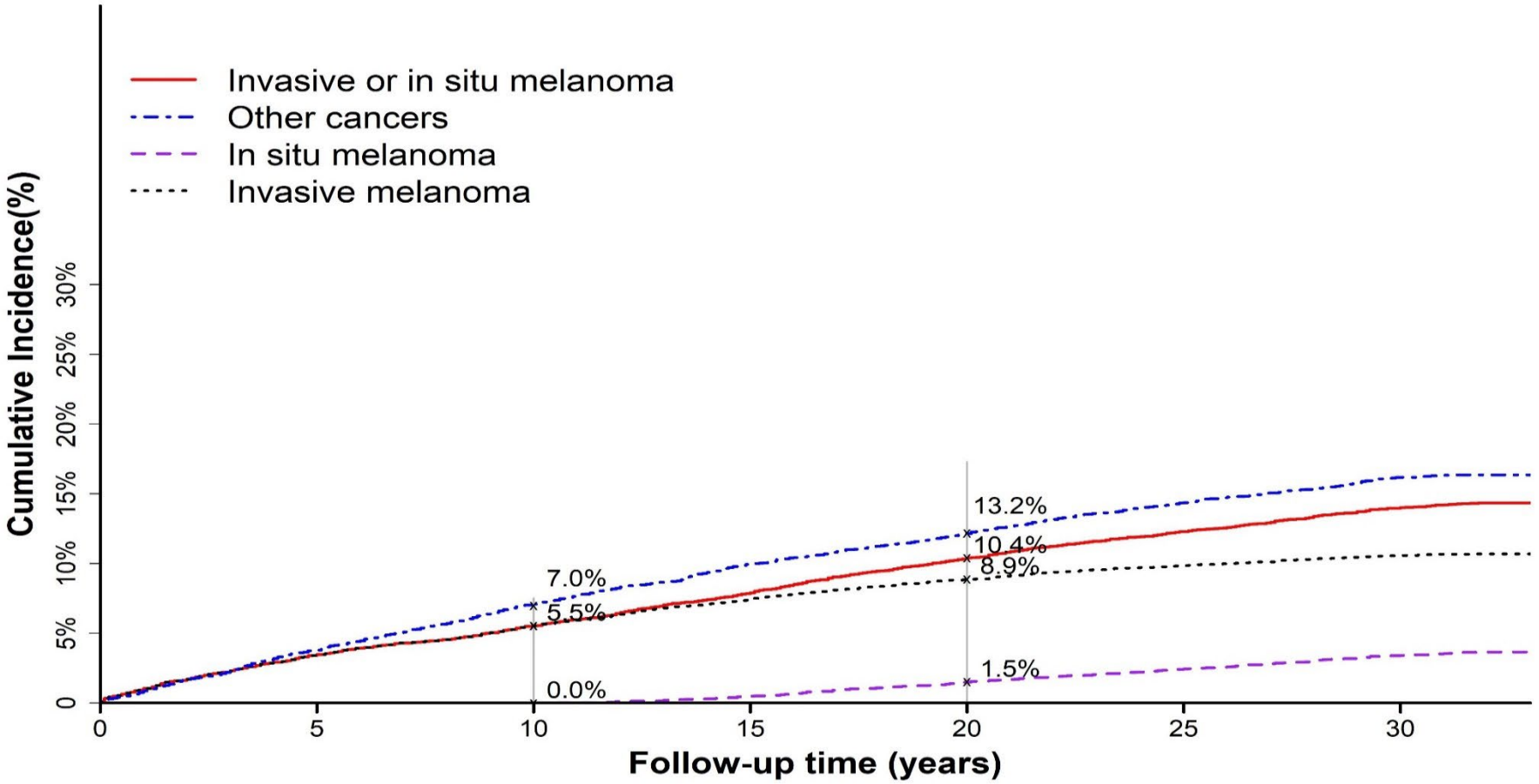


Figure 5 (B). Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive melanoma diagnosed during the period 1982-1991

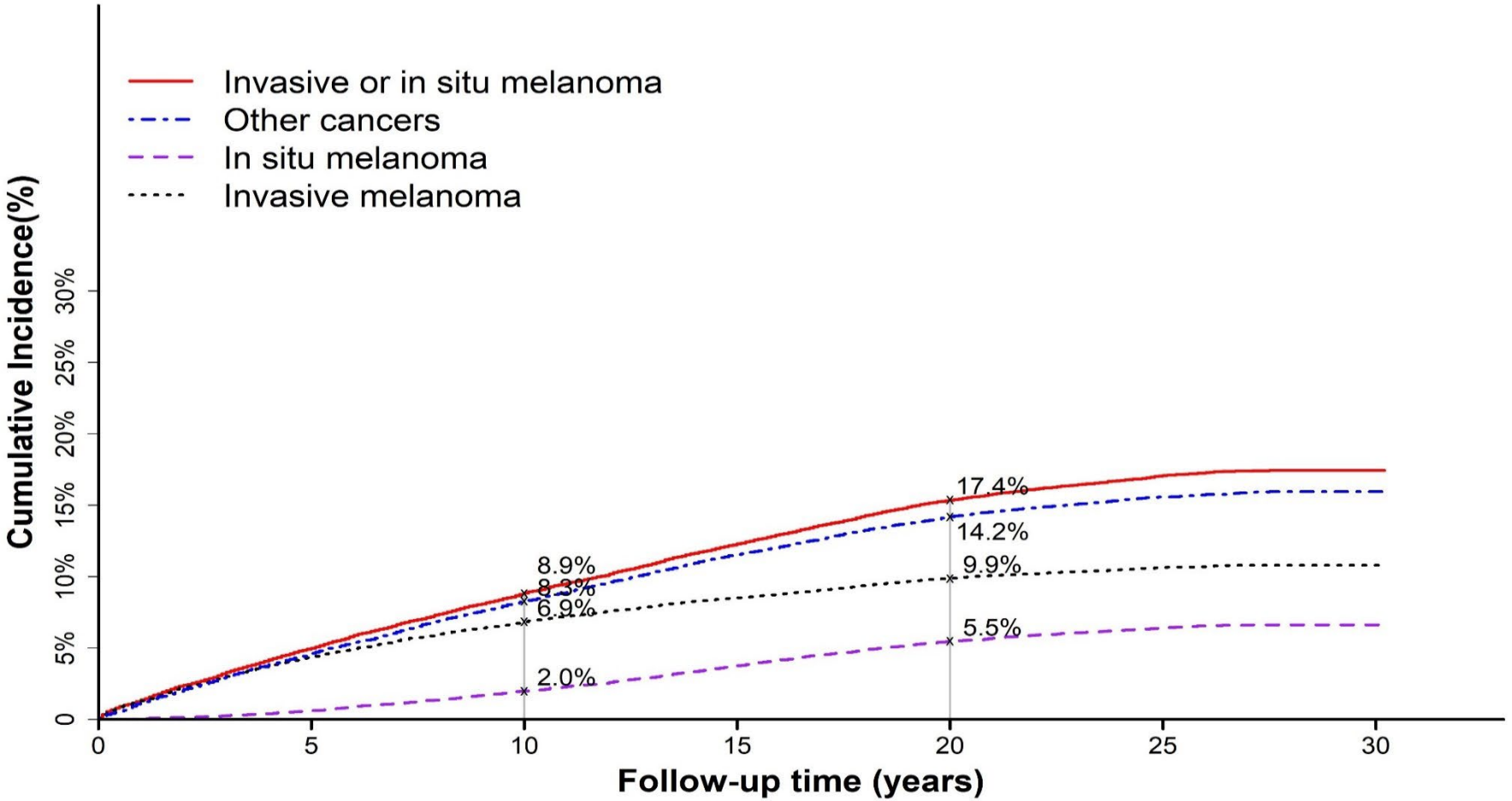


Figure 5 (C). Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive melanoma diagnosed during the period 2002-2011

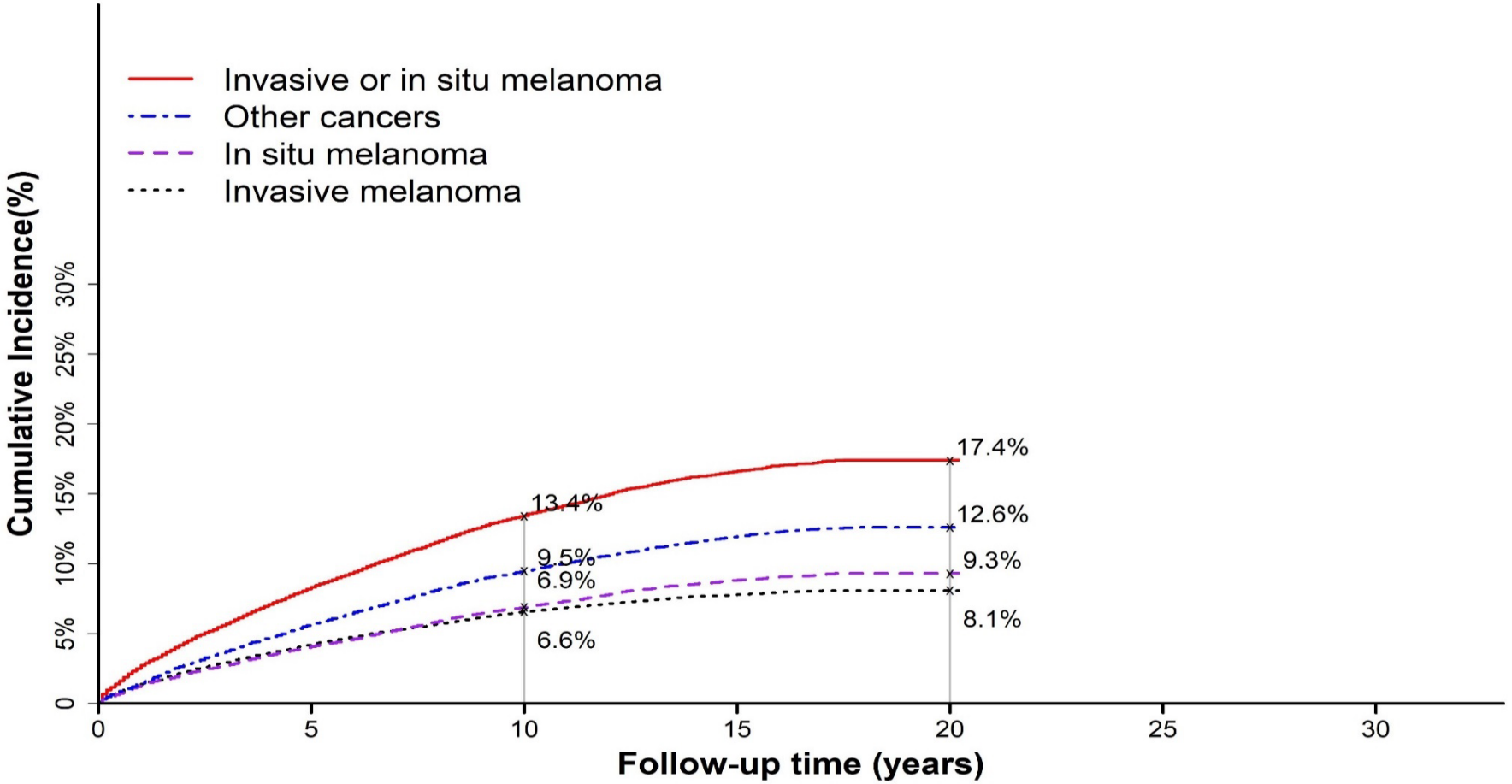


Figure 5 (D). Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive melanoma diagnosed during the period 2012-2019

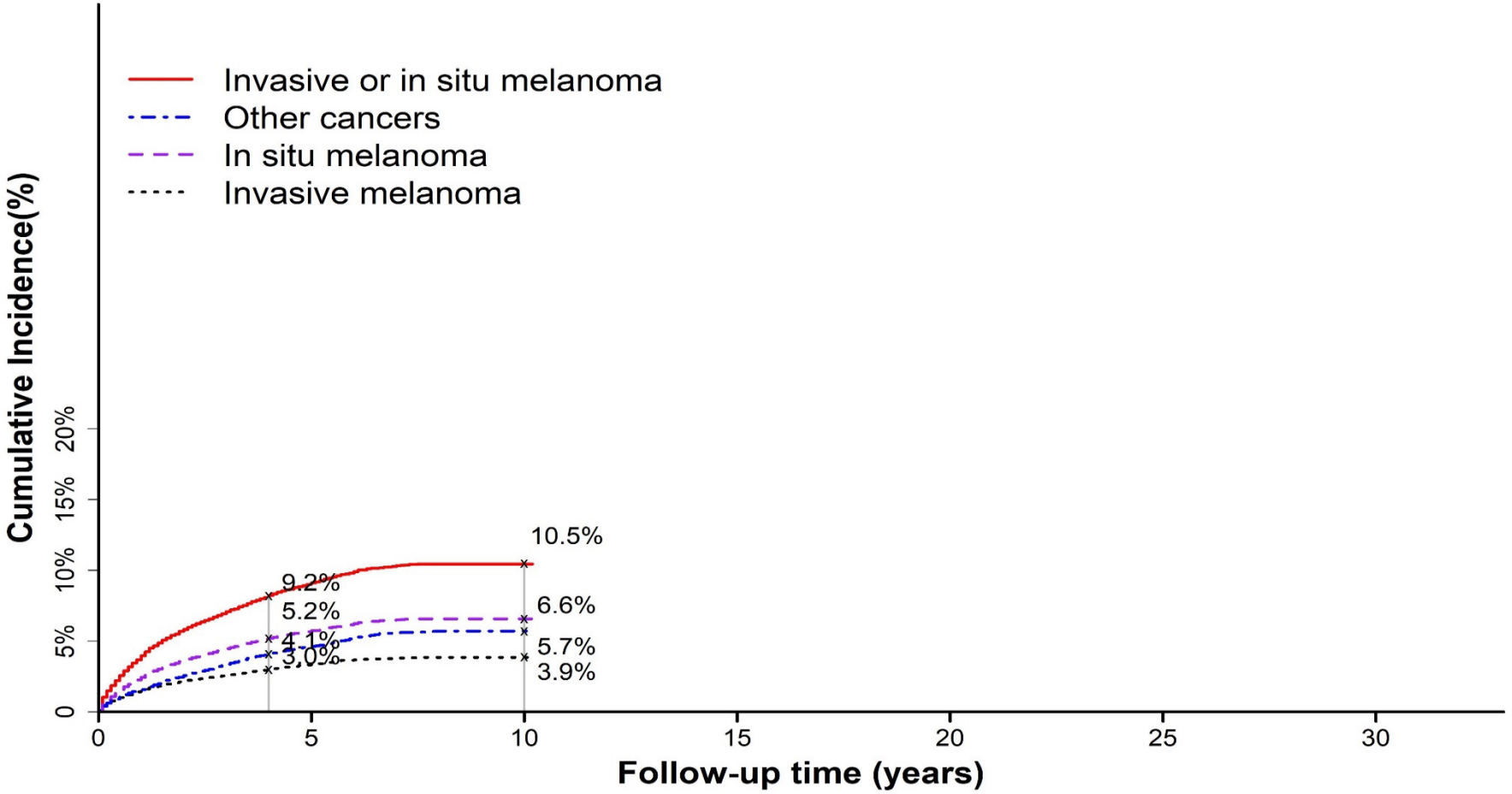


Figure S1. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in <u>males</u> who had a first primary invasive or in situ melanoma

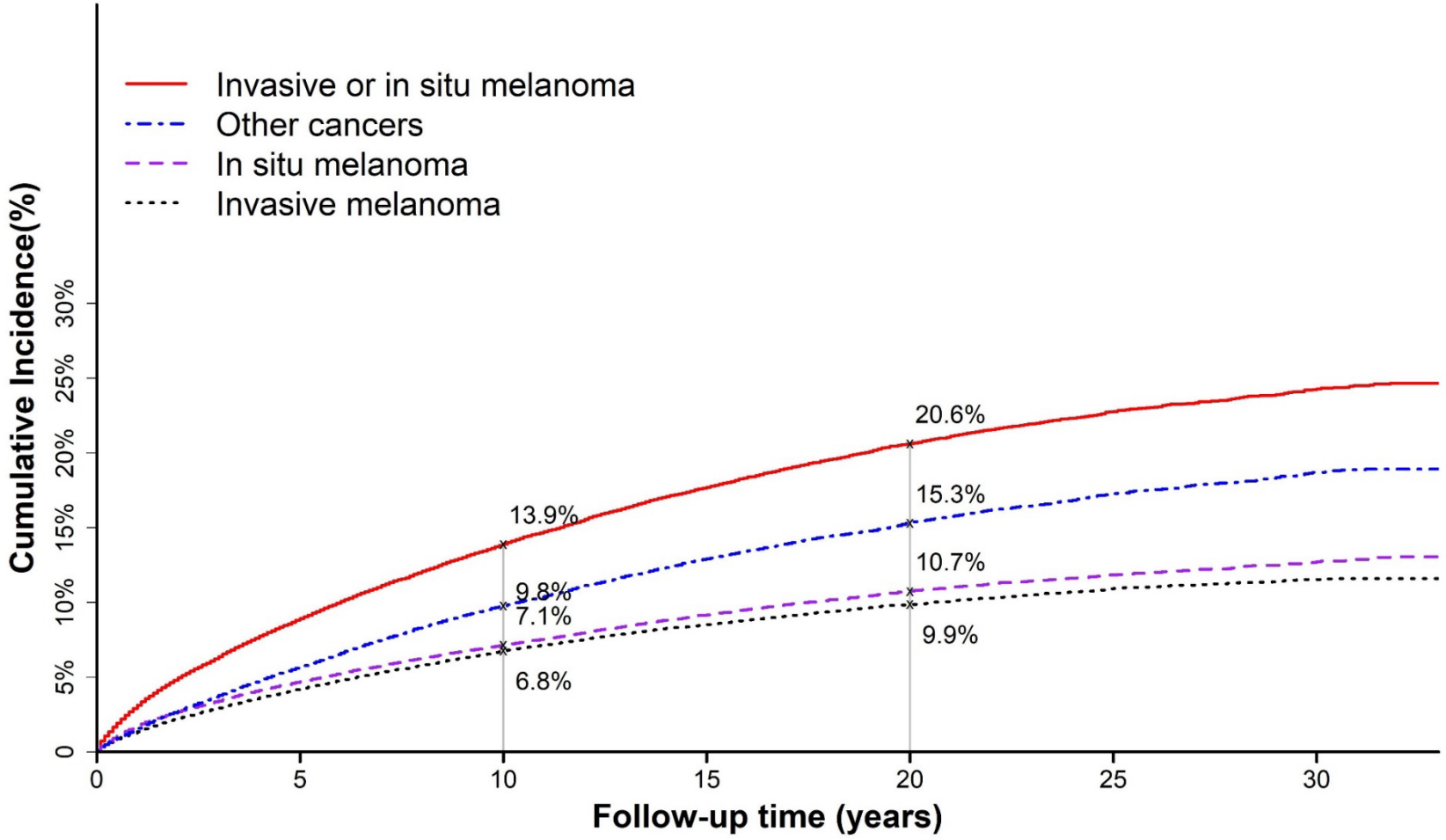


Figure S2. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in females who had a first primary invasive or in situ melanoma

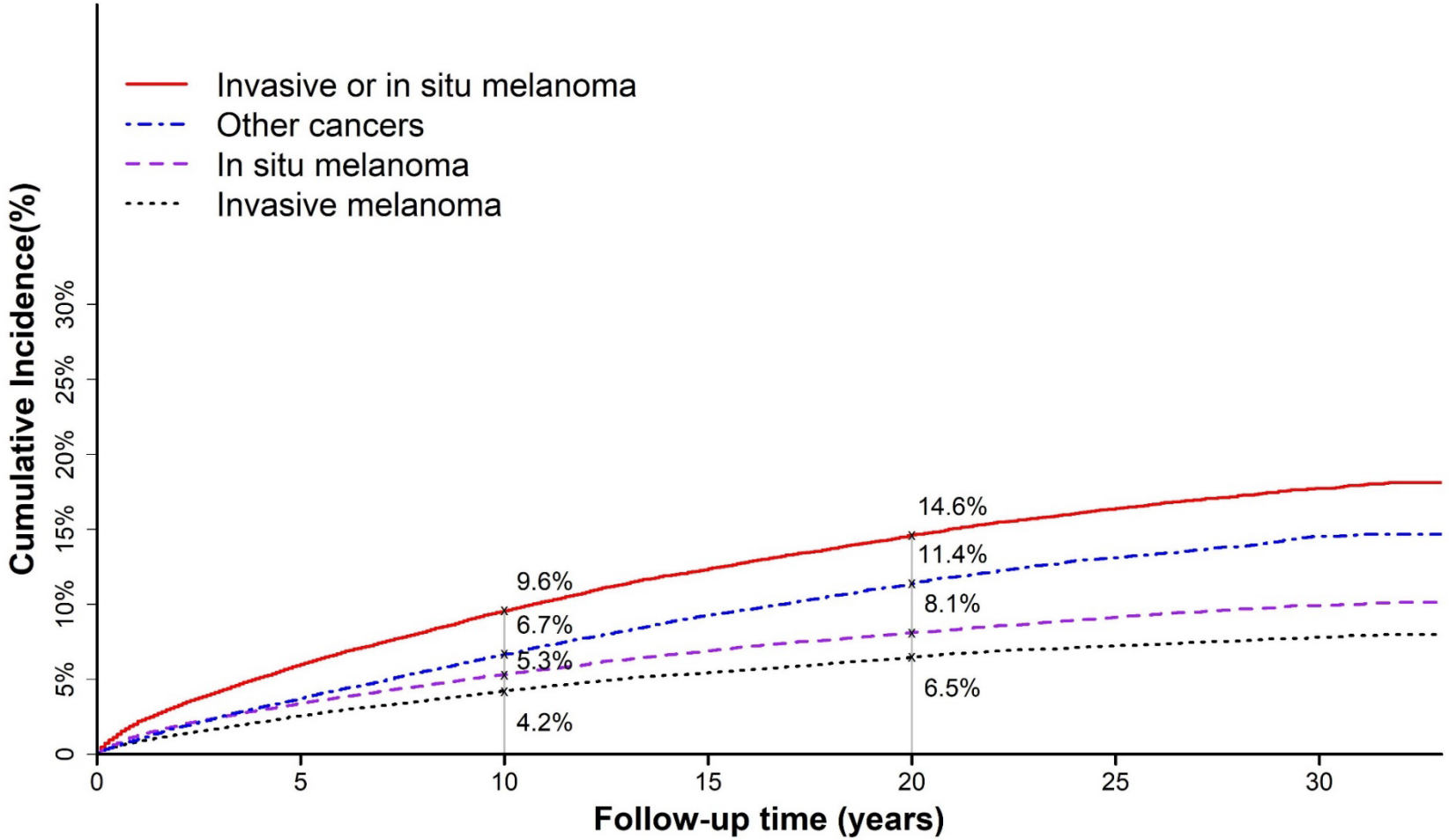


Figure S3. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive or in situ melanoma at age 18-24 years

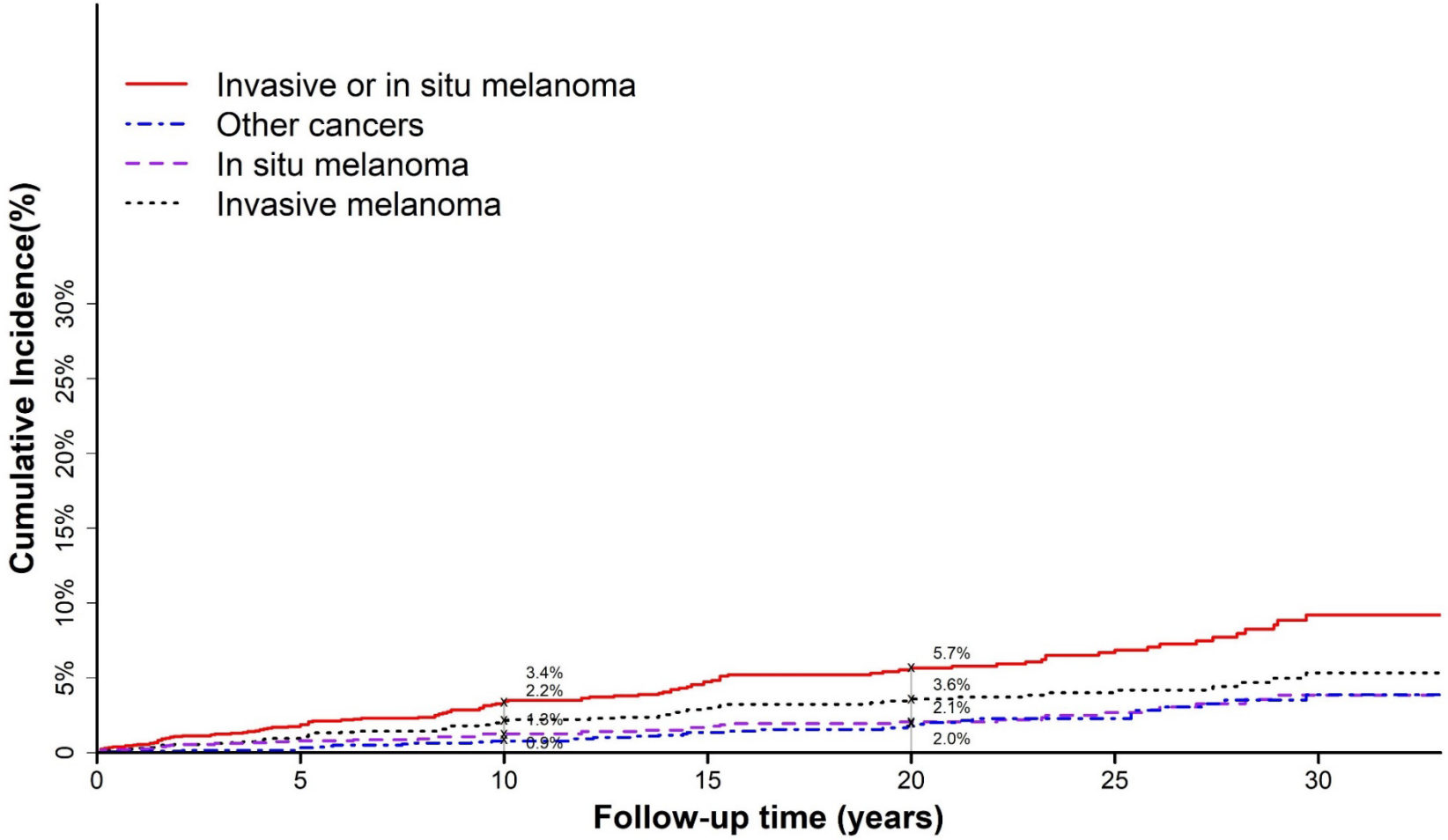


Figure S4. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive or in situ melanoma at age 25-49 years

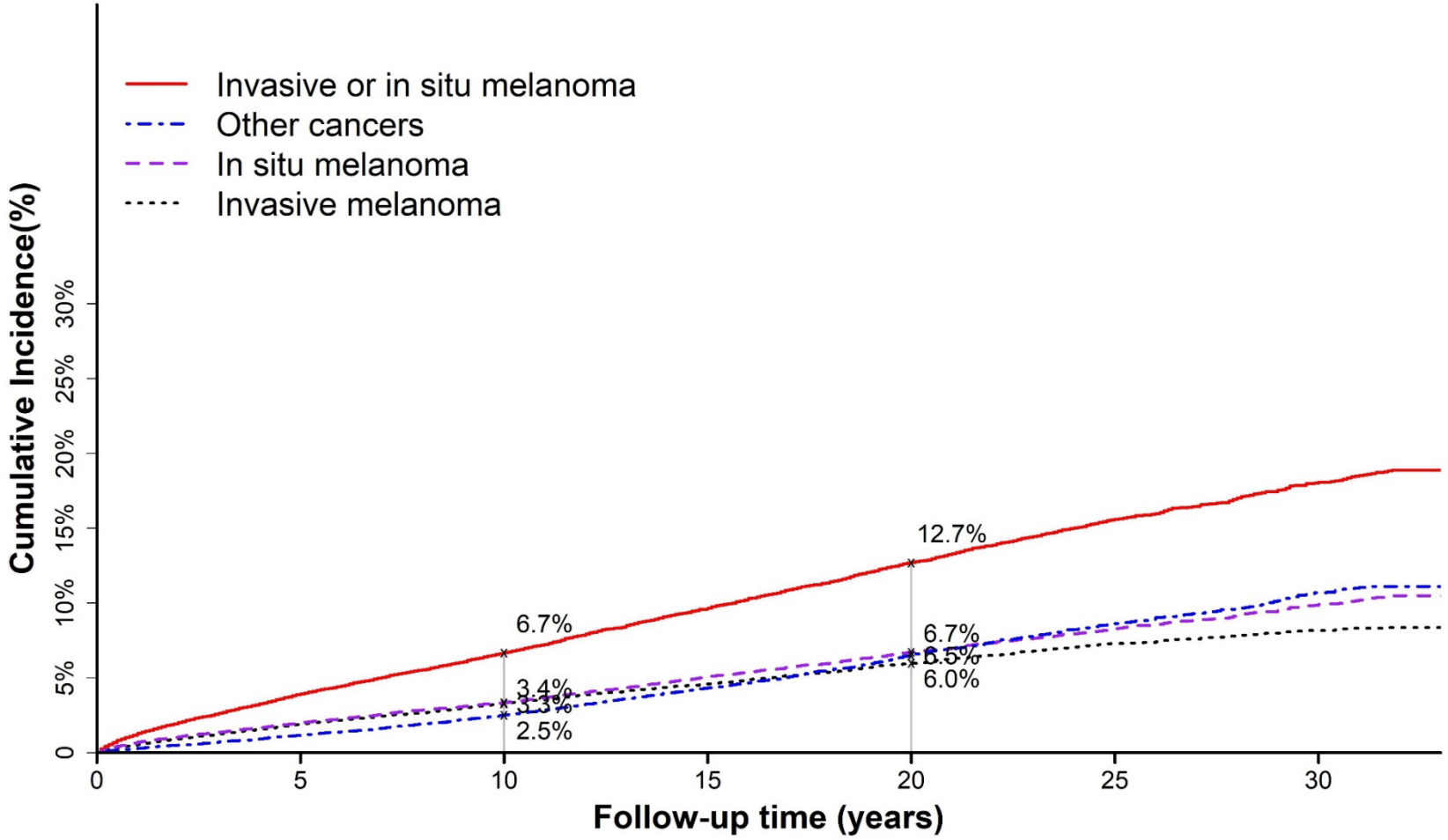


Figure S5. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive or in situ melanoma at age 50-64 years

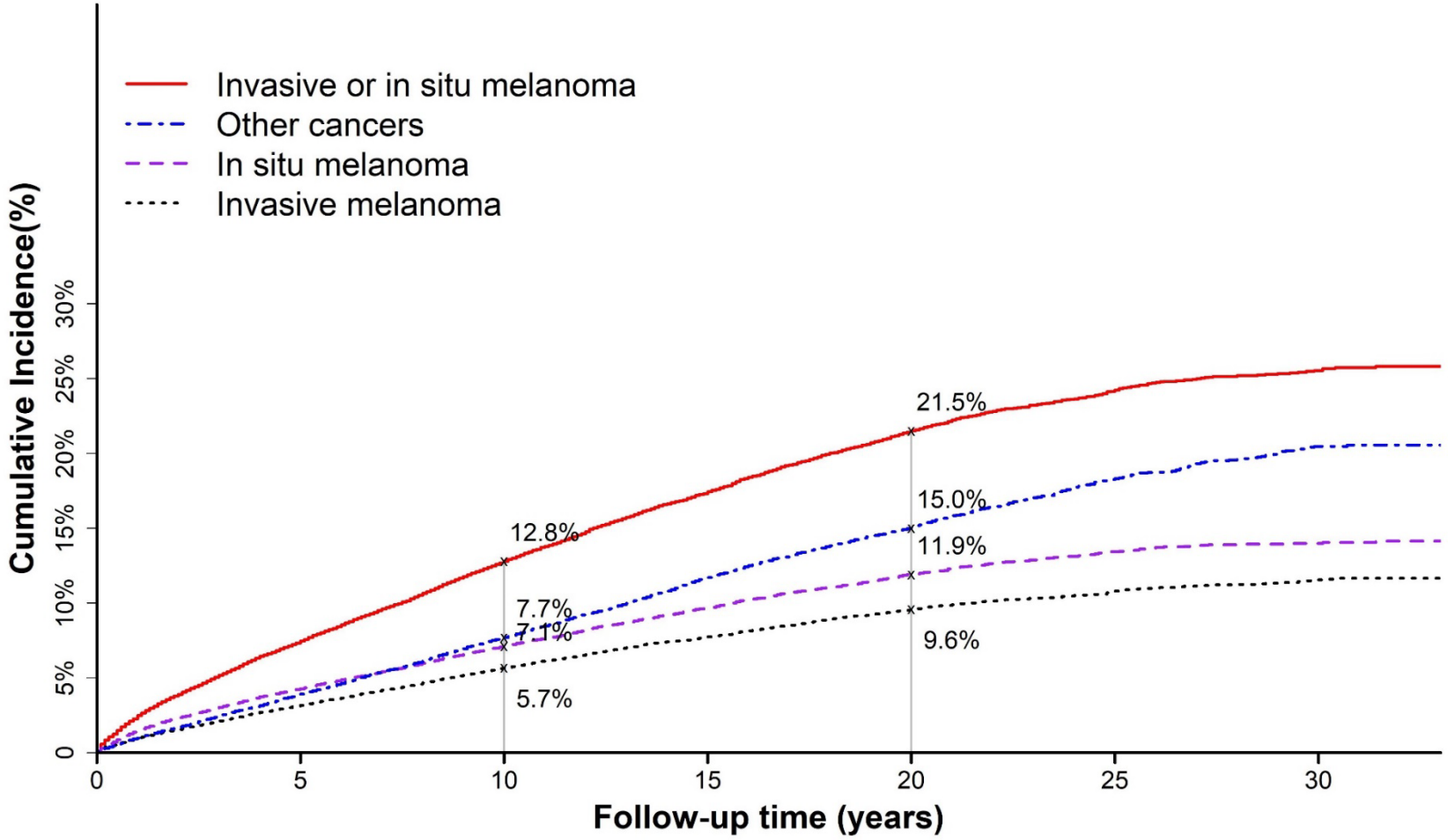


Figure S6. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive or in situ melanoma at age 65-74 years

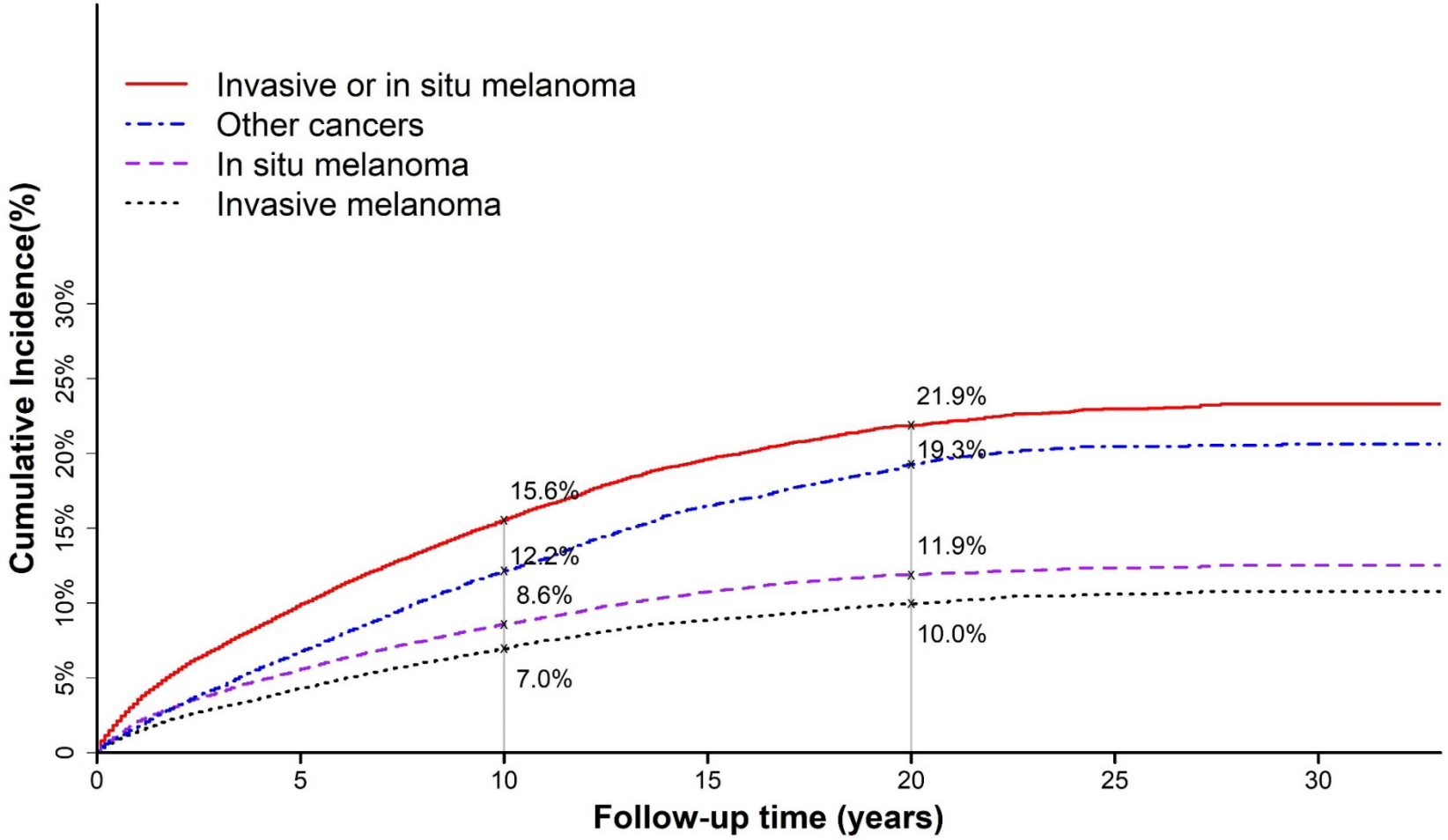
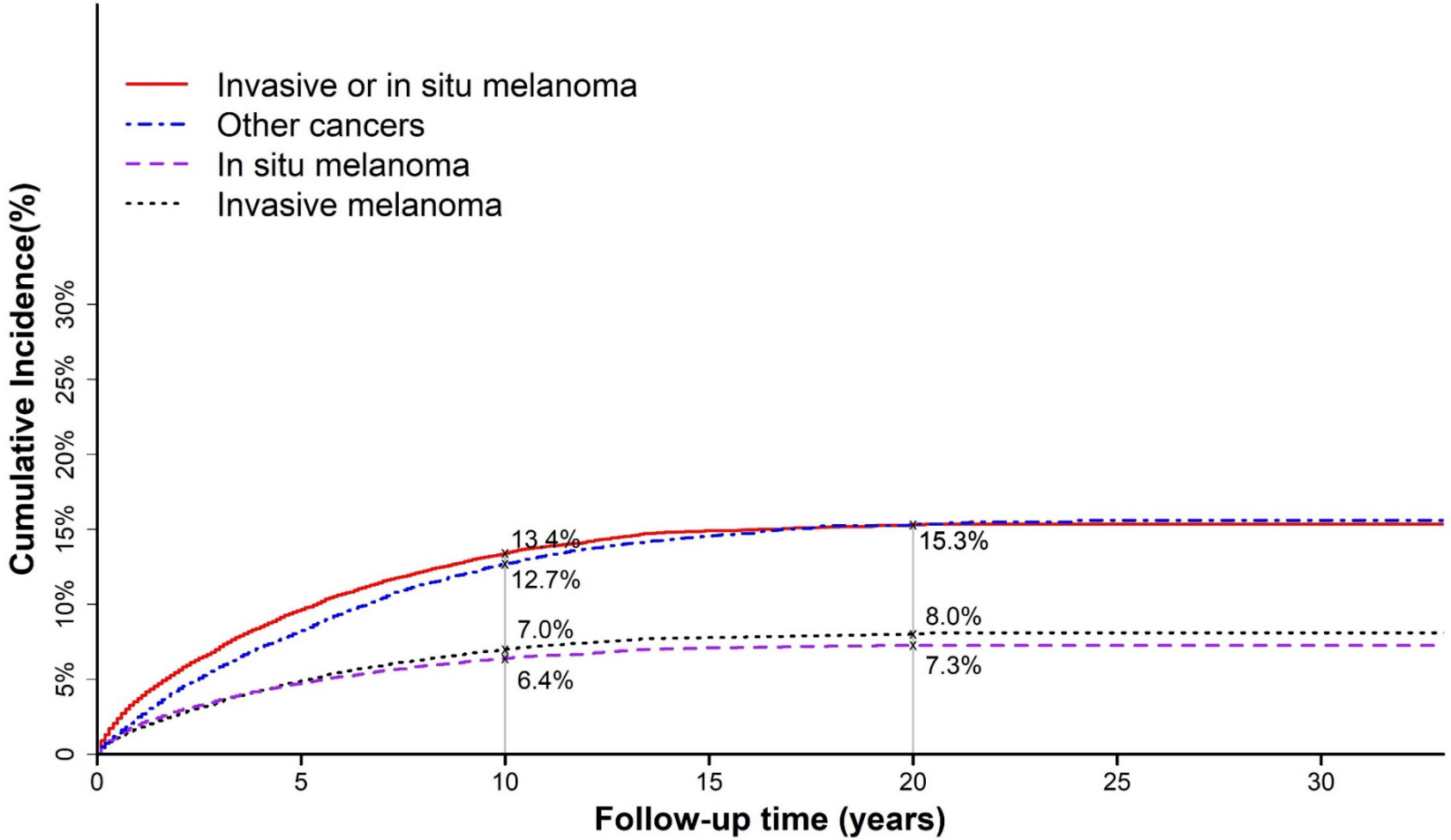


Figure S7. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary invasive or in situ melanoma at age ≥ 75 years



In-situ melanoma was recorded in CanDLe database from 2002 therefore incidence figure for 1982-1991 and 1992-2001 could not be derived

Figure S8. Cumulative incidence of a second primary invasive or in situ melanoma or other type of second primary cancer in people who had a first primary in situ melanoma diagnosed during the period 2002-2011. Data for in situ melanoma were available from 2002.

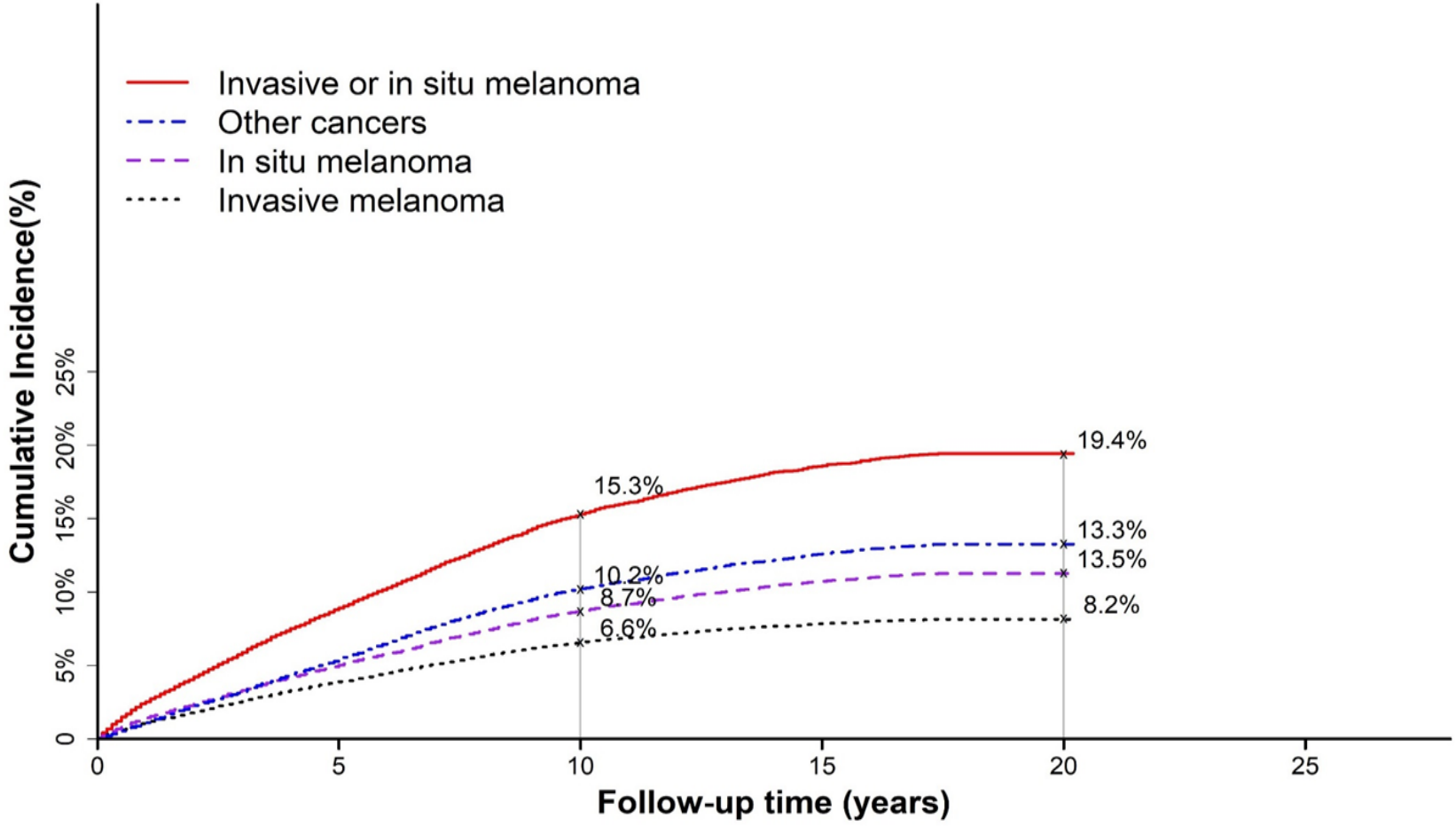


Figure S9. Cumulative incidence of a second primary invasive or in situ melanoma or other type of primary cancer in people who had a first primary in situ melanoma diagnosed during the period 2012-2019. Data for in situ melanoma were available from 2002.

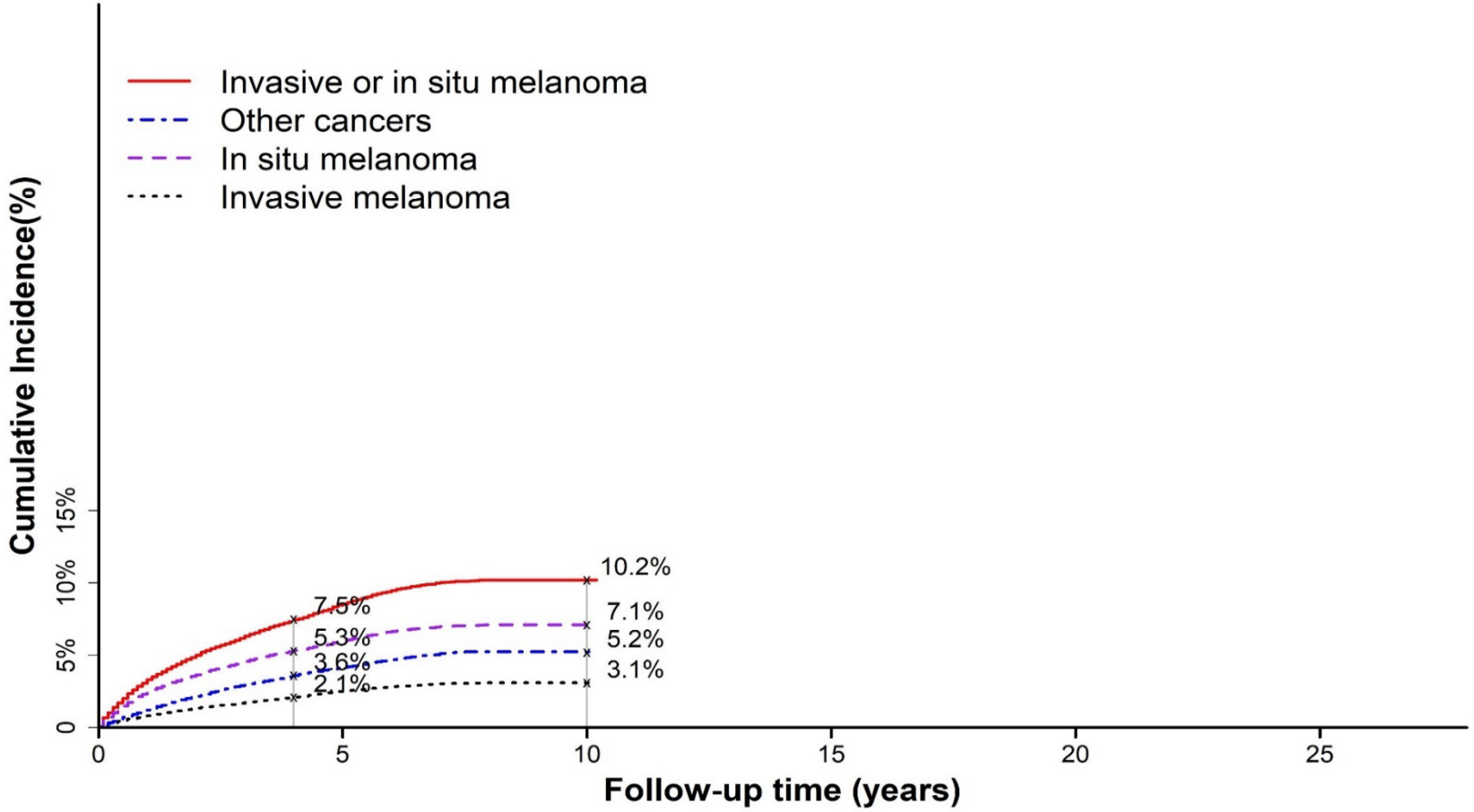


Figure S10. Overall mortality in people who had a first primary invasive or in situ melanoma (Full cohort)

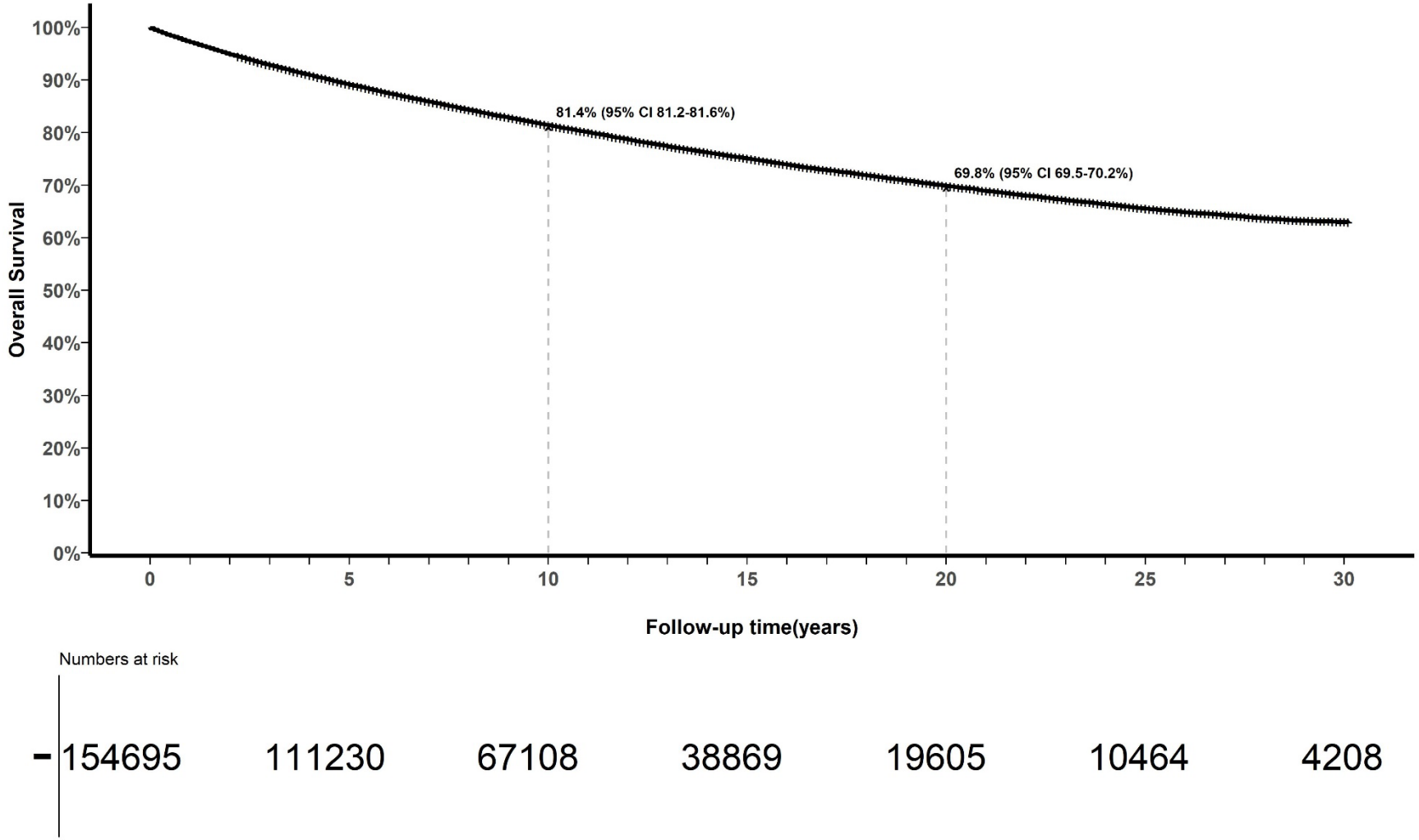


Figure S11. Cancer-Specific mortality in people who had a first primary invasive or in situ melanoma (Full cohort)

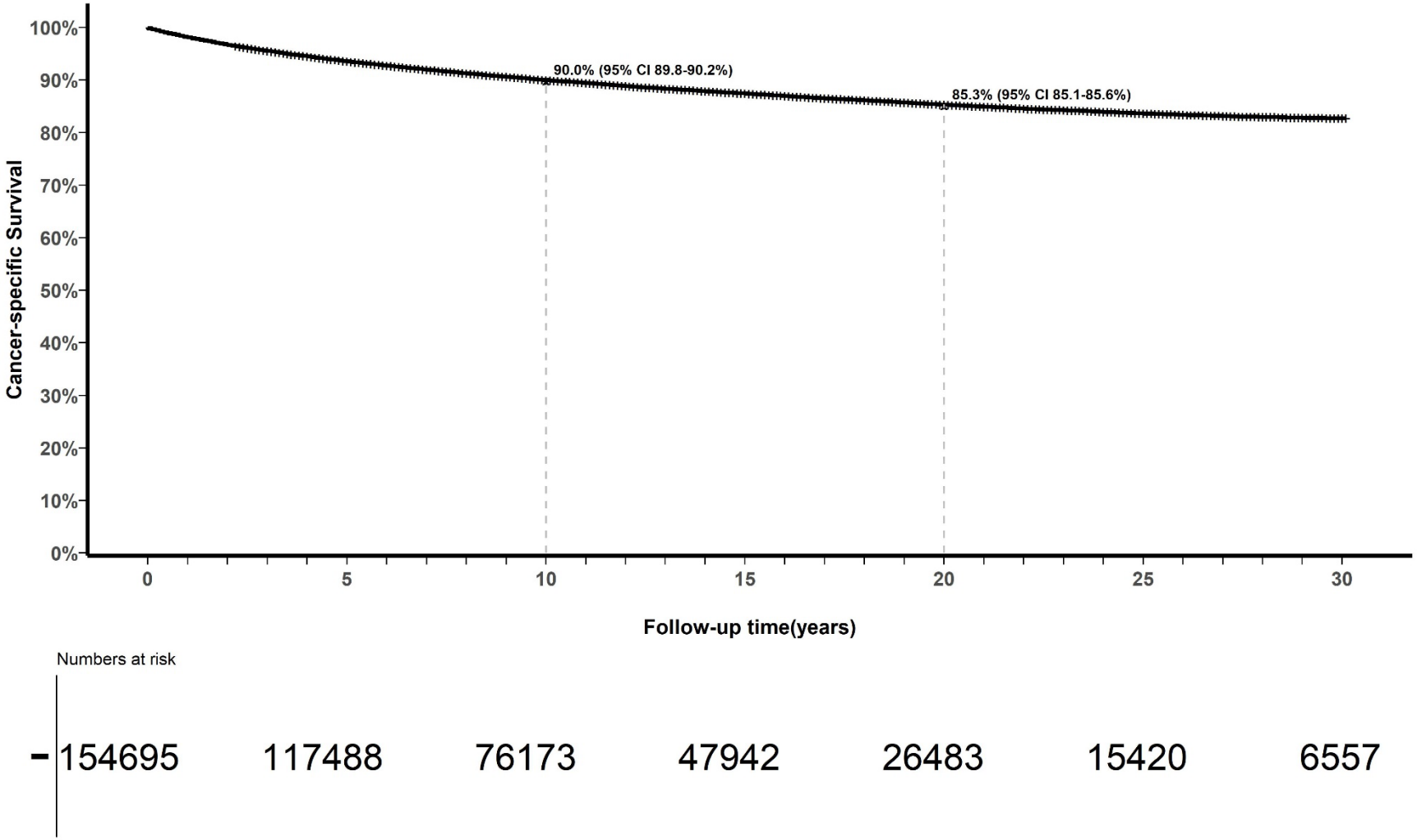


Figure S12. Melanoma-Specific mortality in people who had a first primary invasive or in situ melanoma (Full cohort)

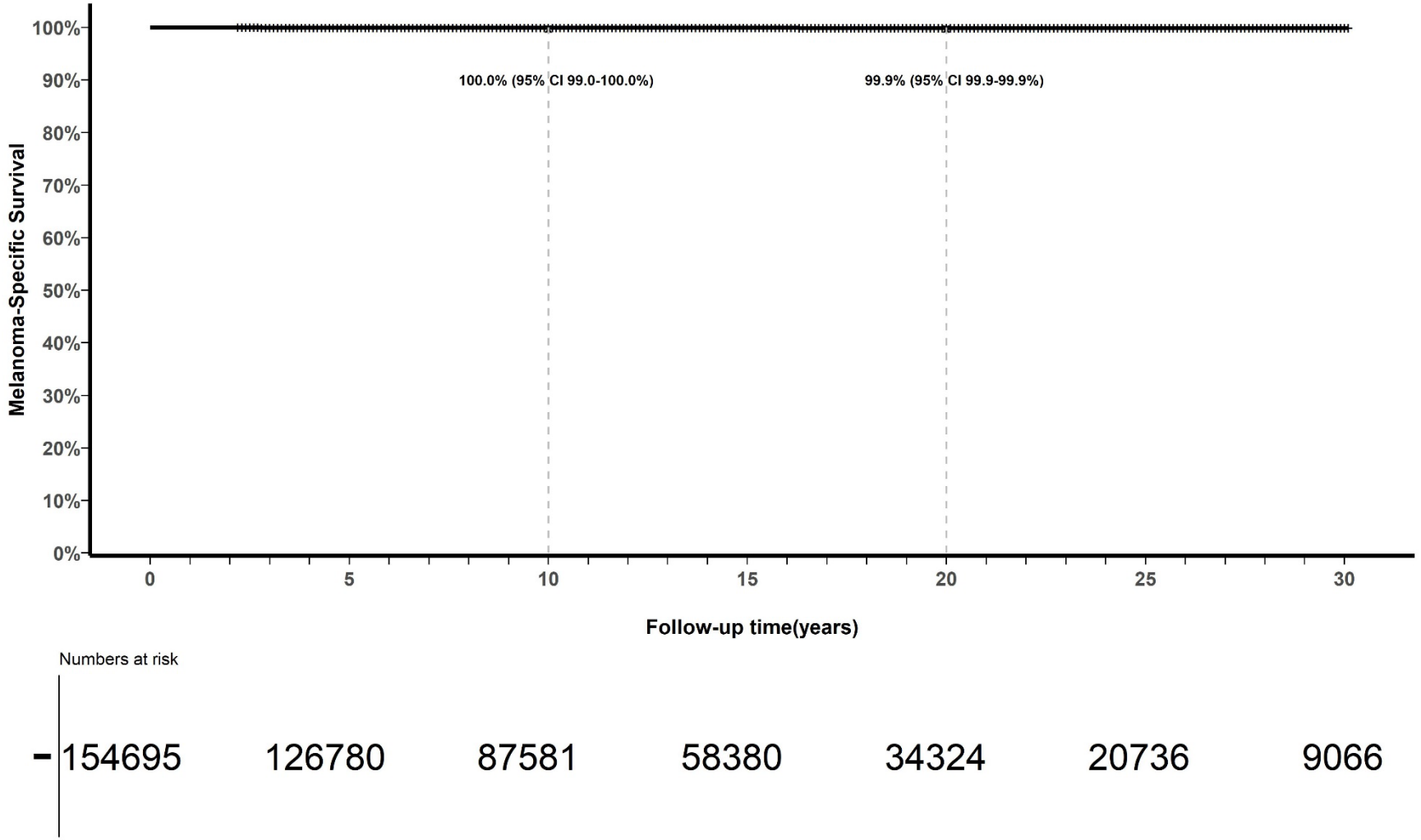


Table S1: Characteristics of patients at the time of their first primary melanoma, stratified by the diagnosis year groups

Characteristics	Overall (N = 154695)	1982-1991 (N = 8525)	1992-2001 (N = 24726)	2002-2011 (N = 52670)	2012-2019 (N = 68774)	P-value
Second cancer type						<.001
Melanoma	19708 (34.8%)	1154 (20.0%)	3953 (25.7%)	8681 (36.8%)	5920 (49.7%)	
Colon	1658 (2.9%)	174 (3.0%)	463 (3.0%)	712 (3.0%)	309 (2.6%)	
Breast	1933 (3.4%)	205 (3.6%)	492 (3.2%)	792 (3.4%)	444 (3.7%)	
Prostate	4380 (7.7%)	391 (6.8%)	1136 (7.4%)	1998 (8.5%)	855 (7.2%)	
Lung	1461 (2.6%)	177 (3.1%)	403 (2.6%)	604 (2.6%)	277 (2.3%)	
Others	7450 (13.2%)	716 (12.4%)	2009 (13.1%)	3228 (13.7%)	1497 (12.6%)	
Death	20058 (35.4%)	2953 (51.2%)	6906 (45.0%)	7600 (32.2%)	2599 (21.8%)	
Sex						<.001
Male	86836 (56.1%)	4688 (55.0%)	14153 (57.2%)	29759 (56.5%)	38236 (55.6%)	
Female	67859 (43.9%)	3837 (45.0%)	10573 (42.8%)	22911 (43.5%)	30538 (44.4%)	
Age at 1st melanoma (yrs)						<.001
Mean (SD)	61 (16)	55 (17)	58 (17)	62 (16)	62 (15)	
1st Quartile, median, 3rd quartile	50 62 73	42 57 69	46 59 71	51 63 74	53 64 73	
Minimum - Maximum	18, 103	18, 101	18, 103	18, 103	18, 103	
Age at 1 melanoma diagnosis (yrs)						<.001
18-24	1915 (1.2%)	272 (3.2%)	548 (2.2%)	570 (1.1%)	525 (0.8%)	
25-49	34470 (22.3%)	2981 (35.0%)	7221 (29.2%)	11170 (21.2%)	13098 (19.0%)	
50-64	48712 (31.5%)	2358 (27.7%)	7018 (28.4%)	17064 (32.4%)	22272 (32.4%)	
65-74	36876 (23.8%)	1759 (20.6%)	5383 (21.8%)	11664 (22.1%)	18070 (26.3%)	
>75	32722 (21.2%)	1155 (13.5%)	4556 (18.4%)	12202 (23.2%)	14809 (21.5%)	
Breslow thickness (mm)						<.001
Mean (SD)	0.8 (1.9)	1.4 (1.9)	1.3 (2.0)	0.8 (2.0)	0.6 (1.7)	
1st Quartile, median, 3rd quartile	0.0 0.3 0.8	0.5 0.7 1.5	0.4 0.7 1.4	0.0 0.3 0.8	0.0 0.0 0.5	
Minimum - Maximum	0.0, 120.0	0.0, 35.0	0.0, 70.0	0.0, 99.0	0.0, 120.0	
Breslow thickness category						<.001
In situ(0)	61971 (40.1%)	0 (0.0%)	0 (0.0%)	21626 (41.1%)	40345 (58.7%)	
0.1-0.7	44683 (28.9%)	3715 (43.6%)	11693 (47.3%)	14855 (28.2%)	14420 (21.0%)	
0.8-1.0	11322 (7.3%)	1106 (13.0%)	3186 (12.9%)	3793 (7.2%)	3237 (4.7%)	
1.1-2.0	13741 (8.9%)	1255 (14.7%)	3700 (15.0%)	4651 (8.8%)	4135 (6.0%)	
2.1-4.0	9051 (5.9%)	801 (9.4%)	2426 (9.8%)	3137 (6.0%)	2687 (3.9%)	
>4.1	5935 (3.8%)	476 (5.6%)	1343 (5.4%)	2010 (3.8%)	2106 (3.1%)	
Unknown	7992 (5.2%)	1172 (13.7%)	2378 (9.6%)	2598 (4.9%)	1844 (2.7%)	
Remoteness residence						<.001
Not available	27885 (18.0%)	8525 (100%)	19300 (78.1%)	5 (0.0%)	55 (0.1%)	
Major Cities	81284 (52.5%)	0 (0.0%)	3532 (14.3%)	33334 (63.3%)	44418 (64.6%)	
Inner Regional	35305 (22.8%)	0 (0.0%)	1463 (5.9%)	14966 (28.4%)	18876 (27.4%)	
Outer Regional	9629 (6.2%)	0 (0.0%)	410 (1.7%)	4085 (7.8%)	5134 (7.5%)	
Remote/very remote	592 (0.4%)	0 (0.0%)	21 (0.1%)	280 (0.5%)	291 (0.4%)	

Characteristics	Overall (N = 154695)	1982-1991 (N = 8525)	1992-2001 (N = 24726)	2002-2011 (N = 52670)	2012-2019 (N = 68774)	P-value
IRSAD						<.001
Not available	25767 (16.7%)	8525 (100%)	16759 (67.8%)	218 (0.4%)	265 (0.4%)	
quntile1	25727 (16.6%)	0 (0.0%)	1706 (6.9%)	11102 (21.1%)	12919 (18.8%)	
quntile2	25125 (16.2%)	0 (0.0%)	1591 (6.4%)	10112 (19.2%)	13422 (19.5%)	
quntile3	24451 (15.8%)	0 (0.0%)	1428 (5.8%)	9585 (18.2%)	13438 (19.5%)	
quntile4	25256 (16.3%)	0 (0.0%)	1552 (6.3%)	10060 (19.1%)	13644 (19.8%)	
quntile5	28369 (18.3%)	0 (0.0%)	1690 (6.8%)	11593 (22.0%)	15086 (21.9%)	

Chapter 4: Time trends in the incidence of multiple primary melanomas in Australia

In recent years, there has been a general increase worldwide in the incidence of melanoma. Some researchers have attributed this increase to overdiagnosis of melanoma (for invasive but particularly in situ melanoma). Most studies have focused on the incidence of first primary melanomas, but changes in incidence may be particularly notable in individuals with a history of melanoma, as they are at higher risk and are more likely to have regular skin examinations, thereby increasing the likelihood of being diagnosed with a new primary melanoma. This chapter investigated the incidence of multiple primary melanomas over time in Australia. The manuscript is currently under revision with an international journal (Journal of Investigative Dermatology). Supplementary materials for this publication are in Appendix E. We have also updated some of the Results to include age-standardisation in the calculation of incidence rates.

Chapter 4 is formatted according to the Journal of Investigative Dermatology original research paper requirement:

Ni Y, Espinoza D, McLoughlin K, Lo SN, and Cust AE. “Time trends in the incidence of multiple primary melanomas in Australia.”

Time trends in the incidence of multiple primary melanomas in Australia

ABSTRACT

The incidence of first primary melanoma has been on the rise internationally, but less is known about the incidence of multiple primary melanomas. We sought to investigate the incidence of multiple primary melanomas in a population-based Australian cohort comprising 521,508 individuals (227,772 females and 293,736 males) diagnosed with a first primary melanoma between 1982 and 2016. The incidence rate of second primary invasive melanoma within 5 years of a first primary invasive melanoma increased for males from 5.8 (95% confidence interval (CI):4.7-7.0) per 1000 person-years in 1982-1986 to 17.2 (95% CI:15.9-18.6) per 1000 person-years in 2012-2016, and for females from 3.1 (95% CI:2.4-4.0) to 11.1 (95%CI:9.8-12.4) respectively. When in situ and invasive melanomas were considered together, the incidence rates over time were more pronounced. For males, the incidence rates surged from10.2 (95% CI:8.9-11.6) to 46.3 (95% CI:44.8-47.8) per 1000 person-years and for females, from 6.0 (95% CI:5.0-7.0) to 31.1 (95% CI:29.7-32.5). Variations in trends were observed among anatomical sites and across different age groups. Incidence rates of second primary melanomas in Australia increased by 3 to 5-fold over three decades, consistent with incidence trends for first primary melanoma, and highlight the need for ongoing skin surveillance for people after their first diagnosis.

INTRODUCTION

The incidence of cutaneous melanoma has been increasing in many fair-skinned populations over the past few decades, although these reports are usually based on first primary melanoma diagnoses (Olsen et al., 2019; Thrift and Gudenkauf, 2020). The majority of melanomas are detected at an early stage and are associated with a good prognosis (Gershenwald et al., 2017); however, ongoing skin surveillance is recommended as patients experience a high risk of developing a second melanoma. Risk of developing a second primary melanoma depends on a number of risk factors, and the incidence varies substantially (Balamurugan et al., 2011; Cust et al., 2020; Ni et al., 2023; Schuurman et al., 2017; Smith et al., 2023; Wiener et al., 2022). Compared to reports of first primary melanoma, there are relatively few studies that have examined incidence of second primary melanomas and trends over time (Helgadottir et al., 2021; McCaul et al., 2008). Similar to observations for first primary melanoma, incidence trends may differ by country, sex, age and anatomical site (Olsen et al., 2020).

This study aimed to investigate the trends in the incidence of multiple primary melanomas over time in Australia, which has the highest melanoma incidence in the world (Arnold et al., 2022). The analyses were based on a large population-based cohort with over three decades of records from Australian state cancer registries.

MATERIALS AND METHODS

Study design and data source

This is a population-based cohort study in Australia, which analysed data from seven state and territory cancer registries (New South Wales, Victoria, Queensland, South Australia, Tasmania, Northern Territory and Western Australia). Cancer registries are required by Australian law to maintain all invasive cancer cases, where they record demographic, clinical and death information

of every individual diagnosed with cancers. We identified the cases of first and subsequent primary melanomas through ICD-O-3 codes C44.0–C44.9 (skin) and C80.9 (melanoma of unknown primary site if not coded C44.9 in some registries) with histology codes 8720–8799 and behaviour codes 2 (in situ) or 3 (invasive) from January 1982 until the latest data available at each cancer registry (all had complete data to at least December 2016). Every state and territory started to collect invasive melanomas data from 1982, while data for in situ melanomas was not collected widely until 2004. Prior to 2004, only Queensland, South Australia, Northern Territory and Western Australia systematically collected data for in situ melanoma. For this study the IARC multiple primary rules have not been applied, therefore numbers reported in this study will not match those reported by the cancer registries.

Ethics and governance approvals were obtained from the NSW Population and Health Service Research Ethics Committee (2020/ETH03109) and all state and territory cancer registries.

Cohort selection

The analysed cohort consisted of data from people diagnosed with either a first primary invasive or in situ melanoma between 1982 and 2016. The Australian Capital Territory was excluded from this analysis because data collection only started in 1994. The primary analysis cohort consisted of people with invasive melanoma which was available from the seven cancer registries. Additionally, a secondary analysis cohort (a "subset") included individuals diagnosed with either invasive or in situ melanomas, sourced from four states that collected in situ data from 1982-2016: Queensland, South Australia, Northern Territory and Western Australia.

Characteristics of patients and their melanomas were collected such as sex, age, body site, invasiveness, date of diagnosis, vital status, and if died – the date and cause of death. To examine time trends in the incidence of multiple primary melanomas, we divided people into seven 5-year

periods from 1982 to 2016 (1982-1986, 1987-1991, 1992-1996, 1997-2001, 2002-2006, 2007-2011, 2012-2016) based on the diagnosis date of their first primary melanoma.

Statistical analysis

Person-years at risk for developing a second primary melanoma of every individual was calculated as the time to second primary melanoma, or time to death, up to 5- or 10-years follow-up. If neither of events had occurred within 5 or 10 years, person-years were calculated as the minimum of either 'time to 31st December 2016' (First melanoma diagnosed after 2012) or '5 or 10 years'. We calculated the incidence rates of second primary melanoma and its associated 95% confidence interval (CI) per 1000 person-years, adjusted for age using direct standardisation by 5-year age groups with the Australian census population in the year 2000 as standard. Analyses were also stratified by sex (male, female) and age at first melanoma diagnosis (<40, 40-59, ⩾ 60 years).

Differences in individuals' characteristics between diagnosis years define by 5-year intervals (1982-1986, 1987-1991, 1992-1996, 1997-2001, 2002-2006, 2007-2011 and, 2012-2016) were assessed using the Chi-square test and ANOVA test for categorical and continuous variables, respectively. All statistical tests were 2-sided with p values < 0.05 considered statistically significant. Statistical analysis was conducted with SAS 9.4 (SAS Institute Inc).

RESULTS

The cohort of eligible people diagnosed with first primary melanoma between 1982 and 2016 consisted of 299,535 individuals (130,368 females and 169,167 males) who had a first primary invasive melanoma and 221,973 (97,404 females and 124,569 males) individuals diagnosed with first primary in situ or invasive melanoma in a subset of cancer registries in four states and territories that collected data on in situ melanomas over the same period.

Characteristics of people diagnosed with first primary melanoma from 1982 to 2016 are summarised in Table 1. Males comprised 56.5% of people diagnosed with first invasive melanoma, and this was 56.1% in the subset. Regardless of whether the full cohort (invasive melanoma only) or the subset (invasive or in situ melanoma), males were older when they were diagnosed with their first melanoma compared to females. For invasive melanomas, the most frequent anatomical locations for melanomas to be diagnosed among females were the lower limb or hip until 2011, and on the upper limb or shoulder region after 2012 (Table 1). Among males, melanoma predominantly manifested on the trunk in comparison to other body sites (Table 1). Figure 1 shows trends of the anatomical site of the first primary invasive or in situ melanoma. Among males, the trunk was consistently the most common site for invasive melanoma, but for in situ melanoma the head and neck region was the most common from 1982 to 2011, though this was surpassed by the trunk from 2012. In females, the most common site was the lower limb or hip for invasive melanomas, and for in situ melanomas the most common site was the head and neck region until 2011, and thereafter the upper limbs and shoulders.

Table 2 shows the age-standardised incidence rates of a second primary melanoma for each of the first 5 years following the first primary melanoma diagnosis, and Table 3 shows 5-year incidence by sex and age-group (⩽55, >55 years). The incidence rate of second primary invasive melanoma increased in the full cohort from 10.7 (95% CI: 9.3-12.2) in first year following the first primary melanoma in 1982-86 to 30.1 (95% CI: 28.7-31.5) in first year following the first primary melanoma in 2012-16 and in the subset including both invasive and in situ melanoma increased from 16.3 (95% CI: 13.9-18.9) to 67.3 (95% CI: 65.1-69.5), respectively (Table 2). The incidence rate of second primary invasive melanoma within 5 years of a first primary invasive melanoma increased for males from 5.8 (95% CI:4.7-7.0) per 1000 person-years in 1982-1986 to 17.2 (95% CI:15.9-18.6) per 1000 person-years in 2012-2016, and for females from 3.1 (95% CI:2.4-4.0) to 11.1 (95% CI:9.8-

12.4) respectively (Table 3). When in situ melanomas were also included, the increased rates over time were more pronounced: from 10.2 (95% CI:8.9-11.6) to 46.3 (95% CI:44.8-47.8) per 1000 person-years for males and from 6.0 (95% CI:5.0-7.0) to 31.1 (95% CI:29.7-32.5) per 1000 person-years for females (Table 3). The incidence of a second primary invasive melanoma was higher for people aged >55 years than for those aged ⩽ 55 years for both males and females, and incidence rates increased over time for both age-groups although more noticeably for the older age-group (Table 3). Male aged over 55 years had the highest incidence rates, reaching 20.5 (95% CI 18.8-22.3) per 1000 person-years for invasive melanoma only and 54.3 (95% CI: 52.4-56.3) per 1000 person-years for invasive and in situ melanoma combined in 2012-2016.

Table 4 shows, among people who developed a second primary melanoma within 5 years, the number of multiple primaries (two, or three or more) diagnosed. Males were more likely than females to develop three or more melanomas, and the proportion of males and females who developed three or more melanomas increased over time, from 13.7% of invasive melanomas in 1982-1986 to 20.8% in 2007-11 for males, and for females from 7.9% in 1982-1986 to 15.5% in 2007-11 for females.

The percentage of second primary melanomas that occurred on the same anatomical site as the first primary melanoma is shown in Table 5. The overall concordant percentages of first and second primary melanoma (for invasive melanoma only, and invasive and in situ melanoma combined) was fairly consistent over time in the range of 30-38% for males and females. However, the proportion concordant at specific anatomical sites differed over time and by sex; for example, for females, there was higher concordance for second primary melanomas occurring on the lower limb and hip (34-46%), and for males the trunk had the highest concordance (43-53%).

Supplementary table 1 shows the age-standardised incidence rates of a second primary melanoma for each of the first 10 years following the first primary melanoma diagnosis. The age-standardised

incidence rate of second primary invasive melanoma in the first year following the first primary melanoma diagnosis increased in the full cohort from 10.7 (95% CI: 9.3-12.2) in 1982-86 to 30.1 (95% CI: 28.7-31.5) in 2012-16 and in the subset including invasive and in situ melanoma increased from 16.3 (95% CI: 13.9-18.9) to 67.3 (95% CI: 65.1-69.5), respectively. The incidence rates were not entirely presented for people diagnosed in 2012-16, because their follow-up time less than 10 years.

DISCUSSION

This population-based Australian study found a rising incidence of multiple primary melanomas in Australia between 1982 and 2016, with incidence rates of second primary melanoma increasing 3 to 5-fold over this time period. Incidence increased for invasive melanomas but was more pronounced when in situ melanomas were also included and for the older age-group. The increased incidence over time was observed for both males and females. The increasing incidence of multiple primary melanomas is consistent with the overall rising trend in incidence of first primary melanomas in fair-skinned populations (Arnold et al., 2022).

To our knowledge, this is the largest cohort investigating trends in incidence of subsequent primary melanomas. Reports from the US Surveillance, Epidemiology, and End Results (SEER) data show increases in 5-year incidence of second primary melanoma from 2.1% in 1973-1997 to 3.9% in 1998-2012 (Goggins and Tsao, 2003; Wiener et al., 2022). A population-based cancer registry study in Sweden observed an approximately 5-fold increase in the incidence of multiple primary melanomas over five decades from the 1960s to the 2000s (Helgadottir et al., 2021). The rising incidence was independent of age, sex, invasiveness, or site of the melanoma, but they observed a steeper increase for males and the older age-group (Helgadottir et al., 2021). Similarly, males aged over 55 years had the highest incidence of a second primary melanoma in our Australian study. The Swedish study reported an incidence rate of second primary invasive or in situ melanoma of

10.3 (95% CI 9.3-11.2) per 1000 person-years for males and 7.5 (95% CI 6.8-8.3) per 1000 person-years for females in the 2000s cohort, which remains considerably (about 60-65%) lower than the incidence rates for second primary invasive or in situ melanoma observed in this Australian study for a similar time-period (2007-2011), at 29.3 (95% CI: 28.3-30.3) per 1000 person-years for males and 18.9 (95% CI 18.0-19.8 for females). This Australian study reported a higher incidence rate for second primary invasive melanoma within the first year of diagnosis than a cohort study using data from the Cancer Registry of Norway, which was 24.1 (95% CI:22.8-25.4) per 1000 person years for Australians (2007-2011) and 16.8 (95% CI:14.9-18.7) per 1000 person years for Norwegians (2008-2020) (Ghiasvand et al., 2024). If we selected Australian incidence rate from 2012 to 2016 to compare, the rate (30.1(95% CI:28.7-31.5) per 1000 person years) was almost twice as high as Norwegian incidence rate (Ghiasvand et al., 2024).

There are several risk factors for multiple primary melanomas, including male sex, increasing age, light skin colour, family history, genetic factors, number of nevi, sun exposure, sun protection behaviours, and histopathological factors (Cust et al., 2020; Smith et al., 2023). UV exposure from artificial and natural sources is an important risk factor for melanoma (El Ghissassi et al., 2009), and over 90% of melanomas in Australia are attributable to this risk factor (Arnold et al., 2018). The number of previous primary melanomas is a strong factor related to risk of a subsequent primary melanoma (Cust et al., 2020; Guitera et al., 2021). Overdiagnosis, representing increased detection of indolent melanomas, may be another reason for the increasing incidence trends, particularly as the trend was strongest when in situ melanoma were included in the incidence rates. Several studies have shown evidence of melanoma overdiagnosis (Olsen et al., 2023; Welch et al., 2021; Whiteman et al., 2022).

Other studies have observed that subsequent primary melanoma have a tendency to develop on the same site as the initial primary melanoma (Begg et al., 2006; Helgadottir et al., 2021). In our

study approximately 30-38% of second melanomas overall occurred on the same site as the first, although for females there was higher concordance for second primary melanomas occurring on the lower limb and hip and for males the trunk had the highest concordance. Similarly, the Swedish study reported higher concordance on the trunk for males but they reported higher concordance for the head and neck region for females (Helgadottir et al., 2021). Both our study and the Swedish study did not observe significant changes over time in the proportion of melanomas occurring at the same site. The body site on which a melanoma occurs has been shown to be associated with different risk factors and is thought to reflect the biological pathway underlying its pathogenesis (Siskind et al., 2005; Whiteman, 2010; Whiteman et al., 2003).

Strengths of our study include the large population-based cohort covering 98% of the Australian population, and follow-up over more than three decades with reliable follow-up data collected through cancer registries. A limitation is that data were not available prior to 1982, so any individuals who developed a first primary melanoma prior to 1982 and then a subsequent primary melanoma in 1982 or later would have their 'subsequent' melanoma misclassified as a 'first' melanoma in the cancer registry; nonetheless this would not have a major impact on the increasing trends observed over time in the dataset. Another limitation common to registry-based data is the unavailability of a comprehensive suite of risk factor data.

In conclusion, we observed that incidence rates of second primary melanomas in Australia increased by 3 to 5-fold over three decades, consistent with incidence trends for first primary melanoma. Our findings highlight the need for ongoing skin surveillance for people after their first melanoma diagnosis, and strengthen support for ongoing prevention programs to reduce the burden of melanoma in the population.

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Table 1: Characteristics of people with a first primary melanoma diagnosed between 1982 and 2016

Characteristic[1]	1982-86	1987-91	1992-96	1997-2001	2002-06	2007-11	2012-16	P-value[3]
FIRST INVASIVE MELANOMA								
Females, N	10314	13476	15877	18585	21424	23303	27389	
Age at diagnosis (y), mean (SD)	50.63 (18.01)	52.58 (18.31)	54.05 (18.30)	55.36 (18.19)	57.70 (17.78)	59.55 (17.30)	61.12 (17.07)	<.0001
Site of melanoma, N (%)								
Head and neck	1470 (15.8)	2022 (16.0)	2464 (16.3)	2800 (15.7)	3254 (15.7)	3463 (15.3)	3790 (14.2)	<.0001
Lower limb or hip	3734 (40.1)	4873 (38.6)	5531 (36.5)	6309 (35.3)	6965 (33.6)	7081 (31.4)	7900 (29.7)	
Trunk	1773 (19.0)	2632 (20.9)	3271 (21.6)	3990 (22.3)	4662 (22.5)	5181 (22.9)	6592 (24.8)	
Upper limb or shoulder	2335 (25.1)	3093 (24.5)	3880 (25.6)	4758 (26.6)	5866 (28.3)	6859 (30.4)	8336 (31.3)	
Other[4]	1002	856	731	728	677	719	771	
Males, N	10054	15376	19514	23809	28939	32814	38661	
Age at diagnosis (y), mean (SD)	54.04 (16.73)	55.18 (17.10)	57.55 (16.97)	59.17 (16.47)	61.34 (16.09)	63.32 (15.48)	64.78 (14.97)	<.0001
Site of melanoma, N (%)								
Head and neck	1799 (20.3)	2823 (20.1)	3899 (21.4)	4636 (20.6)	6005 (21.7)	6976 (22.3)	8240 (22.3)	0.5639
Lower limb or hip	1392 (15.7)	2130 (15.2)	2576 (14.1)	3037 (13.5)	3778 (13.7)	4296 (13.7)	4898 (13.3)	
Trunk	3886 (43.8)	6188 (44.1)	8015 (44.0)	10148 (45.0)	11894 (43.1)	13257 (42.4)	15667 (42.5)	
Upper limb or shoulder	1804 (20.3)	2895 (20.6)	3730 (20.5)	4725 (21.0)	5946 (21.5)	6739 (21.6)	8077 (21.9)	
Other[4]	1173	1340	1294	1263	1316	1546	1779	
FIRST INVASIVE OR IN SITU MELANOMA (SUBSET)[2]								
Females, N	5233	7654	10346	12608	15230	19158	27175	
Age at diagnosis (y), mean (SD)	50.49 (17.81)	52.45 (18.20)	53.52 (18.21)	54.25 (17.83)	56.64 (17.05)	57.72 (16.60)	59.17 (16.13)	<.0001
Site of melanoma, N (%)								
Head and neck	1004 (20.7)	1531 (21.3)	2214 (22.2)	2556 (20.8)	3060 (20.4)	3712 (19.7)	4736 (17.6)	0.0011
Lower limb or hip	1656 (34.1)	2423 (33.7)	3107 (31.2)	3651 (29.7)	4275 (28.6)	4872 (25.8)	6459 (24.1)	
Trunk	922 (19.0)	1408 (19.6)	2126 (21.4)	2813 (22.9)	3400 (22.7)	4626 (24.5)	7370 (27.4)	
Upper limb or shoulder	1273 (26.2)	1821 (25.4)	2504 (25.2)	3272 (26.6)	4234 (28.3)	5664 (30.0)	8289 (30.9)	
Other[4]	378	471	395	316	261	284	321	
Males, N	5222	8601	12355	15758	20390	25705	36538	
Age at diagnosis (y), mean (SD)	54.68 (16.85)	55.68 (16.97)	56.63 (17.08)	58.20 (16.44)	60.23 (15.56)	61.41 (15.11)	62.74 (14.41)	<.0001
Site of melanoma, N (%)								
Head and neck	1257 (26.7)	2090 (26.4)	3159 (26.9)	3795 (24.9)	5310 (26.7)	6617 (26.4)	9226 (25.7)	0.0315
Lower limb or hip	657 (13.9)	1073 (13.5)	1448 (12.3)	1867 (12.2)	2300 (11.6)	2975 (11.8)	3947 (11.0)	
Trunk	1862 (39.5)	3153 (39.8)	4780 (40.8)	6452 (42.3)	8000 (40.2)	10115 (40.3)	14855 (41.4)	
Upper limb or shoulder	936 (19.9)	1604 (20.3)	2338 (19.9)	3142 (20.6)	4303 (21.6)	5402 (21.5)	7821 (21.8)	
Other[4]	510	681	630	502	477	596	689	

[1] Based on the first primary melanoma if the person developed multiple primary melanoma

[2] Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

[3] P indicates a p-value for linear trend over time

[4] 'Other' category excluded from percentage calculations

Table 2. Age-standardised Incidence rates of a second primary melanoma for each of the first 5 years following the first primary melanoma diagnosis, stratified by diagnosis year of the first primary melanoma (5-year intervals)

		Invasive melanomas only				Invasive and in situ melanomas (subset)[3]			
Years	Time from Diagnosis	At-risk[1]	Events[2]	Death	IR (95% CI)	At-risk[1]	Events[2]	Death	IR (95% CI)
82-86	1	20347	209	1233	10.68(9.28-12.18)	10448	164	514	16.29(13.89-18.88)
82-86	2	18905	67	952	3.64(2.82-4.57)	9770	59	374	6.18(4.70-7.85)
82-86	3	17886	55	756	3.15(2.38-4.04)	9337	49	313	5.36(3.97-6.96)
82-86	4	17075	68	696	4.08(3.16-5.10)	8975	52	314	5.91(4.42-7.62)
82-86	5	16311	60	506	3.74(2.85-4.75)	8609	42	238	4.96(3.57-6.57)
87-91	1	28851	444	1328	15.96(14.51-17.48)	16254	339	556	21.57(19.34-23.93)
87-91	2	27079	145	1202	5.49(4.63-6.42)	15359	114	530	7.58(6.25-9.03)
87-91	3	25732	121	949	4.81(3.99-5.70)	14715	102	420	7.06(5.76-8.50)
87-91	4	24662	132	849	5.46(4.57-6.43)	14193	121	371	8.67(7.19-10.28)
87-91	5	23681	110	771	4.73(3.89-5.65)	13701	107	381	7.94(6.51-9.51)
92-96	1	35391	637	1512	18.65(17.23-20.12)	22701	529	644	24.06(22.05-26.15)
92-96	2	33242	219	1431	6.76(5.89-7.68)	21528	202	629	9.57(8.29-10.93)
92-96	3	31592	226	1107	7.31(6.38-8.29)	20697	199	549	9.78(8.47-11.19)
92-96	4	30259	210	1016	7.08(6.16-8.07)	19949	165	547	8.42(7.18-9.75)
92-96	5	29033	200	838	7.01(6.07-8.01)	19237	180	478	9.50(8.16-10.94)
97-01	1	42392	855	1795	20.92(19.54-22.35)	28364	966	782	35.43(33.23-37.70)
97-01	2	39742	332	1474	8.54(7.65-9.48)	26616	280	675	10.70(9.49-11.99)
97-01	3	37936	259	1309	6.97(6.15-7.85)	25661	283	667	11.24(9.97-12.59)
97-01	4	36368	256	1230	7.19(6.34-8.10)	24711	259	597	10.67(9.41-12.01)
97-01	5	34882	232	1016	6.76(5.92-7.66)	23855	242	540	10.31(9.05-11.64)
02-06	1	50362	1070	2083	22.03(20.73-23.37)	35618	1219	845	35.51(33.54-37.53)
02-06	2	47209	363	1887	7.88(7.09-8.71)	33554	402	853	12.21(11.04-13.43)
02-06	3	44959	300	1691	6.83(6.08-7.63)	32299	351	860	11.09(9.96-12.28)
02-06	4	42968	358	1563	8.52(7.66-9.43)	31088	400	811	13.12(11.87-14.44)
02-06	5	41047	286	1227	7.09(6.29-7.94)	29877	318	680	10.81(9.66-12.03)
07-11	1	56115	1300	2479	24.10(22.81-25.43)	44861	1972	1068	45.90(43.89-47.94)
07-11	2	52336	518	2196	10.17(9.31-11.06)	41821	786	1045	19.23(17.91-20.59)
07-11	3	49622	443	1781	9.14(8.31-10.02)	39990	690	972	17.65(16.35-18.99)
07-11	4	47398	450	1733	9.72(8.84-10.64)	38328	723	970	19.28(17.90-20.71)
07-11	5	45215	391	1303	8.81(7.96-9.70)	36635	677	850	18.86(17.47-20.31)
12-16	1	66047	1701	2682	30.09(28.68-31.54)	63708	3594	1165	67.30(65.11-69.51)
12-16	2	48864	435	2228	10.56(9.59-11.57)	45889	948	1068	24.70(23.15-26.29)
12-16	3	34650	247	1720	8.88(7.81-10.03)	32097	549	924	21.69(19.92-23.55)
12-16	4	22046	152	1402	9.66(8.18-11.25)	19751	305	762	21.96(19.57-24.49)
12-16	5	9568	40	848	8.38(5.98-11.17)	8288	86	496	20.85(16.67-25.48)

CI, confidence interval. IR, incidence rate per 1000 person-years

1 Person-years at risk, 2 Events are defined as second primary melanoma

3 Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

Table 3: 5-year incidence rate of a second primary melanoma over time (1982-2016), stratified by sex and age

		Year of first melanoma diagnosis						
Sex	**Age**	**1982-86**	**1987-91**	**1992-96**	**1997-2001**	**2002-06**	**2007-11**	**2012-16**
Invasive melanomas only								
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)[1]
Males	All	101 (2.4)	201 (3.2)	304 (3.7)	465 (4.6)	532 (4.6)	667 (5.1)	-
	≤55	42 (2.0)	68 (2.2)	88 (2.3)	148 (3.3)	129 (2.9)	121 (2.8)	-
	>55	59 (2.8)	133 (4.1)	216 (5.0)	317 (5.7)	403 (5.6)	546 (6.3)	-
Females	All	59 (1.4)	91 (1.7)	149 (2.2)	190 (2.5)	203 (2.3)	301 (3.2)	-
	≤55	31 (1.2)	36 (1.2)	65 (1.7)	78 (1.8)	85 (2.0)	107 (2.5)	-
	>55	28 (1.7)	55 (2.4)	84 (2.9)	112 (3.3)	118 (2.6)	194 (3.8)	-
		IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)
Males	All	5.81 (4.74-7.00)	7.47 (6.48-8.54)	8.57 (7.63-9.56)	10.63 (9.68-11.61)	10.45 (9.59-11.36)	11.84 (10.96-12.75)	17.22 (15.88-18.61)
	≤55	4.48 (3.23-5.93)	4.79 (3.72-6.00)	4.86 (3.90-5.93)	7.04 (5.95-8.22)	6.15 (5.14-7.26)	5.85 (4.86-6.94)	9.67 (7.90-11.61)
	>55	7.38 (5.62-9.38)	10.46 (8.76-12.32)	12.41 (10.81-14.12)	13.94 (12.45-15.52)	13.47 (12.19-14.81)	15.31 (14.05-16.62)	20.49 (18.75-22.30)
Females	All	3.11 (2.37-3.96)	3.72 (2.99-4.52)	4.86 (4.11-5.67)	5.34 (4.61-6.13)	5.07 (4.40-5.79)	7.03 (6.26-7.84)	11.07 (9.84-12.38)
	≤55	2.59 (1.76-3.58)	2.47 (1.73-3.34)	3.59 (2.77-4.51)	3.72 (2.94-4.59)	4.15 (3.31-5.07)	5.21 (4.27-6.25)	7.34 (5.85-9.01)
	>55	4.01 (2.66-5.62)	5.54 (4.17-7.09)	6.69 (5.33-8.19)	7.66 (6.31-9.15)	6.03 (4.99-7.17)	8.70 (7.52-9.96)	13.91 (12.08-15.86)
Invasive and in situ melanomas (subset)[2]								
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)[1]
Males	All	224 (4.3)	494 (5.7)	829 (6.7)	1381 (8.8)	1872 (9.2)	3211 (12.5)	-
	≤55	81 (3.3)	136 (3.5)	226 (4.1)	394 (6.0)	425 (5.8)	644 (7.8)	-
	>55	143 (5.2)	358 (7.6)	603(8.8)	987 (10.8)	1447 (11.1)	2567 (14.8)	-
Females	All	142 (2.7)	289 (3.8)	446 (4.3)	649 (5.1)	818 (5.4)	1637 (8.5)	-
	≤55	72 (2.3)	116 (2.8)	203 (3.6)	272 (4.0)	326 (4.5)	615 (7.2)	-
	>55	70 (3.2)	173 (5.0)	243 (5.1)	377 (6.5)	492 (6.2)	1022 (9.6)	-
		IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)
Males	All	10.24 (8.94-11.63)	13.29 (12.15-14.49)	15.36 (14.33-16.42)	20.26 (19.21-21.35)	21.13 (20.18-22.09)	29.33 (28.32-30.35)	46.25 (44.76-47.77)
	≤55	7.26 (5.77-8.93)	7.41 (6.22-8.70)	8.65 (7.56-9.81)	12.77 (11.54-14.06)	12.33 (11.19-13.53)	16.69 (15.42-18.00)	27.64 (25.56-29.80)
	>55	13.35 (11.25-15.62)	19.04 (17.12-21.06)	21.65 (19.95-23.41)	26.46 (24.83-28.13)	26.73 (25.37-28.12)	36.21 (34.82-37.62)	54.33 (52.39-56.30)
Females	All	5.95 (5.02-6.97)	8.22 (7.30-9.19)	9.33 (8.49-10.22)	11.19 (10.35-12.07)	11.68 (10.90-12.50)	18.92 (18.01-19.84)	31.07 (29.68-32.50)
	≤55	4.92 (3.85-6.12)	5.71 (4.71-6.79)	7.61 (6.60-8.69)	8.30 (7.35-9.32)	9.39 (8.40-10.44)	15.33 (14.14-16.56)	24.61 (22.69-26.61)
	>55	7.60 (5.93-9.48)	11.65 (9.98-13.45)	11.51 (10.11-13.01)	14.94 (13.47-16.49)	13.94 (12.73-15.19)	22.01 (20.69-23.38)	35.56 (33.62-37.55)

CI, confidence interval; IR, incidence rate per 1000 person-years of follow-up time

[1] N (%) is not reported for people diagnosed with a first melanoma between 2012-16 because the dataset does not have a full 5 years of follow-up data for these participants.
[2] Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

Table 4: Numbers of primary melanomas diagnosed within 5 years among people with multiple primary melanomas

Sex	No. of primary melanomas	Year of first melanoma diagnosis						
		82-86	87-91	92-96	97-01	02-06	07-11	12-16[1]
Invasive melanomas only		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Males	2	278 (86.3)	635 (87.2)	998 (85.1)	1402 (83.0)	2180 (81.3)	2814 (79.2)	-
	≥3	44 (13.7)	93 (12.8)	175 (14.9)	287 (17.0)	502 (18.7)	740 (20.8)	-
Females	2	209 (92.1)	375 (91.9)	503 (88.2)	688 (88.3)	1096 (89.0)	1491 (84.5)	-
	≥3	18 (7.9)	33 (8.1)	67 (11.8)	91 (11.7)	136 (11.0)	274 (15.5)	-
Invasive and in situ melanomas (subset)[2]								
Males	2	189 (84.4)	423 (85.6)	685 (82.6)	1128 (81.6)	1528 (81.6)	2527 (78.7)	-
	≥3	35 (15	71 (14.4)	144 (17.4)	254 (18.4)	344 (18.4)	684 (21.3)	-
Females	2	126 (88.7)	268 (92.7)	388 (87.0)	568 (87.5)	734 (89.7)	1374 (83.9)	-
	≥3	16 (11.3)	21 (7.3)	58 (13.0)	81 (12.5)	84 (10.3)	263 (16.1)	-

1 Incidence rates not presented for years 6 to 10 for the 2012-16 time period due to limited follow-up data for this group

2 Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

Table 5: The proportion of second primary melanomas that occurred on the same anatomical site as the first primary melanoma

		% concordance						
		Year of first melanoma diagnosis						
Sex	**Site**	**82-86**	**87-91**	**92-96**	**97-01**	**02-06**	**07-11**	**12-16**
Invasive melanomas only		%	%	%	%	%	%	%
Females	All sites	34.6	31.3	35.4	35.8	38.1	34.9	37.4
	Head and neck	32.5	33.0	32.1	33.1	34.6	29.3	28.5
	Lower limb or hip	38.5	35.1	37.5	42.9	46.0	39.0	42.5
	Trunk	27.6	22.2	36.5	33.5	30.0	36.6	38.6
	Upper limb or shoulder	34.8	31.6	34.7	30.9	38.7	34.3	38.2
Males	All sites	31.5	34.0	34.9	35.1	34.6	36.5	37.8
	Head and neck	16.9	24.0	25.1	22.8	26.2	25.7	29.0
	Lower limb or hip	13.6	24.2	20.2	27.1	25.2	25.6	31.1
	Trunk	46.4	44.5	48.5	48.3	46.4	50.9	52.9
	Upper limb or shoulder	27.3	29.5	25.7	24.3	25.7	27.2	24.5
Invasive and in situ melanomas (subset)[1]								
Females	All sites	33.0	31.6	35.4	35.7	35.5	33.8	34.2
	Head and neck	35.1	34.8	35.3	38.9	37.4	30.8	24.8
	Lower limb or hip	34.6	33.9	34.5	37.4	36.0	34.1	34.5
	Trunk	28.4	24.8	35.8	33.8	31.7	36.4	39.7
	Upper limb or shoulder	32.4	31.3	36.4	32.8	36.4	33.8	34.8
Males	All sites	30.9	32.3	33.6	34.9	34.1	34.1	35.1
	Head and neck	21.8	23.5	27.3	26.8	27.0	24.3	26.1
	Lower limb or hip	13.8	21.0	16.1	22.8	20.4	20.6	23.0
	Trunk	43.6	42.9	46.0	47.4	45.6	48.5	49.7
	Upper limb or shoulder	26.0	26.5	25.6	23.2	26.6	25.3	23.6

[1] Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

Supplementary Table 1 Age-standardised Incidence rates of a second primary melanoma for each of the first 10 years following the first primary melanoma diagnosis, stratified by diagnosis year of the first primary melanoma (5-year intervals)

		Invasive melanomas only				Invasive and in situ melanomas (subset)[3]			
Years	Time from Diagnosis	At-risk	Events[1]	Death[2]	IR (95% CI)	At-risk	Events[1]	Death[2]	IR (95% CI)
82-86	1	20347	209	1233	10.68(9.28-12.18)	10448	164	514	16.29(13.89-18.88)
82-86	2	18905	67	952	3.64(2.82-4.57)	9770	59	374	6.18(4.70-7.85)
82-86	3	17886	55	756	3.15(2.38-4.04)	9337	49	313	5.36(3.97-6.96)
82-86	4	17075	68	696	4.08(3.16-5.10)	8975	52	314	5.91(4.42-7.62)
82-86	5	16311	60	506	3.74(2.85-4.75)	8609	42	238	4.96(3.57-6.57)
82-86	6	15745	55	495	3.55(2.68-4.55)	8329	51	215	6.22(4.63-8.04)
82-86	7	15195	64	403	4.28(3.30-5.39)	8063	51	193	6.43(4.79-8.31)
82-86	8	14728	55	390	3.79(2.85-4.85)	7819	45	183	5.83(4.25-7.66)
82-86	9	14283	50	357	3.55(2.63-4.60)	7591	54	167	7.21(5.42-9.26)
82-86	10	13876	68	316	4.97(3.86-6.22)	7370	47	165	6.47(4.75-8.44)
87-91	1	28845	444	1328	15.96(14.51-17.48)	16254	339	556	21.57(19.34-23.93)
87-91	2	27073	145	1202	5.49(4.63-6.42)	15359	114	530	7.58(6.25-9.03)
87-91	3	25726	121	949	4.81(3.99-5.70)	14715	102	420	7.06(5.76-8.50)
87-91	4	24656	132	849	5.46(4.57-6.43)	14193	121	371	8.67(7.19-10.28)
87-91	5	23675	110	771	4.73(3.89-5.65)	13701	107	381	7.94(6.51-9.51)
87-91	6	22794	119	624	5.31(4.40-6.30)	13213	97	325	7.47(6.06-9.03)
87-91	7	22051	98	573	4.51(3.66-5.45)	12791	92	284	7.30(5.89-8.87)
87-91	8	21380	86	633	4.09(3.27-5.00)	12415	90	346	7.38(5.93-8.98)
87-91	9	20661	110	426	5.39(4.43-6.44)	11979	98	237	8.29(6.73-10.01)
87-91	10	20125	104	446	5.24(4.28-6.29)	11644	92	238	8.01(6.46-9.73)
92-96	1	35389	637	1512	18.65(17.23-20.12)	22701	529	644	24.06(22.05-26.15)
92-96	2	33240	219	1431	6.76(5.89-7.68)	21528	202	629	9.57(8.29-10.93)
92-96	3	31590	226	1107	7.31(6.38-8.29)	20697	199	549	9.78(8.47-11.19)
92-96	4	30257	210	1016	7.08(6.16-8.07)	19949	165	547	8.42(7.18-9.75)
92-96	5	29031	200	838	7.01(6.07-8.01)	19237	180	478	9.50(8.16-10.94)
92-96	6	27993	168	772	6.10(5.22-7.06)	18579	175	417	9.57(8.20-11.04)
92-96	7	27053	140	711	5.26(4.42-6.16)	17987	142	405	8.02(6.76-9.39)
92-96	8	26202	153	727	5.94(5.04-6.92)	17440	151	433	8.80(7.45-10.26)
92-96	9	25322	157	628	6.29(5.35-7.31)	16856	154	360	9.27(7.86-10.79)
92-96	10	24537	154	596	6.37(5.40-7.41)	16342	149	372	9.26(7.83-10.80)
97-01	1	42391	855	1795	20.92(19.54-22.35)	28364	966	782	35.43(33.23-37.70)
97-01	2	39741	332	1474	8.54(7.65-9.48)	26616	280	675	10.70(9.49-11.99)
97-01	3	37935	259	1309	6.97(6.15-7.85)	25661	283	667	11.24(9.97-12.59)
97-01	4	36367	256	1230	7.19(6.34-8.10)	24711	259	597	10.67(9.41-12.01)
97-01	5	34881	232	1016	6.76(5.92-7.66)	23855	242	540	10.31(9.05-11.64)
97-01	6	33633	221	963	6.69(5.83-7.60)	23073	222	544	9.78(8.54-11.11)
97-01	7	32449	191	795	5.98(5.16-6.85)	22307	194	450	8.83(7.63-10.11)
97-01	8	31463	210	876	6.79(5.90-7.74)	21663	202	533	9.48(8.22-10.83)
97-01	9	30377	196	688	6.55(5.66-7.49)	20928	207	431	10.04(8.72-11.46)
97-01	10	29493	184	723	6.33(5.45-7.28)	20290	233	466	11.68(10.23-13.23)

		Invasive melanomas only				Invasive and in situ melanomas (subset)[3]			
Years	Time from Diagnosis	At-risk	Events[1]	Death[2]	IR (95% CI)	At-risk	Events[1]	Death[2]	IR (95% CI)
02-06	1	50362	1070	2083	22.03(20.73-23.37)	35618	1219	845	35.51(33.54-37.53)
02-06	2	47209	363	1887	7.88(7.09-8.71)	33554	402	853	12.21(11.04-13.43)
02-06	3	44959	300	1691	6.83(6.08-7.63)	32299	351	860	11.09(9.96-12.28)
02-06	4	42968	358	1563	8.52(7.66-9.43)	31088	400	811	13.12(11.87-14.44)
02-06	5	41047	286	1227	7.09(6.29-7.94)	29877	318	680	10.81(9.66-12.03)
02-06	6	39534	271	1094	6.98(6.17-7.83)	28879	371	678	13.08(11.78-14.44)
02-06	7	38169	292	981	7.79(6.92-8.70)	27830	386	591	14.12(12.74-15.56)
02-06	8	36896	303	1031	8.36(7.45-9.33)	26853	449	669	17.08(15.54-18.69)
02-06	9	35562	271	833	7.73(6.84-8.68)	25735	416	578	16.47(14.92-18.09)
02-06	10	34458	246	750	7.24(6.37-8.18)	24741	411	525	16.91(15.32-18.59)
07-11	1	56115	1300	2479	24.10(22.81-25.43)	44861	1972	1068	45.90(43.89-47.94)
07-11	2	52336	518	2196	10.17(9.31-11.06)	41821	786	1045	19.23(17.91-20.59)
07-11	3	49622	443	1781	9.14(8.31-10.02)	39990	690	972	17.65(16.35-18.99)
07-11	4	47398	450	1733	9.72(8.84-10.64)	38328	723	970	19.28(17.90-20.71)
07-11	5	45215	391	1303	8.81(7.96-9.70)	36635	677	850	18.86(17.47-20.31)
07-11	6	43521	306	1200	8.01(7.14-8.93)	35108	589	747	19.35(17.82-20.94)
07-11	7	33621	208	1044	7.26(6.31-8.28)	26387	385	610	17.31(15.62-19.08)
07-11	8	24487	178	973	9.02(7.74-10.39)	18860	289	614	19.13(16.98-21.39)
07-11	9	14941	97	701	8.65(7.02-10.46)	11305	143	385	17.02(14.34-19.92)
07-11[5]	10	7405	29	495	8.32(5.57-11.61)	5437	54	321	21.46(16.12-27.55)
12-16	1	66047	1701	2682	30.09(28.68-31.54)	63708	3594	1165	67.29(65.11-69.51)
12-16	2	48875	435	2228	10.55(9.58-11.56)	45898	948	1068	24.68(23.13-26.27)
12-16	3	34716	247	1720	8.84(7.77-9.97)	32156	549	924	21.59(19.83-23.44)
12-16	4	22286	152	1402	9.43(7.99-10.99)	19938	305	762	21.55(19.20-24.04)
12-16	5	10111	40	848	7.26(5.18-9.67)	8645	86	496	18.74(14.99-22.91)
12-16[4]	6	949	0	539	-	583	0	321	-
12-16[4]	7	410	0	267	-	262	0	149	-
12-16[4]	8	143	0	112	-	113	0	89	-
12-16[4]	9	31	0	23	-	24	0	17	-
12-16[4]	10	8	0	8	-	7	0	7	-

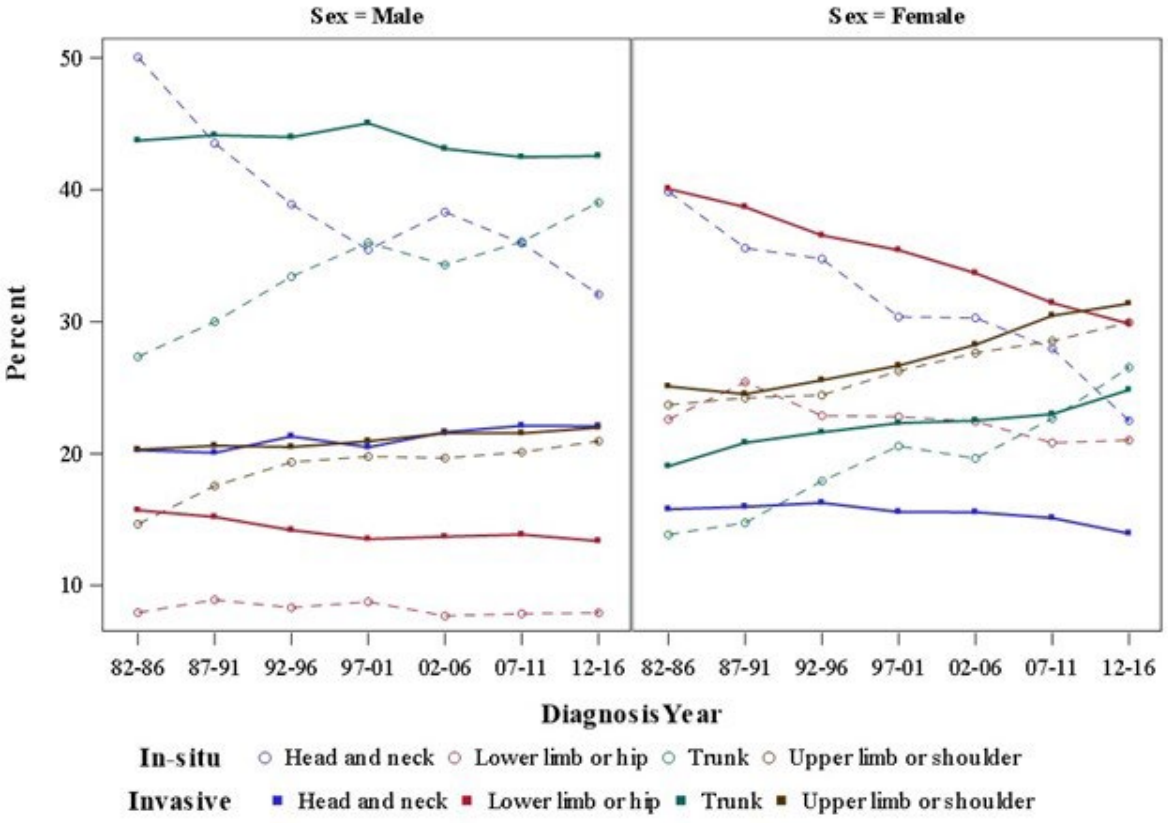
CI, confidence interval. IR, incidence rate per 1000 person-years

[1] Person-years at risk [2] Events are defined as second primary melanoma

[3] Based on data from cancer registries in Qld, NT, SA and WA who collected long-term data on in-situ melanomas

[4] Incidence rates not presented for years 6 to 10 for the 2012-16 time period due to limited follow-up data for this group.

Figure 1. Trends in the anatomical site of the first primary invasive or in situ melanoma



Chapter 5: Factors associated with 10-year overall and melanoma-specific mortality for people with multiple primary melanomas compared with a single primary melanoma

This chapter presents the findings from the sub-study that aimed to compare survival for people who were diagnosed with single primary melanoma versus multiple primary melanomas. This chapter contributes to the knowledge of risk factors associated with mortality for people diagnosed with multiple primary melanomas, and the increased numbers of primary melanomas may not influence mortality. The manuscript was originally submitted as a research article to the Journal of the American Academy of Dermatology (JAAD). The editor invited us to convert the manuscript to a research letter as part of the review process. The article was accepted after one peer-review round and published in JAAD as a research letter.

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Factors associated with 10-year overall and melanoma-specific mortality for people with multiple primary melanomas compared with a single primary melanoma

Abstract

Background: People with a history of primary melanoma have a higher risk of developing a subsequent primary melanoma compared to the general population; however, a differing prognosis for those with multiple primary melanomas (MPMs) and a single primary melanoma (SPM) has not been established.

Methods: We studied an Australian population-based cohort with 3,404 patients diagnosed with a first primary cutaneous melanoma in 2006-07 and followed up for subsequent melanomas and mortality until 2018 (median 11.9 years), analyzing ten-year melanoma-specific mortality and overall mortality.

Results: The cohort included 2,830 patients with SPM and 574 with MPMs. The crude 10-year melanoma-specific mortality was 7.3% (95% CI 6.4-8.4%) for SPM and 7.8% (5.8-10.4%) for MPMs. The adjusted odds ratio (OR) for melanoma-specific mortality was 0.85 (95%CI 0.58-1.24) for MPMs vs SPM. The crude 10-year overall mortality was 32.7% (95%CI 31.0-34.5%) for SPM and 35.4% (31.5-39.5%) for MPMs, but MPMs were associated with lower overall mortality (adjusted OR 0.78, 95%CI 0.61-0.99 compared to SPM).

Conclusions: The occurrence of multiple primary melanomas does not appear to worsen prognosis.

INTRODUCTION

Cutaneous melanoma is a relatively common cancer in countries with populations of predominantly European origin [181]. In Australia, which has the highest incidence rate in the world, the age-standardised incidence of melanoma has increased from 40.7 cases per 100,000 people in 1992 to 56.9 per 100,000 in 2022[182], whereas the mortality from melanoma has decreased [182]. In addition, many people develop more than one primary melanoma [103,183,184], as there is approximately a 10-fold increased risk of a second primary [156]. Published mortality statistics and follow-up guidelines for people diagnosed with melanoma are usually based on data for those who have a single primary melanoma (SPM). However, it is uncertain whether people with multiple primary melanomas (MPMs) have a prognosis that differs from that of people with a SPM. Previous studies have obtained mixed results, with some reporting similar survival for the two groups[185], and others reporting worse [186,187] or better survival for people with MPMs [187,188]. A recent systematic review and meta-analysis [184] found that study results varied markedly depending on the statistical methods used; overall the pooled hazard ratio (1.39, 95% confidence interval 1.07-1.81) indicated a survival disadvantage for patients with MPMs compared with SPM, although there was significant heterogeneity. Factors such as increased surveillance after an initial diagnosis of melanoma and survival bias may confound the assessment of such associations. In addition, many of the previous studies were limited by non-population-based samples and lack of information on important prognostic confounders.

Accurate information about the prognosis of individuals with MPMs and SPM is important for guiding follow-up strategies and providing patients with prognostic information. Using a comprehensive, population-based dataset with long-term follow-up, we sought to compare

10-year melanoma-specific mortality and overall mortality between people with MPMs and those with a SPM.

MATERIALS AND METHODS

Recruitment

New South Wales (NSW) is the most populous state in Australia with over eight million residents [189]. The Melanoma Patterns of Care study is a population-based observational study conducted among residents in the state of NSW, Australia in 2006-07, with follow-up until 2018.[190] Ethics approval was obtained from the NSW Population and Health Services Research Ethics Committee, the Australian Capital Territory (ACT) Health Human Research Ethics Committee (the ACT is geographically located within NSW) and the University of Sydney Human Research Ethics Committee. Governance approvals were obtained from each data custodian contributing to the data linkage.

Collection of data

The first primary melanoma was identified from the Melanoma Patterns of Care Study between 2006 to 2007. Patients were followed up for diagnosis of new primary melanomas and death over a median period of 11.9 years. Dates and causes of death were obtained from 2006-2018 through linkage of patients' identities with the Cause of Death Unit Record File and Registry of Births, Deaths and Marriages in NSW and the ACT, which also incorporates national death registry data. Therefore, patients without evidence of death were assumed to be alive and censored on 31st December 2018. Record linkage was performed by the NSW Centre for Health Record Linkage (CHeReL). Invasive and *in situ* melanomas that had occurred before or after the 2006-07 study period were identified in

the NSW cancer registry, and were available for the period 1972-2018 for invasive melanomas and 2002-2018 for in-situ melanomas. Histopathological data from 2006-2018 were extracted for all patients from pathology reports held by the NSW cancer registry, and clinico-pathological and treatment data for a subset of patients (n=1032) were also obtained from the Melanoma Institute Australia research database, which contains records of melanoma patients diagnosed since the 1960s. Socioeconomic status was estimated using the Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) [145], which ranks the social and economic levels based on patients' postcode of residence area. Level of residential remoteness was classified using Remoteness Area classification based on postcode [191].

Statistical analysis

Patients' characteristics and clinicopathological features were summarised according to SPM and MPM status. Frequencies and percentages were used to describe categorical variables, whilst median and interquartile ranges were used to summarise continuous variables. Differences in patients' characteristics were assessed using the Chi-square test and the Wilcoxon Signed Rank test for categorical and continuous variables, respectively.

All patients in the analysis were followed-up for at least 10 years. For each patient, the death status and cause of death, if dead, within 10 years of diagnosis were recorded. The primary outcome was 10-year melanoma-specific mortality and the secondary outcome was 10-year overall mortality, with the survival time starting from the date that their first melanoma was diagnosed in the period October 2006-07. Due to the violation of Cox proportional hazards regression assumptions (Figures 1,2), univariable and multivariable logistic regression models were constructed to compare the prognosis for people diagnosed with MPMs versus

a SPM. Outcome variables included survival status and causes of death. Covariates included age, sex, residence-based socioeconomic status and remoteness of area, family history of melanoma, 'lots of moles' (yes/no/don't know), Breslow thickness of the melanoma, body site of the melanoma, subtype, ulceration, regression, mitotic rate, and spread of melanoma at diagnosis. The primary analysis was based on pathological features of the thickest tumour for MPM patients, and sensitivity analyses were performed using pathological factors associated with the first tumour and last tumour, respectively. Variables with a p-value of <0.2 in the univariable analysis were included in the multivariable models. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were reported. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc). All statistical tests were two-sided with a p-value < 0.05 considered statistically significant.

RESULTS

Study cohort

Of the 3,404 people in the analysis, 2,830 (83.1%) had a SPM and 574 (16.9%) developed a second or higher order primary melanoma (MPM) during the follow-up period (1,385 melanomas). There were 1,385 primary melanomas in the MPM group, of which 423 had two melanomas, 97 had three melanomas, 39 had four melanomas, and 15 had five or more (maximum eight) primary melanomas. The median age of first melanoma diagnosis for patients who developed MPMs was 67 years (interquartile range 57-76) compared with 62 years (interquartile range 50-75) for SPM (P<0.0001; Table 1). The MPM group had a higher proportion of males (70.4%) than the SPM group (58.1%). The median length of time between first and second primary melanoma among people who developed MPM was 3.1 years (interquartile range 0.7-5.7).

Tumour Characteristics

Table 1 shows the clinicopathological characteristics of the first and the thickest subsequent melanoma diagnosed in each group within the study period for the SPM and MPM groups. The MPM group had a smaller proportion of thick melanomas than the SPM group for the first primary diagnosis, but a higher proportion of thick melanomas than the SPM group when the thickest of each person's melanomas were compared. For people with MPMs, the median Breslow thickness was *in situ* for the second (interquartile range 0-0.65), third (interquartile range 0-0.50) and fourth (interquartile range 0-0.60) melanomas. Comparing subtypes of the first tumour, the MPM group had a higher proportion of lentigo maligna melanomas and a lower proportion of nodular melanomas compared to the SPM group. Ulceration was more frequent in the SPM group than first melanomas in the MPM group, but was higher for the thickest melanomas in the MPM group. Regression was more frequent in the MPM group (41.1% compared to 34.6% in the SPM group for the first melanoma, and 36.6% compared to 34.6%, respectively, for the thickest melanoma).

Mortality outcomes

The 10-year crude melanoma-specific mortality was 7.3% (95% CI 6.4-8.4%) for patients with SPM and 7.8% (5.8-10.4%) for those with MPMs (p=0.19). The multivariable analysis adjusted for pathological characteristics of the thickest lesion in the MPM group showed no significant differences in 10-year melanoma-specific mortality between those with MPMs and SPM (OR 0.85, 95% CI: 0.58-1.24, p=0.40, Table 2). These findings were consistent with the sensitivity analyses using the pathological characteristics of the first melanoma among patients with MPMs (Supplemental Table 1). The 10-year overall crude mortality was 32.7% (95% CI 31.0-34.5%) for patients with SPM and 35.4% (95% CI 31.5-39.5%) for patients with

MPMs (p=0.22). Multivariable logistic regression adjusted for pathological features of the thickest lesion showed that patients with MPMs had lower 10-year overall mortality compared to those with SPM (OR 0.78, 95% CI: 0.61-0.99, p=0.04). However, in contrast, the sensitivity analyses adjusted for pathological features of the first lesion (OR 0.94, 95% CI: 0.74-1.19, p=0.60; Supplemental Table 1) or the last lesion (OR 1.07, 95% CI: 0.83-1.38, p=0.61; Supplemental Table 2) showed no differences in 10-year overall mortality for patients with SPM and MPMs. Other factors that were independently associated with higher melanoma-specific mortality in the multivariable analysis included male sex, disadvantaged socio-economic status, and Breslow thickness.

DISCUSSION

People diagnosed with their first primary melanoma have an elevated risk of developing subsequent primary melanomas [162,192-196]. Understanding the impact of MPM on patient survival is important for guiding the frequency and type of follow-up surveillance and for patients to receive accurate information about their prognosis. We examined melanoma-specific mortality and overall mortality for patients diagnosed with a SPM versus MPM in a large Australian population-based study with comprehensive long-term follow-up. We found that 16.9% of participants developed a second primary melanoma within 10 years of their first primary melanoma diagnosis. When accounting for other prognostic factors, developing MPMs did not lead to worse melanoma-specific survival compared to a SPM, a finding that is reassuring to patients.

Overall survival was higher for patients with MPMs than for those with SPM in a multivariable regression model adjusted for other risk factors. However, this might be explained by residual confounding from risk factors included in the model or that were not

measured, such as skin examination behaviours, or biological or other clinical or treatment factors. For example, people with a personal history of melanoma are advised to have regular skin checks and it is possible that they also increase other screening behaviours and have more contact with the health system that may improve other aspects of their health. The availability of new therapies for melanoma in the past decade may have also improved the outcomes for people who developed another primary melanoma. Well-established prognostic factors [185] that were independently associated with melanoma-specific survival and overall survival in our study included sex, Breslow thickness and ulceration status. We also observed worse survival for patients living in socio-economically disadvantaged areas, which is consistent with prior Australian research [197], and may be related to poorer access to medical care or education.

Analysis of mortality associated with MPMs is not straightforward, as heightened intensity of surveillance skin checks following an initial melanoma diagnosis has been reported to result in subsequent melanomas being detected at an earlier stage and hence with a better prognosis [188,198]. Consistent with this, we found that more than half of subsequent primary melanomas among people who developed MPMs were diagnosed at the *in situ* stage. However, some subsequent primary melanomas were thicker than the first primary melanoma for the MPM group, which led to a thicker median Breslow thickness for the MPM group than the SPM group when comparing the thickest tumour. Pigmented lesions detected through routine screening may be more likely to be 'overdiagnosed' as melanomas [199,200], defined as correctly classified melanomas but which if left undetected would not have caused any harm in a person's lifetime. Overdiagnosed lesions, by definition, would not increase mortality risk; thus, overdiagnosis may partly explain our findings if we assume that the MPM group had a greater frequency of skin examinations over the study period.

To minimise survival bias, we excluded people with melanomas diagnosed before the study period. We also evaluated the impact of possible bias by partitioning multiple index melanomas into the thickest lesion, first lesion, and last lesion. A recent systematic review[184] found that using the *first* melanoma in patients with MPMs in the analysis may introduce more survival bias, as people must live until the development of subsequent melanomas to be included as a MPM case, and this may result in a bias towards better survival for patients with MPMs.

Some researchers have proposed that a better or equivalent prognosis for people with MPMs compared to those with SPMs may represent either an immunisation effect against common melanoma tumour antigens in people exposed to MPM [201], genetic factors, or better surveillance [188,202]. In support of the first proposal, we found an increase in tumour regression in MPMs vs SPMs [201]. We did not evaluate genetic features in our study, but suspect that the observation of similar melanoma-specific survival for people with MPMs and SPMs in our study may relate to health-related behaviours and health system factors such as closer surveillance that ensured a subsequent primary melanoma did not worsen mortality outcomes. Thus, the generalisability of this finding to other countries might be influenced by the clinical surveillance recommendations and practices for people with melanoma in those countries. A limitation was that our analysis did not adjust for treatment modality (such as radiation therapy or systemic therapy). At the time of the baseline survey, survival rates for advanced melanoma were poor and effective systemic therapies were not available. Given that death from melanoma can occur many years after diagnosis [203], subsequent treatments given during the later years of follow-up may have improved patients' survival; it is possible that this had more impact in the MPM group as individuals who developed a SPM in the earlier years may have died before developing a MPM and

before systemic treatments became available. However, this limitation is common across other studies.

Strengths of our study include the population-based design, large sample size, availability of data for a comprehensive suite of socio-demographic and clinic-pathological prognostic-related variables, and long follow-up with reliable follow-up information. We analysed the data using 10-year outcomes (from the first melanoma) and logistic regression rather than time-to-event outcomes because the proportional hazard assumption did not hold when analysed in Cox proportional hazards regression models; the relative hazard between SPM and MPM was not constant over time as the Kaplan-Meier survival curves between the two groups crossed, and this result was consistent with the Schoenfeld residuals analysis. We lacked adjustment for treatment in the analysis, because treatment after melanoma diagnosis may improve prognosis in the MPM group. We included *in situ* lesions in the analysis, although they represented only 20% of all melanomas in the study (because numbers were capped at study entry). A previous Australian study reported that an additional *in situ* lesion after an invasive primary melanoma diagnosis did not impact survival [204].

In conclusion, our study found that the number of primary melanomas is not an independent risk factor for mortality. The development of multiple primary melanomas does not seem to impair prognosis. Early detection of melanoma rather than biological factors still has the biggest impact on melanoma mortality.

DATA AVAILABILITY: Due to ethical restriction, the data that support the findings of this study are not available publicly; however, interested people may contact AEC for potential collaborations.

CONFLICTS OF INTEREST: RAS has received fees for professional services from MetaOptima Technology Inc., F. Hoffmann-La Roche Ltd, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, AMGEN Inc., Bristol-Myers Squibb, Myriad Genetics, GlaxoSmithKline. SWM has received fees for advisory board participation from MoleMap Australia and Scibase AB. JFT has received honoraria for advisory board participation from BMS Australia, MSD Australia, GSK and Provectus Inc, and travel and conference support from GSK, Provectus Inc and Novartis.

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Table 1 Patient and lesion characteristics for the first and thickest melanoma for patients with single primary melanoma (SPM) and multiple primary melanomas (MPM)

Characteristic	SPM First lesion N = 2,830 (83.1%) N (%)	MPM First lesion N = 574 (16.9%) N (%)	P value*	MPM Thickest lesion N= 574 (16.9%) N (%)	P value*
Age, median (IQR)	62.0 (50.0-75.0)	67.0 (57.0-76.0)	<0.0001	N/A	N/A
Gender					
Males	1645 (58.1)	404 (70.4)	<0.0001	N/A	N/A
Females	1185 (41.9)	170 (29.6)			
Socioeconomic status			<0.0001		
Quintile 1	244 (8.6)	46 (8.0)		N/A	N/A
Quintile 2	447 (15.8)	76 (13.3)			
Quintile 3	881 (31.1)	185 (32.2)			
Quintile 4	543 (19.2)	94 (16.4)			
Quintile 5	715 (25.3)	173 (30.1)			
Remoteness Area			<0.0001		
Major cities	1176 (41.6)	256 (44.6)		N/A	N/A
Inner regional	1159 (40.9)	228 (39.7)			
Outer regional	472 (16.7)	85 (14.8)			
Remote	23 (0.8)	5 (0.9)			
Family history			<0.0001		
Absent	1360 (48.1)	235 (40.9)		N/A	N/A
Present	159 (5.6)	33 (5.8)			
Unknown	1311 (46.3)	306 (53.3)			
Lots of moles			<0.0001		
Absent	1284 (45.4)	231 (40.2)		N/A	N/A
Present	369 (13.0)	95 (16.6)			
Unknown	1177 (41.6)	248 (43.2)			
Breslow thickness (mm), median, IQR	0.60 (0.35-1.30)	0.60 (0.34-1.10)		0.75 (0.45-1.76)	
In situ	337 (11.9)	62 (10.8)	<0.0001	36 (6.3)	<0.0001
0-0.8	1289 (45.6)	301 (52.4)		254(44.2)	
0.9-1.0	198 (7.0)	33 (5.8)		37 (6.4)	
1.1 – 2.0	478 (16.9)	96 (16.7)		118 (20.6)	
2.1 – 4.0	315 (11.1)	55 (9.6)		78 (13.6)	
> 4.0	204 (7.2)	27 (4.7)		51 (8.9)	
Missing	9 (0.3)	0 (0.0)		0 (0.0)	
Body site			<0.0001		<0.0001
Head and neck	588 (20.8)	103 (18.0)		120 (20.9)	
Trunk	977 (34.5)	220 (38.3)		218 (38.0)	
Upper limbs	709 (25.0)	155 (27.0)		145 (25.3)	
Lower limbs	556 (19.7)	96 (16.7)		91 (15.8)	
Melanoma subtype			<0.0001		<0.0001
Superficial spreading	1362 (48.1)	271 (47.2)		248 (43.2)	
Nodular	376 (13.3)	61 (10.6)		88 (15.3)	
Lentigo maligna	357 (12.6)	101 (17.6)		84 (14.6)	
Other	180 (6.4)	31 (5.4)		35 (6.1)	
Not specified	555 (19.6)	110 (19.2)		119 (20.8)	
Ulceration			<0.0001		<0.0001
No	1964 (69.4)	402 (70.0)		401 (69.9)	
Yes	344 (12.2)	57 (9.9)		85 (14.8)	
Missing	522 (18.4)	115 (20.1)		88 (15.3)	
Regression			<0.0001		<0.0001
No	1016 (35.9)	160 (27.9)		186 (32.4)	
Yes	979 (34.6)	236 (41.1)		210 (36.6)	

Missing	835 (29.5)	178 (31.0)		178 (31.0)	
Mitotic rate (n/mm^2)			<0.0001		<0.0001
<1	847 (29.9)	175 (30.5)		163 (28.4)	
1-2	568 (20.1)	96 (16.7)		112 (19.5)	
3-10	444 (15.7)	77 (13.4)		103 (17.9)	
>10	120 (4.2)	18 (3.2)		35 (6.1)	
Missing	851 (30.1)	208 (36.2)		161 (28.1)	

*P-value for the MPM compared with SPM group

Table 2: Logistic regression model for 10-year overall and melanoma-specific mortality, using pathological factors from the thickest primary melanoma

Characteristics	N	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%)	P-value
Status									
SPM	**2830**	**1.00**	**0.66**	**1.00**	**0.40**	**1.00**	**0.22**	**1.00**	**0.04**
MPM	**574**	**1.08 (0.77-1.51)**		**0.85 (0.58-1.24)**		**1.13 (0.93-1.36)**		**0.78 (0.61-0.99)**	
Gender									
Males	2049	1.00	<0.01	1.00	0.03	1.00	<0.01	1.00	<0.01
Females	1355	0.58 (0.44-0.77)		0.70 (0.51-0.97)		0.54 (0.46-0.63)		0.60 (0.49-0.73)	
Age Categories									
Quartile 1	909	1.00	<0.01	1.00	0.12	1.00	<0.01	1.00	<0.01
Quartile 2	858	1.37 (0.93-2.03)		1.29 (0.84-1.98)		2.46 (1.82-3.32)		2.29 (1.68-3.13)	
Quartile 3	800	1.59 (1.08-2.33)		1.33 (0.86-2.05)		6.43 (4.85-8.52)		5.80 (4.31-7.81)	
Quartile 4	837	1.84 (1.27-2.68)		0.88 (0.57-1.35)		35.46 (26.58-47.32)		30.20 (22.24-41.03)	
Socioeconomic status[1]									
Quintile 1	290	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
Quintile 2	523	1.58 (0.95-2.63)		1.72 (0.97-3.04)		0.92 (0.69-1.23)		0.83 (0.57-1.19)	
Quintile 3	1066	0.75 (0.45-1.25)		0.78 (0.45-1.36)		0.77 (0.59-1.00)		0.67 (0.48-0.93)	
Quintile 4	637	1.02 (0.60-1.71)		1.13 (0.63-2.04)		0.73 (0.55-0.98)		0.71 (0.50-1.03)	
Quintile 5	888	0.87 (0.52-1.44)		1.02 (0.58-1.80)		0.61 (0.46-0.80)		0.57 (0.40-0.81)	
Remoteness Area									
Major cities	1432	1.00	0.89	N/A		1.00	0.33	N/A	
Inner regional	1387	0.91 (0.69-1.21)				1.08 (0.92-1.26)			
Outer regional	557	1.04 (0.72-1.50)				1.21 (0.99-1.49)			
Remote	28	0.93 (0.22-3.99)				1.02 (0.46-2.27)			
Family history[2]									
Absent	1595	1.00	0.19	1.00	0.69	1.00	<0.01	1.00	0.95
Present	192	0.84 (0.44-1.59)		0.88 (0.44-1.78)		0.58 (0.41-0.83)		1.04 (0.67-1.60)	
Unknown	1617	1.23 (0.95-1.61)		1.15 (0.79-1.66)		1.12 (0.96-1.29)		0.97 (0.81-1.16)	
Lots of moles[2]									
Absent	1515	1.00	0.15	1.00	0.34	1.00	0.20	N/A	
Present	464	1.18 (0.79-1.76)		1.40 (0.89-2.22)		0.82 (0.65-1.02)			
Unknown	1425	1.32 (1.00-1.74)		1.15 (0.78-1.69)		0.94 (0.80-1.09)			
Breslow thickness									
In situ (0)	399	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
0-0.8	1590	1.63 (0.48-5.51)		1.26 (0.34-4.64)		0.82 (0.64-1.06)		1.05 (0.73-1.52)	
0.9-1.0	231	6.64 (1.85-23.77)		3.89 (0.98-15.38)		0.85 (0.58-1.23)		1.06 (0.64-1.75)	
1.1-2.0	574	12.54 (3.89-40.38)		5.88 (1.63-21.21)		1.22 (0.92-1.62)		1.67 (1.09-2.56)	
2.1-4.0	370	29.27 (9.14-93.72)		11.80 (3.24-42.98)		3.03 (2.24-4.10)		2.82 (1.74-4.58)	
>4.0	231	60.94 (18.99-195.53)		22.40 (6.04-83.12)		7.52 (5.24-10.80)		4.85 (2.77-8.52)	
Missing	9								
Body site									
Head and neck	708	1.00	0.03	1.00	0.07	1.00	<0.01	1.00	0.17
Trunk	1195	0.95 (0.68-1.33)		1.23 (0.83-1.83)		0.59 (0.49-0.72)		0.87 (0.68-1.13)	
Upper limbs	854	0.58 (0.39-0.88)		0.72 (0.46-1.14)		0.49 (0.40-0.61)		0.73 (0.56-0.96)	
Lower limbs	647	1.02 (0.70-1.50)		1.17 (0.75-1.83)		0.48 (0.39-0.61)		0.84 (0.62-1.13)	
Melanoma subtype									
Superficial spreading	1610	1.00	<0.01	1.00	0.55	1.00	<0.01	1.00	0.19

Characteristics	N	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%)	P-value
Nodular	464	5.69 (4.14-7.82)		1.17 (0.79-1.73)		3.45 (2.78-4.27)		1.23 (0.89-1.71)	
Lentigo	441	0.52 (0.27-0.98)		0.88 (0.43-1.81)		2.09 (1.68-2.61)		1.26 (0.94-1.70)	
Other	215	3.79 (2.46-5.84)		1.19 (0.72-1.97)		2.09 (1.56-2.80)		0.83 (0.56-1.23)	
Not specified	674	0.91 (0.59-1.41)		0.78 (0.47-1.29)		1.13 (0.92-1.38)		1.01 (0.78-1.30)	
Spread of disease[4]									
In situ	373	1.00	<0.01	N/A		1.00	<0.01	N/A	
Localised	2852	8.26 (2.63-25.99)				1.23 (0.97-1.57)			
Regional	127	97.28 (29.63-319.42)				3.85 (2.53-5.87)			
Distant	20	229.05 (53.13-987.47)				14.66 (4.21-51.06)			
Missing	32	3.98 (0.40-39.39)				1.55 (0.73-3.29)			
Ulceration									
Absent	2365	1.00	<0.01	1.00	0.06	1.00	<0.01	1.00	0.26
Present	429	4.84 (3.65-6.42)		1.35 (0.96-1.91)		3.47 (2.81-4.28)		1.27 (0.94-1.72)	
Missing	610	0.41 (0.24-0.70)		0.62 (0.31-1.24)		1.15 (0.95-1.39)		1.12 (0.82-1.52)	
Regression									
Absent	1202	1.00	<0.01	1.00	0.12	1.00	0.19	1.00	0.78
Present	1189	0.32 (0.23-0.45)		0.79 (0.53-1.15)		0.86 (0.72-1.01)		1.09 (0.86-1.37)	
Missing	1013	0.55 (0.40-0.74)		1.26 (0.85-1.85)		0.91 (0.76-1.08)		1.03 (0.79-1.33)	
Mitotic rate (n/mm^2)									
<1	1010	1.00	<0.01	1.00	0.06	1.00	<0.01	1.00	0.66
1-2	680	5.04 (2.90-8.77)		1.88 (1.02-3.48)		1.24 (1.00-1.54)		1.01 (0.79-1.33)	
3-10	547	13.71 (8.11-23.17)		2.31 (1.23-4.34)		2.58 (2.07-3.22)		1.14 (0.81-1.61)	
>10	155	20.31 (11.16-36.99)		1.88 (0.91-3.90)		5.45 (3.81-7.81)		1.17 (0.70-1.98)	
Missing	1012	2.22 (1.24-3.96)		1.31 (0.66-2.59)		1.29 (1.06-1.56)		0.88 (0.66-1.16)	

CI, confidence interval; SPM, single primary melanoma; MPM, multiple primary melanomas

Pathological factors are from the thickest primary melanoma diagnosed during the study period. The survival time starts from their first melanoma diagnosed in the period October 2006-07. A missing category was set for Breslow thickness to keep the samples consistent between models.

[1]Socioeconomic status is based on postcode of residence. Quintile 1 represents the most disadvantaged status and quintile 5 represents the least disadvantaged status.

[2]These characteristics were collected by clinician questionnaire and were not available for every patient.

[3]Degree of spread is excluded from the multivariable analysis because of multicollinearity.

Figure 1: Kaplan-Meier Curve for Overall Survival for people diagnosed with single and multiple primary melanomas

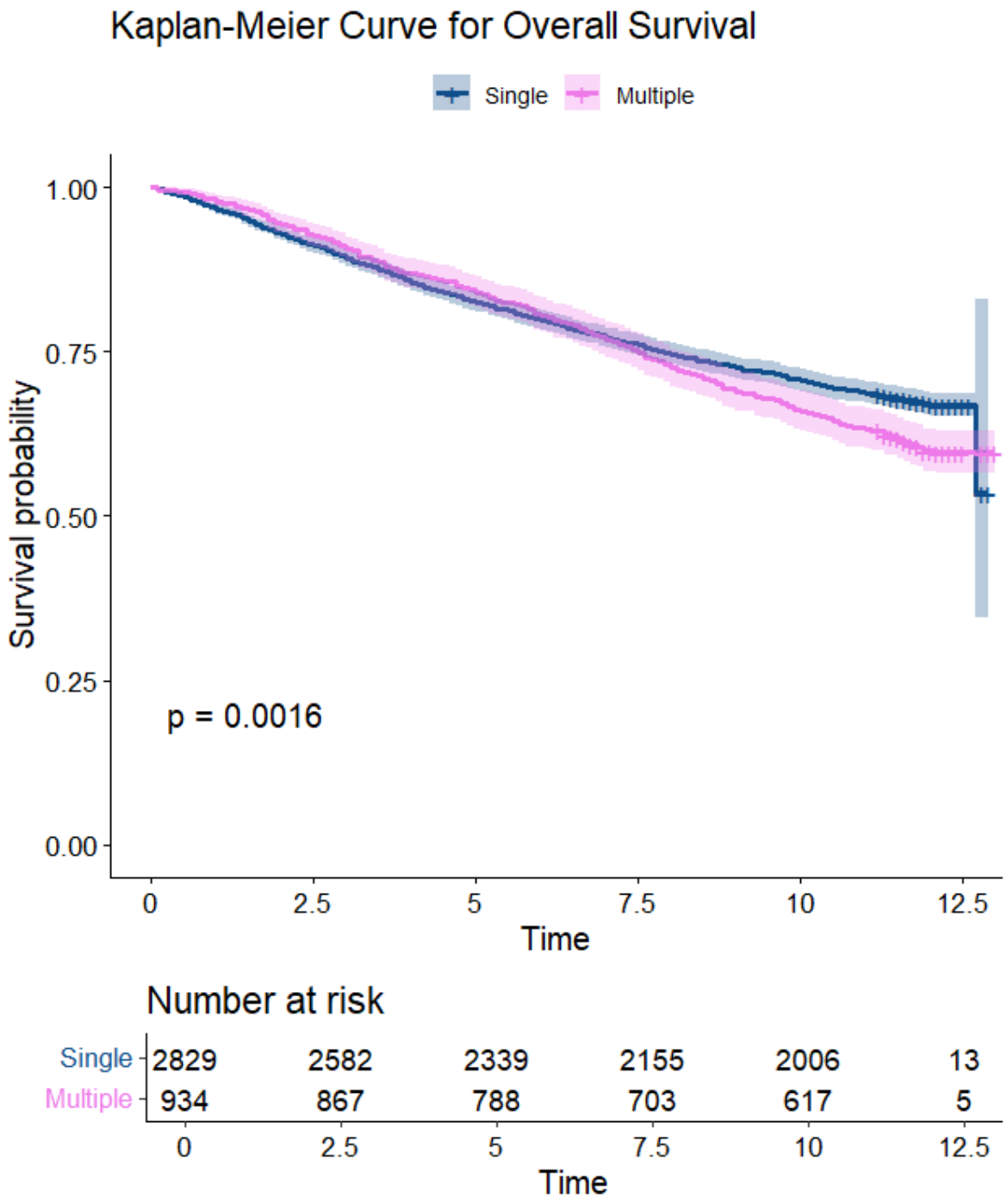
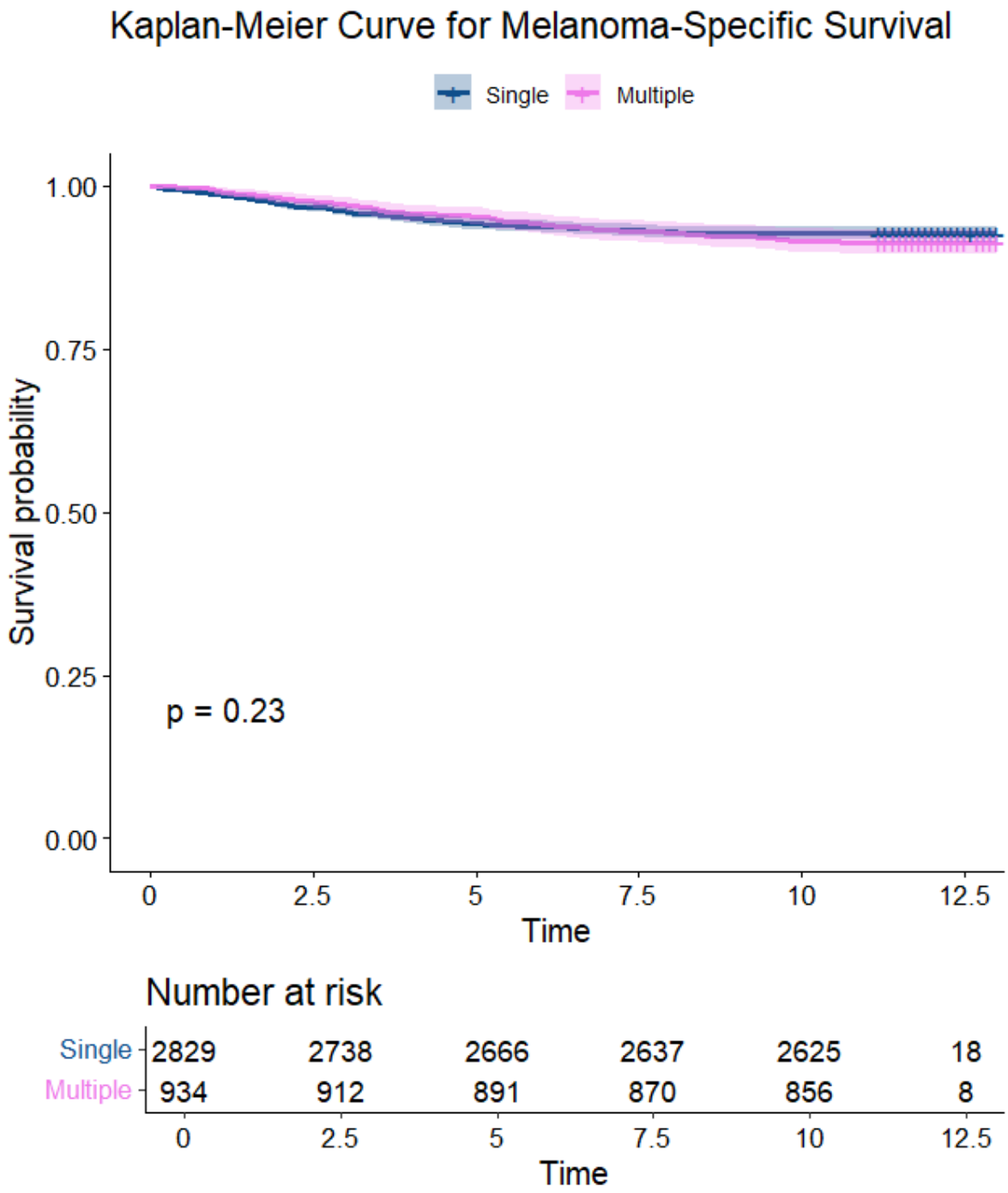


Figure 2: Kaplan-Meier Curve for Melanoma-Specific Survival for people diagnosed with single and multiple primary melanomas



Published research letter

Prognosis for people with multiple primary melanomas compared with a single primary melanoma

To the Editor: People with a history of melanoma have a higher risk of developing subsequent primary melanomas than the general population; however, a difference in outcome between those with multiple primary melanomas (MPMs) and a single primary melanoma (SPM) is not established.[1] Using a comprehensive, population-based dataset with long-term follow-up, we compared 10-year melanoma-specific mortality and overall mortality between people with MPMs and SPM.

The Melanoma Patterns of Care study is a population-based observational study of residents in the state of New South Wales, Australia, who had a melanoma reported to the state cancer registry over 12 months in 2006-07, with follow-up until 2018 (median 11.9 years).[2] People with a melanoma before study entry were excluded. Logistic regression analyses were performed to assess 10-year

Table I. Logistic regression model for 10-year melanoma-specific mortality, using pathological factors from the first and thickest primary melanoma (selected factors)

		Thickest lesion				First lesion			
		Univariable		Multivariable*		Univariable		Multivariabsle*	
Characteristics	*N*	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95%)	*P* value
Status									
SPM	2830	1.00	.66	1.00	.40	1.00	.66	1.00	.12
MPM	574	1.08 (0.77-1.51)		0.85 (0.58-1.24)		1.08 (0.77-1.51)		1.34 (0.92-1.96)	
Gender									
Males	2049	1.00	<.01	1.00	.03	1.00	<.01	1.00	.03
Females	1355	0.58 (0.44-0.77)		0.70 (0.51-0.97)		0.58 (0.44-0.77)		0.70 (0.51-0.96)	
Age categories									
Quintile 1	909	1.00	<.01	1.00	.12	1.00	0.01	1.00	0.22
Quintile 2	858	1.37 (0.93-2.03)		1.29 (0.84-1.98)		1.37 (0.93-2.03)		1.27 (0.83-1.95)	
Quintile 3	800	1.59 (1.08-2.33)		1.33 (0.86-2.05)		1.59 (1.08-2.33)		1.33 (0.86-2.06)	
Quintile 4	837	1.84 (1.27-2.68)		0.88 (0.57-1.35)		1.84 (1.27-2.68)		0.93 (0.61-1.44)	
Socioeconomic status†									
Quintile 1	290	1.00	<.01	1.00	<.01	1.00	<.01	1.00	<.01
Quintile 2	523	1.58 (0.95-2.63)		1.72 (0.97-3.04)		1.58 (0.95-2.63)		1.62 (0.92-2.86)	
Quintile 3	1066	0.75 (0.45-1.25)		0.78 (0.45-1.36)		0.75 (0.45-1.25)		0.75 (0.43-1.30)	
Quintile 4	637	1.02 (0.60-1.71)		1.13 (0.63-2.04)		1.02 (0.60-1.71)		1.06 (0.59-1.89)	
Quintile 5	888	0.87 (0.52-1.44)		1.02 (0.58-1.80)		0.87 (0.52-1.44)		0.91 (0.51-1.59)	
Family history‡									
Absent	1595	1.00	.19	1.00	.69	1.00	.19	1.00	.64
Present	192	0.84 (0.44-1.59)		0.88 (0.44-1.78)		0.84 (0.44-1.59)		0.90 (0.45-1.81)	
Unknown	1617	1.23 (0.95-1.61)		1.15 (0.79-1.66)		1.23 (0.95-1.61)		1.17 (0.81-1.70)	
Breslow thickness									
In situ (0)	399	1.00	<.01	1.00	<.01	1.00	<.01	1.00	<.01
0-0.8	1590	1.63 (0.48-5.51)		1.26 (0.34-4.64)		1.37 (0.52-3.58)		1.18 (0.41-3.40)	
0.9-1.0	231	6.64 (1.85-23.77)		3.89 (0.98-15.38)		5.47 (1.96-15.26)		3.54 (1.14-11.03)	
1.1-2.0	574	12.54 (3.89-40.38)		5.88 (1.63-21.21)		8.18 (3.24-20.65)		4.10 (1.42-11.82)	
2.1-4.0	370	29.27 (9.14-93.72)		11.80 (3.24-42.98)		19.50 (7.78-48.86)		8.15 (2.79-23.77)	
>4.0	231	60.94 (18.99-195.53)		22.40 (6.04-83.12)		38.13 (15.13-96.07)		14.56 (4.87-43.58)	
Body site									
Head and neck	708	1.00	.03	1.00	.07	1.00	.03	1.00	.02
Trunk	1195	0.95 (0.68-1.33)		1.23 (0.83-1.83)		1.10 (0.78-1.55)		1.56 (1.04-2.35)	
Upper limbs	854	0.58 (0.39-0.88)		0.72 (0.46-1.14)		0.65 (0.43-0.98)		0.86 (0.54-1.36)	
Lower limbs	647	1.02 (0.70-1.50)		1.17 (0.75-1.83)		1.11 (0.75-1.64)		1.34 (0.85-2.11)	

Continued

Table I. Cont'd

Characteristics	*N*	Thickest lesion				First lesion			
		Univariable		Multivariable*		Univariable		Multivariabsle*	
		Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95%)	*P* value
Melanoma subtype									
Superficial spreading	1610	1.00	<.01	1.00	.55	1.00	<.01	1.00	.82
Nodular	464	5.69 (4.14-7.82)		1.17 (0.79-1.73)		5.32 (3.86-7.34)		1.18 (0.80-1.75)	
Lentigo	441	0.52 (0.27-0.98)		0.88 (0.43-1.81)		0.62 (0.35-1.11)		1.16 (0.60-2.25)	
Other	215	3.79 (2.46-5.84)		1.19 (0.72-1.97)		3.52 (2.27-5.45)		1.35 (0.81-2.24)	
Not specified	674	0.91 (0.59-1.41)		0.78 (0.47-1.29)		1.06 (0.70-1.60)		1.13 (0.71-1.80)	
Ulceration									
Absent	2365	1.00	<.01	1.00	.06	1.00	<.01	1.00	.07
Present	429	4.84 (3.65-6.42)		1.35 (0.96-1.91)		4.70 (3.52-6.27)		1.42 (1.00-2.02)	
Missing	610	0.41 (0.24-0.70)		0.62 (0.31-1.24)		0.49 (0.30-0.79)		0.78 (0.41-1.46)	
Regression									
Absent	1202	1.00	<.01	1.00	.12	1.00	<.01	1.00	.56
Present	1189	0.32 (0.23-0.45)		0.79 (0.53-1.15)		0.37 (0.27-0.52)		0.86 (0.59-1.25)	
Missing	1013	0.55 (0.40-0.74)		1.26 (0.85-1.85)		0.53 (0.39-0.72)		1.09 (0.73-1.62)	
Mitotic rate (n/mm^2)									
<1	1010	1.00	<.01	1.00	.06	1.00	<.01	1.00	<.01
1-2	680	5.04 (2.90-8.77)		1.88 (1.02-3.48)		5.44 (3.14-9.46)		2.46 (1.34-4.50)	
3-10	547	13.71 (8.11-23.17)		2.31 (1.23-4.34)		14.57 (8.61-24.64)		3.24 (1.73-6.07)	
>10	155	20.31 (11.16-36.99)		1.88 (0.91-3.90)		20.86 (11.32- 38.46)		2.67 (1.27-5.62)	
Missing	1012	2.22 (1.24-3.96)		1.31 (0.66-2.59)		2.32 (1.31-4.12)		1.48 (0.77-2.87)	

Pathological factors are from the thickest and first primary melanoma diagnosed during the study period. The survival time starts from their first melanoma diagnosed in the period between October 2006 and October 2007. A missing category was set for Breslow thickness to keep the samples consistent between models.

CI, Confidence interval; *MPM*, multiple primary melanomas; *SPM*, single primary melanoma.

*Variables with a *P* value of <0.2 in the univariable analysis were included in multivariable models as adjustment factors.

†Socioeconomic status is based on postcode of residence. Quintile 1 represents the most disadvantaged status and quintile 5 represents the least disadvantaged status.

‡These characteristics were collected by clinician questionnaire and were not available for every patient.

melanoma-specific mortality difference between groups.

The analyzed data were from 3404 people (2830 had SPM, 574 developed a MPM during the follow-up period). Supplementary Table I, available via Mendeley at https://doi.org/10.17632/yknjyk9tfz.1 shows the patient and lesion characteristics for the first and thickest melanomas stratified by SPM and MPMs. The multivariable regression adjusted for pathological characteristics of the thickest lesion in the MPM group showed no significant differences in 10-year melanoma-specific mortality between the two groups (odds ratio 0.85, 95% confidence interval: 0.58-1.24, *P* .40, Table I). These findings were consistent with the sensitivity analyses using parameters of the first primary melanoma among patients with MPMs (odds ratio 1.34, 95% confidence interval: 0.92-1.96, *P* .12), although using first lesion characteristics may introduce survival bias.[1] Other factors independently associated with higher

melanoma-specific mortality in the multivariable analysis using data from the thickest lesion were male sex, disadvantaged socioeconomic status (based on location of residence), and Breslow thickness; and there were borderline-significant associations with body site, ulceration, and mitotic rate (Table I). The 10-year overall mortality results are presented in Supplementary Table II, available via Mendeley at https://doi.org/10.17632/yknjyk9tfz.1.

Sex, Breslow thickness, ulceration status, and socioeconomic disadvantage have been identified in other studies as factors independently associated with melanoma-specific survival.[3,4] The worse prognosis for patients living in socioeconomically disadvantaged areas may be related to poorer access to medical care or education.

The main limitation is the lack of adjustment for treatment modality (eg systemic therapy) in the multivariable analysis. At the time of the baseline survey, effective systemic therapies were unavailable and survival rates for patients with advanced melanoma were very poor. Given that death from melanoma can occur many years after diagnosis,[5] treatment during later years of follow-up may have improved survival outcomes. It is possible that this had more impact in the MPM group as people who developed a SPM in the earlier years may have died before developing a MPM and before systemic treatments became available.

The results of our study suggest that the number of primary melanomas is not an independent risk factor for mortality. In addition, the detection of melanoma at an early stage (with a thin Breslow thickness) rather than an intrinsic biologic factor remains the biggest influence on melanoma mortality after diagnosis of 1 or more melanomas.

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Conflicts of interest

Richard A Scolyer has received fees for professional services from MetaOptima Technology Inc., F. Hoffmann-La Roche Ltd, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, AMGEN Inc., Bristol-Myers Squibb, Myriad

Genetics, GlaxoSmithKline. Scott W Menzies has received fees for advisory board participation from MoleMap Australia and Scibase AB. John F Thompson has received honoraria for advisory board participation from BMS Australia, MSD Australia, GSK and Provectus Inc, and travel and conference support from GSK, Provectus Inc and Novartis. Yuan Ni, Caroline G Watts, Christine Madronio, Bruce K Armstrong, Rachael L Morton, Graham J Mann, Anne E Cust, and Serigne N Lo have no conflicts of interest to declare.

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Supplementary Table 1: Logistic regression model for overall and melanoma-specific mortality, using pathological factors from the first primary melanoma

Characteristics	No. (%)	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%)	P-value
Status									
SPM	**2830**	**1.00**	**0.66**	**1.00**	**0.12**	**1.00**	**0.22**	**1.00**	**0.60**
MPM	**574**	**1.08 (0.77-1.51)**		**1.34 (0.92-1.96)**		**1.13 (0.93-1.36)**		**0.94 (0.74-1.19)**	
Gender									
Males	2049	1.00	<0.01	1.00	0.03	1.00	<0.01	1.00	<0.01
Females	1355	0.58 (0.44-0.77)		0.70 (0.51-0.97)		0.54 (0.46-0.63)		0.59 (0.48-0.72)	
Age Categories									
Quartile 1	909	1.00	0.01	1.00	0.22	1.00	<0.01	1.00	<0.01
Quartile 2	858	1.37 (0.93-2.03)		1.27 (0.83-1.95)		2.46 (1.82-3.32)		2.33 (1.71-3.18)	
Quartile3	800	1.59 (1.08-2.33)		1.33 (0.86-2.06)		6.43 (4.85-8.52)		5.94 (4.41-7.98)	
Quartile 4	837	1.84 (1.27-2.68)		0.93 (0.61-1.44)		35.46 (26.58-47.32)		30.93 (22.79-41.99)	
Socioeconomic status[1]									
Quintile 1	290	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
Quintile 2	523	1.58 (0.95-2.63)		1.62 (0.92-2.86)		0.92 (0.69-1.23)		0.82 (0.57-1.18)	
Quintile 3	1066	0.75 (0.45-1.25)		0.75 (0.43-1.30)		0.77 (0.59-1.00)		0.66 (0.47-0.92)	
Quintile 4	637	1.02 (0.60-1.71)		1.06 (0.59-1.89)		0.73 (0.55-0.98)		0.69 (0.48-1.00)	
Quintile 5	888	0.87 (0.52-1.44)		0.91 (0.51-1.59)		0.61 (0.46-0.80)		0.55 (0.39-0.78)	
Remoteness Area									
Major cities	1432	1.00	0.89	N/A		1.00	0.33	N/A	
Inner regional	1387	0.91 (0.69-1.21)				1.08 (0.92-1.26)			
Outer regional	557	1.04 (0.72-1.50)				1.21 (0.99-1.49)			
Remote	28	0.93 (0.22-3.99)				1.02 (0.46-2.27)			
Family history[2]									
Absent	1595	1.00	0.19	1.00	0.64	1.00	<0.01	1.00	0.95
Present	192	0.84 (0.44-1.59)		0.90 (0.45-1.81)		0.58 (0.41-0.83)		1.02 (0.66-1.58)	
Unknown	1617	1.23 (0.95-1.61)		1.17 (0.81-1.70)		1.12 (0.96-1.29)		0.98 (0.81-1.17)	
Lots of moles[2]									
Absent	1515	1.00	0.15	1.00	0.42	1.00	0.20	N/A	
Present	464	1.18 (0.79-1.76)		1.35 (0.86-2.13)		0.82 (0.65-1.02)			
Unknown	1425	1.32 (1.00-1.74)		1.13 (0.77-1.65)		0.94 (0.80-1.09)			
Breslow thickness									
In situ (0)	399	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
0-0.8	1590	1.37 (0.52-3.58)		1.18 (0.41-3.40)		0.79 (0.62-1.01)		0.92 (0.65-1.31)	
0.9-1.0	231	5.47 (1.96-15.26)		3.54 (1.14-11.03)		0.88(0.61-1.26)		0.97 (0.59-1.58)	
1.1-2.0	574	8.18 (3.24-20.65)		4.10 (1.42-11.82)		1.17(0.89-1.54)		1.35 (0.88-2.05)	
2.1-4.0	370	19.50 (7.78-48.86)		8.15 (2.79-23.77)		2.87(2.13-3.87)		2.30 (1.42-3.71)	
>4.0	231	38.13 (15.13-96.07)		14.56 (4.87-43.58)		7.24(5.01-10.45)		3.89 (2.21-6.84)	
Missing	9								
Body site									
Head and neck	708	1.00	0.03	1.00	0.02	1.00	<0.01	1.00	0.14
Trunk	1195	1.10 (0.78-1.55)		1.56 (1.04-2.35)		0.59 (0.48-0.71)		0.88 (0.69-1.14)	
Upper limbs	854	0.65 (0.43-0.98)		0.86 (0.54-1.36)		0.49 (0.39-0.60)		0.73 (0.56-0.96)	
Lower limbs	647	1.11 (0.75-1.64)		1.34 (0.85-2.11)		0.48 (0.38-0.60)		0.85 (0.63-1.15)	
Melanoma subtype									
Superficial spreading	1610	1.00	<0.01	1.00	0.82	1.00	<0.01	1.00	0.65

Characteristics	No. (%)	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	Odds ratio (95%)	P-value
Nodular	464	5.32 (3.86-7.34)		1.18 (0.80-1.75)		3.20 (2.58-3.98)		1.16 (0.83-1.62)	
Lentigo	441	0.62 (0.35-1.11)		1.16 (0.60-2.25)		2.03 (1.63-2.51)		1.14 (0.85-1.52)	
Other	215	3.52 (2.27-5.45)		1.35 (0.81-2.24)		2.01 (1.50-2.70)		0.89 (0.60-1.31)	
Not specified	674	1.06 (0.70-1.60)		1.13 (0.71-1.80)		1.10 (0.90-1.34)		0.99 (0.77-1.29)	
Spread of disease[3]									
In situ	373	1.00	<0.01	N/A		1.00	<0.01	N/A	
Localised	2852	5.48 (2.24-13.41)				1.17 (0.93-1.47)			
Regional	127	62.08 (23.91-161.14)				3.44 (2.25-5.26)			
Distant	20	236.36 (48.86-999.99)				26.78 (3.42-209.40)			
Missing	32	2.63 (0.30-23.21)				1.54 (0.73-3.28)			
Ulceration									
Absent	2365	1.00	<0.01	1.00	0.07	1.00	<0.01	1.00	0.24
Present	429	4.70 (3.52-6.27)		1.42 (1.00-2.02)		3.27 (2.64-4.07)		1.29 (0.95-1.75)	
Missing	610	0.49 (0.30-0.79)		0.78 (0.41-1.46)		1.14 (0.94-1.37)		1.09 (0.81-1.47)	
Regression									
Absent	1202	1.00	<0.01	1.00	0.56	1.00	0.32	N/A	
Present	1189	0.37 (0.27-0.52)		0.86 (0.59-1.25)		0.88 (0.74-1.04)			
Missing	1013	0.53 (0.39-0.72)		1.09 (0.73-1.62)		0.91 (0.77-1.09)			
Mitotic rate (n/mm^2)									
<1	1010	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	0.41
1-2	680	5.44 (3.14-9.46)		2.46 (1.34-4.50)		1.29 (1.04-1.60)		1.09 (0.82-1.45)	
3-10	547	14.57 (8.61-24.64)		3.24 (1.73-6.07)		2.66 (2.13-3.33)		1.27 (0.90-1.79)	
>10	155	20.86 (11.32- 38.46)		2.67 (1.27-5.62)		5.32 (3.66-7.75)		1.26 (0.73-2.15)	
Missing	1012	2.32 (1.31-4.12)		1.48 (0.77-2.87)		1.32 (1.09-1.60)		0.90 (0.68-1.18)	

CI, confidence interval; SPM, single primary melanoma; MPM, multiple primary melanomas

Pathological factors are from the thickest primary melanoma diagnosed during the study period. The survival time starts from their first melanoma diagnosed in the period October 2006-07. A missing category was set for Breslow thickness to keep the samples consistent between models.

[1]Socioeconomic status is based on postcode of residence. Quintile 1 represents the most disadvantaged status and quintile 5 represents the least disadvantaged status.

[2]These characteristics were collected by clinician questionnaire and were not available for every patient.

[3]Degree of spread is excluded from the multivariable analysis because of multicollinearity.

Supplementary Table 2: Logistic regression model for overall and melanoma-specific mortality, using pathological factors from the last primary melanoma

Characteristic	No. (%)	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%)	P-value	Odds ratio (95%)	P-value	Odds ratio (95%)	P-value	Odds ratio (95%)	P-value
Status									
SPM	**2830**	**1.00**	**0.66**	**1.00**	**<0.01**	**1.00**	**0.22**	**1.00**	**0.61**
MPM	**574**	**1.08 (0.77-1.51)**		**1.97 (1.31-2.97)**		**1.13 (0.93-1.36)**		**1.07 (0.83-1.38)**	
Gender									
Males	2049	1.00	<0.01	1.00	0.02	1.00	<0.01	1.00	<0.01
Females	1355	0.58 (0.44-0.77)		0.69 (0.50-0.95)		0.54 (0.46-0.63)		0.59 (0.48-0.72)	
Age Categories									
Quartile 1	909	1.00	<0.01	1.00	0.09	1.00	<0.01	1.00	<0.01
Quartile 2	858	1.37(0.93-2.03)		1.31 (0.85-2.01)		2.46 (1.82-3.32)		2.34 (1.72-3.20)	
Quartile 3	800	1.59(1.08-2.33)		1.42 (0.92-2.19)		6.43 (4.85-8.52)		6.07 (4.51-8.17)	
Quartile 4	837	1.84 (1.27-2.68)		0.91 (0.59-1.41)		35.46 (26.58-47.32)		31.26 (23.01-42.46)	
Socioeconomic status[1]									
Quintile 1	290	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
Quintile 2	523	1.58 (0.95-2.63)		1.59 (0.90-2.79)		0.92 (0.69-1.23)		0.80 (0.55-1.15)	
Quintile 3	1066	0.75 (0.45-1.25)		0.71 (0.41-1.24)		0.77 (0.59-1.00)		0.64 (0.46-0.90)	
Quintile 4	637	1.02 (0.60-1.71)		1.03 (0.58-1.85)		0.73 (0.55-0.98)		0.69 (0.48-0.99)	
Quintile 5	888	0.87 (0.52-1.44)		0.97 (0.55-1.70)		0.61 (0.46-0.80)		0.56 (0.39-0.79)	
Remoteness Area									
Major cities	1432	1.00	0.89	N/A		1.00	0.33	N/A	
Inner regional	1387	0.91 (0.69-1.21)				1.08 (0.92-1.26)			
Outer regional	557	1.04 (0.72-1.50)				1.21 (0.99-1.49)			
Remote	28	0.93 (0.22-3.99)				1.02 (0.46-2.27)			
Family history[2]									
Absent	1595	1.00	0.19	1.00	0.87	1.00	<0.01	1.00	0.82
Present	192	0.84 (0.44-1.59)		0.95 (0.47-1.90)		0.58 (0.41-0.83)		1.04 (0.68-1.60)	
Unknown	1617	1.23 (0.95-1.61)		1.09 (0.75-1.57)		1.12 (0.96-1.29)		0.95 (0.79-1.14)	
Lots of moles[2]									
Absent	1515	1.00	0.15	1.00	0.43	1.00	0.20	N/A	
Present	464	1.18 (0.79-1.76)		1.33 (0.85-2.09)		0.82 (0.65-1.02)			
Unknown	1425	1.32 (1.00-1.74)		1.16 (0.80-1.70)		0.94 (0.80-1.09)			
Breslow thickness									
In situ (0)	399	1.00	<0.01	1.00	<0.01	1.00	<0.01	1.00	<0.01
0-0.8	1590	0.91 (0.47-1.77)		1.02 (0.45-2.32)		0.82 (0.67-1.02)		1.17 (0.84-1.64)	
0.9-1.0	231	2.55 (1.13-5.78)		2.22 (0.85-5.82)		0.79 (0.56-1.14)		1.03 (0.63-1.67)	
1.1-2.0	574	5.24 (2.82-9.73)		3.77 (1.66-8.56)		1.21 (0.94-1.56)		1.76 (1.17-2.66)	
2.1-4.0	370	12.01 (6.54-22.08)		7.49 (3.24-17.33)		3.07 (2.34-4.03)		2.78 (1.73-4.48)	
>4.0	231	23.93 (12.94-44.24)		13.65 (5.66-32.95)		7.83 (5.53-11.11)		4.98 (2.81-8.83)	
Missing	9								
Body site									
Head and neck	708	1.00	0.07	1.00	0.05	1.00	<0.01	1.00	0.22
Trunk	1195	1.15 (0.81-1.61)		1.43 (0.96-2.13)		0.60 (0.50-0.73)		0.87 (0.68-1.12)	
Upper limbs	854	0.71 (0.47-1.07)		0.84 (0.53-1.33)		0.55 (0.44-0.67)		0.76 (0.58-1.00)	
Lower limbs	647	1.08 (0.73-1.61)		1.20 (0.76-1.89)		0.49 (0.39-0.61)		0.79 (0.59-1.07)	
Melanoma subtype									
Superficial spreading	1610	1.00	<0.01	1.00	0.41	1.00	<0.01	1.00	0.39

Characteristic	No. (%)	Melanoma mortality				Overall mortality			
		Univariable		Multivariable		Univariable		Multivariable	
		Odds ratio (95%)	P-value	Odds ratio (95%)	P-value	Odds ratio (95%)	P-value	Odds ratio (95%)	P-value
Nodular	464	5.48 (3.96-7.56)		1.19 (0.80-1.78)		3.51 (2.81-4.40)		1.22 (0.87-1.72)	
Lentigo	441	0.51 (0.28-0.90)		0.80 (0.41-1.54)		1.83 (1.49-2.26)		1.07 (0.81-1.43)	
Other	215	3.46 (2.23-5.38)		1.15 (0.68-1.92)		2.07 (1.53-2.79)		0.83 (0.55-1.24)	
Not specified	674	0.87 (0.57-1.32)		0.74 (0.46-1.20)		1.08 (0.89-1.32)		0.93 (0.72-1.20)	
Spread of disease[3]									
In situ	373	1.00	<0.01	N/A		1.00	<0.01	N/A	
Localised	2852	3.41 (1.93-6.03)				1.21 (1.00-1.47)			
Regional	127	37.30 (19.27-72.20)				3.68 (2.44-5.54)			
Distant	20	88.29 (30.27-257.52)				14.20 (4.11-49.04)			
Missing	32	1.32 (0.17-10.38)				1.71 (0.87-3.37)			
Ulceration									
Absent	2365	1.00	<0.01	1.00	0.56	1.00	<0.01	1.00	0.42
Present	429	4.40 (3.28-5.90)		1.12 (0.78-1.62)		3.52 (2.82-4.40)		1.21 (0.88-1.67)	
Missing	610	0.49 (0.32-0.75)		0.79 (0.43-1.45)		1.11 (0.93-1.32)		1.11 (0.83-1.47)	
Regression									
Absent	1202	1.00	<0.01	1.00	0.46	1.00	0.31	N/A	
Present	1189	0.38 (0.27-0.52)		0.92 (0.63-1.33)		0.89 (0.75-1.06)			
Missing	1013	0.52 (0.39-0.71)		1.20 (0.81-1.78)		0.89 (0.75-1.06)			
Mitotic rate (n/mm^2)									
<1	1010	1.00	<0.01	1.00	0.03	1.00	<0.01	1.00	0.56
1-2	680	3.99 (2.38-6.70)		1.81 (1.01-3.24)		1.24 (0.99-1.55)		1.02 (0.76-1.37)	
3-10	547	11.19 (6.88-18.21)		2.47 (1.35-4.51)		2.76 (2.19-3.47)		1.23 (0.86-1.77)	
>10	155	17.64 (9.99-31.17)		2.17 (1.06-4.41)		6.36 (4.33-9.36)		1.39 (0.80-2.41)	
Missing	1012	1.79 (1.06-3.03)		1.29 (0.68-2.43)		1.33 (1.10-1.61)		0.94 (0.71-1.25)	

CI, confidence interval; SPM, single primary melanoma; MPM, multiple primary melanomas

Pathological factors are from the thickest primary melanoma diagnosed during the study period. The survival time starts from their first melanoma diagnosed in the period October 2006-07. A missing category was set for Breslow thickness to keep the samples consistent between models.

[1]Socioeconomic status is based on postcode of residence. Quintile 1 represents the most disadvantaged status and quintile 5 represents the least disadvantaged status.

[2]These characteristics were collected by clinician questionnaire and were not available for every patient.

[3]Degree of spread is excluded from the multivariable analysis because of multicollinearity.

Chapter 6. Discussion and conclusions

This chapter presents an overview of the thesis, a summary of the principal findings along with the strengths and limitations of this research. I provide an overview of the implications for clinical practice and policy, and discuss future research directions.

1. Overview of the thesis

Most clinical practice guidelines provide guidance and management recommendations based on a first primary melanoma, despite multiple primary melanomas being a common occurrence. Prior to my PhD thesis, there was limited information on the epidemiology of multiple primary melanomas, including trends in incidence over time, prognosis, and on risk factors for new primary melanoma and other primary cancers, particularly in Australia. Given that Australia has the highest rate of melanoma in the world and skin cancer is the most expensive cancer for Australia's healthcare system,[205] this was an important evidence gap to address to guide more effective and cost-effective melanoma prevention and control.

This thesis aimed to provide insights into risk, survival, and patterns of subsequent primary melanomas after a first primary melanoma in Australia, using population-based data. My PhD research was accomplished through four original studies, of which two were published in high impact international dermatology journals and two articles ready for submission to journals. The theme of first two papers was multiple malignancies by providing overview of risk of developing second melanoma or other malignancy after the first primary melanoma. Chapter 2 identified risk factors for developing a second primary melanoma and quantified the risk. Chapter 3 investigated the competing risks and cumulative incidence of developing a second primary cancer - including a new primary melanoma or other cancer type - after a first primary invasive or in situ melanoma in NSW, Australia. Incidence was the theme of second section; chapter 4 presented trends in the incidence rates of subsequent primary melanoma in Australia since 1982, using a national dataset comprising data from all but the ACT cancer registry. The last paper (chapter 5) investigated prognosis,

comparing melanoma-specific and overall survival of people with single versus multiple primary melanomas, using data from a population-based cohort in NSW, Australia. The key findings from these four chapters are summarised below.

1.1 What is the risk of developing a second primary melanoma after a first primary melanoma?

It is well known that people with a previous primary melanoma are at higher risk of developing subsequent primary melanomas.[125] However, risk estimate vary considerably between studies, and skin surveillance recommendations to guide early detection of new primary melanomas are based on limited evidence.[125] Chapter 2 estimated the absolute risk of a second primary melanoma after diagnosis of a first primary melanoma and identified risk factors associated with the development of a second primary melanoma among participants in the Melanoma Patterns of Care study. My analysis identified that male sex, older age, high naevus count and body site were risk factors independently associated with the development of second primary melanomas. The mean absolute risk of developing a second primary melanoma within 10 years of the first primary melanoma was 16.4%. These findings can help to inform discussions with patients and guide individuals' surveillance recommendations.

1.2 What is the risk of developing a subsequent primary melanoma or other type of cancer in people with history of first primary melanoma?

Chapter 3 used data from the NSW Enduring Cancer Data Linkage (CanDLe) dataset to estimate the competing risk of developing a second primary melanoma or other type of cancer among people diagnosed with a first primary melanoma. It also explored differences in the risk of in situ and invasive melanoma. In conventional studies, researchers often right censor data where events other than the event of particular interest occurs. Censoring data in statistical survival analysis occurs when the event of interest is not fully observed in the recorded dataset. This typically arises due to various reasons, such as inherent measurement limitations or incomplete data collection. For instance,

consider a study investigating the time until the occurrence of a second cancer among individuals. If some participants have not yet developed a second cancer by the end of the study period, their data is considered right-censored. This means that the exact timing of the event (second cancer) remains unknown due to reasons such as participants not experiencing the event yet, loss to follow-up (e.g., individuals changing residence and becoming unreachable), or mortality before the event occurs. To gain a broader view of a person's cancer risk after a first diagnosis of primary melanoma, we used competing risk analysis. This analysis approach allowed to evaluate the risk of a second primary cancer, whether it be another new primary melanoma or a different type of cancer.

My analysis showed that a person with history of first primary melanoma cancer was most likely to be diagnosed with a second primary melanoma than another type of cancer, but this differed by age, being more apparent for the younger age group whereas for the older age group (>74 years) a different type of cancer was more likely to be diagnosed than a new primary melanoma. The mean absolute risk of developing a second primary melanoma within 5 years was 7.6%. The next most common second primary cancer types were prostate cancer, breast cancer and colon cancer, with 5-year absolute risks after the initial melanoma diagnosis of 1.6% (5.0% male-specific incidence), 0.7% (2.8% female-specific incidence), and 0.6%, respectively. The 20-year cumulative incidence of second primary (invasive or in situ) melanoma was 18.5% after diagnosis of a first in situ melanoma and 17.3% after a first primary invasive melanoma. This analysis showed that the risk of developing a second primary melanoma was higher if the first primary melanoma was diagnosed at the *in situ* stage than if it was invasive. This probably reflects a screening effect whereby people who have routine skin checks are more likely to have melanomas detected at the *in situ* stage and more likely to experience overdiagnosis (detection of indolent disease). This is the first Australian population-based study that we know of to examine risk of a second primary melanoma taking into account risk of other types of cancer. This type of information is very helpful for communicating with patients who may be concerned about their risk of developing another melanoma but also other types of cancer. It also shows how a person's second cancer risk profile changes with age.

1.3 What are the trends in the incidence of multiple primary melanomas in Australia?

Chapter 4 investigated the trends in the incidence of multiple primary melanomas in Australia since 1982, overall and by age group and sex. We also examined the proportion of second primary melanomas that occurred on the same anatomical site as the first primary melanoma. The analysis was based on over three decades of records from seven Australian state and territory cancer registries representing 98% of the Australian population.

The incidence of first primary melanoma has been increasing in many countries with populations of European ancestry over several decades. In Australia, first primary melanoma incidence has also increased substantially over time, although this differs by age-group, with younger generations experiencing a decline in incidence (attributed to improved sun protection behaviours) whilst older age-groups experienced a significant increase.[152] We found that incidence rates of second primary melanomas in Australia increased by 3 to 5-fold over the period from 1982-2016, and differences in trends were found among different age groups and across anatomical sites. Incidence rates increased more notably when incorporating in situ melanomas into the analysis alongside invasive melanomas.

1.4 What is the mortality of people diagnosed with multiple primary melanomas compared to single primary melanoma?

Chapter 5 focused on comparing the mortality rates (overall mortality and melanoma-specific mortality) between people with single primary melanoma and those diagnosed with multiple primary melanomas. I quantitatively estimated the mortality rate among 3,404 people diagnosed with melanoma in 2006-07 in the NSW Melanoma Patterns of Care study. Previous studies on this topic had reported conflicting results, thought to be due to differences in study populations, study designs, and calculation methods. Regarding the methodological differences of previous studies, a common approach was to include the time interval between diagnosis of the first and second primary melanoma in the survival period. The main limitation with this method is survival bias, as

people who die shortly after their first primary melanoma do not live long enough to develop a second primary melanoma, whereas those who develop second primary melanomas remain alive long enough for this to occur, artificially improving survival for those diagnosed with multiple primary melanomas. An alternative approach with less bias is to calculate survival time based on the diagnosis of the thickest melanoma. I applied both methods in Chapter 5, and concluded that the number of primary melanomas is not an independent factor influencing melanoma-specific prognosis. However, in contrast, people diagnosed with multiple primary melanomas had better overall prognosis than those with single primary melanoma. The diagnosis of multiple primary melanomas is not associated with worse overall prognosis.

2. Strengths and limitations

Each of the chapters comprising original research in this thesis have incorporated some discussion of strengths and limitations. Here, I provide further insights into this topic across the four studies presented.

The main strength of this thesis is the comprehensive analysis of population-based data including linkage to administrative databases (which are known to be virtually complete) to investigate the epidemiology of multiple primary melanomas across Australia. Using data from population-based datasets and cancer registries ensures that the findings are generalisable and minimises selection bias that is usually associated with clinic-based studies.

Another strength was the inclusion of data for in situ and invasive primary melanomas. Data for in situ melanomas have only started to be reported in Australian Institute of Health and Welfare cancer reports in recent years, a contributing factor to our limited knowledge on this topic prior to this thesis. However, in chapter 4, data for in situ melanomas were only available for a subset of cancer registries since 1982, and data for the ACT cancer registry were unable to be included in the analysis as they did not have data for invasive melanomas from 1982. The Melanoma Patterns of Care study did include some in situ melanomas in its initial recruitment to the study – but only a subset

collected over a few months and not for the full year like they were for invasive melanomas. Inclusion of in situ lesions, even though a small proportion, for the analysis of survival may be a weakness because in theory in situ melanoma should not impact mortality, although in practice some deaths do occur.[206]

I used a variety of statistical methods to analyse the data from the different studies in this thesis. Specifically, in chapter 3, the application of competing risk analysis to examine survival data was a novel approach that took into account the likelihood of dying or developing other types of primary cancers in addition to another primary melanoma. Consequently, the results offer an alternative way to estimate and interpret risks. Conventional analyses of survival data take into consideration only one event of interest. For chapter 5, I used logistic regression to analyse the 10-year survival outcomes due to the failure of the Cox proportional hazards assumption, leading to unreliable statistics. This issue surfaced during the data exploration phase, wherein we observed that the Kaplan-Meier survival curves for both the single primary melanoma group and the multiple primary melanomas group crossed. Considering the lack of restrictive assumptions and the extensive follow-up information exceeding 10 years obtained through data linkage for all patients in this cohort, logistic regression using 10-year mortality rates as clinical outcome seemed to be a suitable alternative method in these circumstances.

A limitation of our research of risk factors for second primary melanoma after a first primary melanoma (Chapter 2) is that not all known risk factors confirmed by prior studies were available in our analysis. While the use of administrative datasets like the cancer registry offers strengths such as long-term follow-up and large sample size, certain important pathological variables were not available (e.g. TNM stage, histological subtype, ulceration, among others) or may be missed for some patients.

In chapter 4, a limitation is that we may have misclassified some people as having a single primary melanoma if their actual first melanoma occurred before 1982, the year corresponding to when

cancer registry data are considered accurate. Any rise in the incidence of multiple primary melanomas in Australia over time could be considered to represent a genuine increase, though it also stems from overdiagnosis of skin cancer.[165] The recent nationals programs at raising awareness and screening initiatives might contribute to the identification of 'indolent' lesions, often referred to as instances of overdiagnosis.[207]

3. Implications and recommendations for further research

For analysis of the survival implications of multiple primaries, methodological issues remain a key challenge. Future research should consider the potential biases from different approaches to the analysis, and perform sensitivity analyses to evaluate the impact of different methodological approaches. In addition to this, further research could explore how melanoma treatments in the past decade have contributed to the prognosis of people diagnosed with multiple primary melanomas, as it was a limitation that we were unable to address this in our analysis.

The findings from Chapters 2 and 3 contributed to knowledge of the risk of developing subsequent primary melanomas or other types of primary cancers among people diagnosed with a first primary melanoma. These findings could be used to update educational materials for patients and to guide follow-up guidelines for optimal risk-tailored skin surveillance schedules, in particular to target people at very high risk of a subsequent primary melanoma who might benefit from more frequent skin checks.[208] The findings can also help clinicians in communicating with the patients with regards to risk of a second primary melanoma and how that compares to their risk of developing another type of primary cancer.

Given the huge cost of skin cancer to Australia's healthcare system, the findings from Chapter 4 on the increasing incidence of multiple primary melanomas over time provide important impetus to policymakers to allocate more resources to skin cancer prevention initiatives at all ages and to research that can provide high-quality evidence on optimal skin screening and surveillance for people with melanoma or at high risk of developing melanoma. At present, an organised population-

based skin cancer screening program is unavailable across the country due to insufficient high-quality evidence of the potential benefits and harms. People diagnosed with a first primary melanoma should be informed about sun protection and their risk of developing subsequent primary melanomas and be given education of skin self-examination, especially as a high proportion of subsequent primary melanomas develop on the same site as the first melanoma. Finally, further research is needed to understand the proportion of subsequent primary melanomas that may be overdiagnosed and how to minimise overdiagnosis whilst obtaining the maximum benefits of early detection of melanoma.

4. Conclusions

Using epidemiological methods applied to population-based data, this thesis provides important new information on multiple primary melanomas in Australia including its incidence over time, risk factors and survival. It shows that multiple primary melanomas are an increasing burden in Australia although does not appear to worsen survival. These findings further emphasise the importance of the primary prevention of skin cancer, and can be used to update clinical guidelines regarding risk-tailored screening and surveillance recommendations and to provide educational materials to patients and health professionals regarding estimates of risk and risk factors for multiple primary melanomas.

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Appendices

Appendix A. The Melanoma Patterns of Care Study Ethical approval letter

1 December 2017

Associate Professor Anne Cust
Chris O'Brien Lifehouse
Level 6-North
119-143 Missenden Road
Camperdown NSW 2050

Dear Associate Professor Cust,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/17/CIPHS/40

Cancer Institute NSW Reference: 2017/HRE1004

Project Title: Melanoma Patterns of Care Study 10 year follow up outcomes study

Thank you for your correspondence dated 13 November 2017 responding to a request for further information/clarification of the above referenced study, submitted to the NSW Population & Health Services Research Ethics Committee. The Committee has reviewed your response and has agreed that the aforementioned application meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007)*. This approval is for a maximum of five years from the date of this letter, after which time a renewal application will be required if the protocol has not been completed.

The Committee granted a waiver of the usual requirement of consent for the use of re-identifiable information held by NSW agencies, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW) and the Guidelines approved under Section 95A of the Privacy Act 1988.

The documents reviewed and approved include:

- Letter of Response, dated 13 November 2017
- NSW National Ethics Application Form, v2.2, submission code AU/1/2741320, dated 9 October 2017
- Protocol version 2, dated 13 November 2017
- Data Linkage Flowchart
- CHeReL Technical Feasibility Letter, dated 17 August 2017
- CHeReL Application for Data
- NSW RBDM Data Variable Checklist
- COD URF Data Variable Checklist
- NSW RBDM & COD URF Data Custodian Sign Off Form, dated 31 August 2017
- NSW CR Data Variable Checklist
- NSW CR Data Custodian Sign Off Form, dated 19 September 2017
- MIA MRD Data Variable Checklist
- MIA MRD Data Custodian Sign Off Form, dated 5 October 2017
- NSW Privacy Form
- Anne Cust CV

Approval is now valid for the following site for unit record data:

- Sydney School of Public Health, The Chris O'Brien Lifehouse NSW

Other approved sites:

- The Westmead Institute for Medical Research NSW
- Rural Health Northern Rivers NSW
- Royal Prince Alfred Hospital

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Ministry of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* and relevant legislation and guidelines.

Please note that ethical approval is valid for **5 years**, conditional on the following:

- Principal investigators will immediately report anything which might warrant a review of ethical approval of the research, including unforeseen events that might affect continued ethical acceptability.
- Proposed amendments to the research proposal or conduct of the research which may affect the ethical acceptability of the research are to be provided to the NSW Population & Health Services Research Ethics Committee for review.
- The NSW Population & Health Services Research Ethics Committee will be notified giving reasons, if the research is discontinued before the expected date of completion.
- The Principal Investigator will provide a progress report to the NSW Population & Health Services Research Ethics Committee annually and at the completion of the study.

Your first progress report will be due on **01/12/2018** and the duration of approval is until **01/12/2022** after which time a new submission to the Ethics Committee will be required.

You are reminded that this letter constitutes *'ethical approval'* only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site's Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website https://www.cancerinstitute.org.au/Data-research/Research-ethics-committee.

Should you have any queries about the ethical review of your research proposal, please contact ethics at ethics@cancerinstitute.org.au.

Yours sincerely,

[redacted]

Professor David Roder
Chairperson
NSW Population & Health Services Research Ethics Committee

Appendix B. The Melanoma Patterns of Care Study Questionnaire 1 – Primary Treatment Questionnaire - General Practitioners

1. In what practice setting did you see this patient?
- ❑ General Practice
- ❑ Skin cancer clinic
- ❑ Other *Please specify.* _____

Patient's presentation with this melanoma

2. Date of first presentation to you with this melanoma? __ / __ / __

Melanoma history

Did the patient have a:

3. Personal history of melanoma?
- ❑ No
- ❑ Yes
- ❑ Don't know

4. Family history of melanoma in a blood relative?
- ❑ No
- ❑ Yes
- ❑ Don't know

Melanoma risk

5. Did this patient have lots of moles?
- ❑ No
- ❑ Yes
- ❑ Don't know

Details of primary melanoma

6. How did this melanoma present? *(Tick one only)*
- ❑ Patient reported this skin lesion
- ❑ Found incidentally when checking another skin lesion
- ❑ Found in a routine skin check
- ❑ Other *Please specify*. _____
- ❑ Don't know

7. Was there a history of: *(Tick all that apply)*
- ❑ Change in colour, size, elevation or shape of lesion?
- ❑ Bleeding?
- ❑ Itch?
- ❑ Ulceration?

8. What was the lesion's site? *(Tick one only)*
- ❑ Head or neck
- ❑ Anterior trunk
- ❑ Posterior trunk
- ❑ Upper limb
- ❑ Lower limb

9. Did you observe this lesion for a period before biopsy?
- ❑ No
- ❑ Yes *If yes, how long?* _____

10. Was the lesion clinically a melanoma?
- ❑ No
- ❑ Suspicious
- ❑ Yes

Metastases

Were there:

11. Any clinically suspicious lymph nodes?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____
- ❑ Don't know

12. Any clinical signs of distant spread (other than suspicious lymph nodes)?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____
- ❑ Don't know

Investigations

13. What investigations did you do?
(Tick all that apply)
- ❑ None *If none, jump to Q15.*
- ❑ Chest x-ray
- ❑ Biochemistry or haematology
- ❑ CT scan
- ❑ MRI scan
- ❑ PET scan
- ❑ Bone scan
- ❑ Other *Please specify*. _____

14. Was there any investigational evidence of metastatic spread?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____

15. Did you assess the lesion with a dermoscope?
- ❑ No
- ❑ Yes ❑ Don't know

Biopsy of melanoma

16. Did you refer the patient to another doctor before biopsy?
- ❑ No
- ❑ Yes *If yes, jump to Q22.*

17. Did you attempt a complete excision biopsy?
- ❑ No
- ❑ Yes

If yes, was it complete?
- ❑ No
- ❑ Yes

Please continue to next page.

If yes, please specify.
Excision margin ____ mm
Did you remove subcutaneous tissue with this lesion? ❑ No
❑ Yes *Jump to Q19.*

18. Did you do a partial biopsy?
❑ No
❑ Yes *If yes, please specify type.*
❑ Punch biopsy
❑ Shave biopsy
❑ Partial incision biopsy

If yes, did you think it was a non-melanocytic lesion?
❑ No
❑ Yes

Your post-biopsy treatment of the primary melanoma

19. How did you manage the primary lesion next?
❑ Wide excision
Please specify:
Date of wide excision ___ / ___ / ___
Time from biopsy to wide excision ____ days
Excision margin ____ mm
❑ Observation only *Jump to Q22.*
❑ Referral to a specialist *Jump to Q22.*

If you did a wide excision:
20. How was surgical repair done?
❑ Primary closure
❑ Flap
❑ Skin graft

21. Were there any post-op complications?
❑ No
❑ Wound infection
❑ Wound breakdown
❑ Lymphoedema
❑ Prolonged pain
❑ Seroma or haematoma
❑ Other *Please specify.* _____
❑ Don't know

Follow-up

22. Did you recommend follow-up?
❑ No
❑ Yes
Who did you recommend do the follow-up?
❑ Yourself
❑ GP
❑ Dermatologist
❑ Surgeon
❑ Other *Please specify.* _____

How frequently will follow-up be done initially?
At intervals of ____ months

23. Did you do any of the following?
Advise patient on specific changes that suggest melanoma?
❑ Yes
❑ No
Encourage patient to perform skin self-examination?
❑ Yes *If yes, how often?* _____
❑ No
Recommend a skin surveillance program?
❑ Yes
❑ No

Referrals

Please give us the names and addresses of any other doctors to whom you referred this patient for melanoma management.

Surgeon

Dermatologist

Medical oncologist

Radiation oncologist

Other doctor *Please state specialty if applicable.*

Who is this patient's usual family doctor?
If you are, tick this box ☐
Or give name and contact details

This is the end of the questionnaire.
Thank you for your help.

Appendix C. The Melanoma Patterns of Care Study Questionnaire 2 – Primary Treatment Questionnaire - Specialists

1. In what practice setting did you see this patient?
- ❑ Skin cancer clinic
- ❑ Dermatology
- ❑ Surgery
- ❑ Plastic surgery
- ❑ Other *Please specify.* _____

Patient's presentation with this melanoma

2. Date of first presentation to you with this melanoma? __ / __ / __

Melanoma history

Did the patient have a:

3. Personal history of melanoma?
- ❑ No
- ❑ Yes
- ❑ Don't know

4. Family history of melanoma in a blood relative?
- ❑ No
- ❑ Yes
- ❑ Don't know

Melanoma risk

5. Did this patient have lots of moles?
- ❑ No
- ❑ Yes
- ❑ Don't know

Details of primary melanoma

6. How did this melanoma present?
(Tick one only)
- ❑ Patient reported this skin lesion
- ❑ Found incidentally when checking another skin lesion
- ❑ Found in a routine skin check
- ❑ Other *Please specify*. _____
- ❑ Don't know

7. Was there a history of: *(Tick <u>all</u> that apply)*
- ❑ Change in colour, size, elevation or shape of lesion?
- ❑ Bleeding?
- ❑ Itch?
- ❑ Ulceration?

8. What was the lesion's site? *(Tick one only)*
- ❑ Head or neck
- ❑ Anterior trunk
- ❑ Posterior trunk
- ❑ Upper limb
- ❑ Lower limb

9. Did you observe this lesion for a period before biopsy?
- ❑ No
- ❑ Yes *If yes, how long?* _____

10. Was the lesion clinically a melanoma?
- ❑ No
- ❑ Suspicious
- ❑ Yes

Metastases

Were there:

11. Any clinically suspicious lymph nodes?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____
- ❑ Don't know

12. Any clinical signs of distant spread (other than suspicious lymph nodes)?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____
- ❑ Don't know

Investigations

13. What investigations did you do?
(Tick <u>all</u> that apply)
- ❑ None *If none, jump to Q15.*
- ❑ Chest x-ray
- ❑ Biochemistry or haematology
- ❑ CT scan
- ❑ MRI scan
- ❑ PET scan
- ❑ Bone scan
- ❑ Other *Please specify*. _____

14. Was there any investigational evidence of metastatic spread?
- ❑ No
- ❑ Yes *If yes, please specify location(s).* _____

15. Did you assess the lesion with a dermoscope?
- ❑ No
- ❑ Don't know
- ❑ Yes

Biopsy of melanoma

16. Did you refer the patient to another doctor before biopsy?
- ❑ No
- ❑ Yes *If yes, jump to Q26.*

Please continue to next page.

17. Did you attempt a complete excision biopsy?
❑ No
❑ Yes *If yes, was it complete?*
❑ No
❑ Yes

If yes, please specify.
Excision margin ____ mm
Did you remove subcutaneous tissue with this lesion? ❑ No
❑ Yes *Jump to Q19.*

18. Did you do a partial biopsy?
❑ No
❑ Yes *If yes, please specify type.*
❑ Punch biopsy
❑ Shave biopsy
❑ Partial incision biopsy

If yes, did you think it was a non-melanocytic lesion?
❑ No
❑ Yes

Your post-biopsy treatment of the primary melanoma

19. Did you do a wide excision or wide re-excision?
❑ Yes *If yes, please specify.*
Date of excision ___ / ___ / ___
Time from biopsy to excision ____ days
Excision margin ____ mm
❑ No *If no, jump to Q22.*

If you did a wide excision or wide re-excision:

20. How was surgical repair done?
❑ Primary closure
❑ Flap
❑ Skin graft

21. Were there any post-op complications?
❑ No
❑ Wound infection
❑ Wound breakdown
❑ Lymphoedema
❑ Prolonged pain
❑ Seroma or haematoma
❑ Other *Please specify.* _____
❑ Don't know

Your management of lymph nodes

22. Did you do any of these? *(Tick all that apply)*
❑ Needle aspiration of a lymph node
❑ Lymphatic mapping
(Tick all that apply)
❑ Gamma radiation mapping
❑ Vital blue dye mapping
❑ Mapping done as part of a clinical trial
❑ Sentinel lymph node biopsy
Number of sentinel nodes removed _____
❑ Other staging procedures *Please specify.*
_____
❑ Didn't do any of these

23. What lymph node pathology was done?
(Tick all that apply)
❑ None
❑ H & E
❑ Immunohistochemistry
❑ RT-PCR
❑ Other *Please specify.* _____

24. Did you do a complete dissection of regional lymph nodes?
❑ No
❑ Yes
Any post-operative complications?
❑ No
❑ Wound infection
❑ Wound breakdown
❑ Lymphoedema
❑ Prolonged pain
❑ Seroma or haematoma
❑ Other *Please specify.*
_____
❑ Don't know

Were margins clear?
❑ Yes
❑ No

Intention of complete node dissection?
(Tick all that apply)
❑ Curative intent
❑ Palliative intent

Other treatment

25. Did you give any other specific treatment for this melanoma?
❑ No
❑ Yes *If yes, please specify.*
_____

Please continue to next page.

Stage at diagnosis

26. What was this patient's "new" AJCC stage of melanoma *at diagnosis*?
(Tick the most accurate stage you can)

❑ 0
❑ I ❑ IA ❑ IB
❑ II ❑ IIA ❑ IIB ❑ IIC
❑ III ❑ IIIA ❑ IIIB ❑ IIIC
❑ IV
❑ Don't know

Follow-up

27. Did you recommend follow-up?
❑ No
❑ Yes
Who did you recommend do the follow-up?
❑ Yourself
❑ GP
❑ Dermatologist
❑ Surgeon
❑ Other *Please specify.* _____

How frequently will follow-up be done initially?
At intervals of ____ months

28. Did you do any of the following?
Advise patient on specific changes that suggest melanoma?
❑ Yes
❑ No
Encourage patient to perform skin self-examination?
❑ Yes *If yes, how often?* _____
❑ No
Recommend a skin surveillance program?
❑ Yes
❑ No

29. Has the patient's melanoma recurred or progressed since they were first treated for this or a synchronous melanoma?
❑ No
❑ Yes *If yes, please specify.*
Date of relapse/progression __ / __ / __
Sites *(Tick <u>all</u> that apply)*
❑ Local recurrence
❑ Regional lymph nodes
❑ Distant Metastasis
Evidence of recurrence or progression
(Tick <u>all</u> that apply)
❑ Clinical assessment
❑ Histopathology
❑ Radiology (CT or MRI scan)
❑ Ultrasound
❑ Nuclear medicine (PET, bone, liver scan)

Treatment for recurrence *(Tick <u>all</u> that apply)*
❑ Re-excision or node dissection
❑ Immunotherapy
❑ Chemotherapy
❑ Radiotherapy

30. Did you refer the patient for psychological care?
❑ Not applicable
❑ No
❑ Referred for psychological care
If referred for psychological care, who provided the care? Please specify discipline.

_____

Referrals

Please give us the names and addresses of any other doctors to whom you referred this patient for melanoma management.

Surgeon

Dermatologist

Medical oncologist

Radiation oncologist

Other doctor *Please state specialty if applicable.*

Who is this patient's usual family doctor?
If you are, tick this box ☐
Or give name and contact details

This is the end of the questionnaire.

Thank you for your help.

Appendix D. Supplementary material for Chapter 3

D.1. Enduring Cancer Data Linkage (CanDle) Study Ethics Approval letter

Anne Cust

From: no_reply@regis.health.nsw.gov.au
Sent: Thursday, 8 September 2022 12:29 PM
To: Sarah McGill (Cancer Institute NSW)
Cc: Leighna Carmichael (Cancer Institute NSW); CINSW-CandleProgram; Emma Heeley (Cancer Institute NSW); CINSW-Ethics
Subject: 2019/ETH12584: Notification of an amendment to a research study - General Amendment (101670) - Approved

Date of Decision Notification: 08 Sep 2022
Greater than low risk review pathway

Dear Ms Sarah McGill,

Thank you for submitting an Amendment for the following study;
2019/ETH12584: Enduring Cancer Data Linkage (CanDLe) for health services research in New South Wales

The Amendment has been reviewed by the NSW Population and Health Services Research Ethics Committee Executive Committee who have determined the Amendment has been approved.

The PHSREC approves the sub protocol amendment. Following discussion with the NSWCR Data Custodian, the PHSREC has noted that the intention is to include the multi-file as part of the CanDLe dataset at a later date. Please note that an amendment to the CanDLe protocol will be required at that time, as well as updates to additional documentation (e.g. study ATDs).

Notification of an amendment to a research study - General Amendment with form ID 101670

- Approval of Professor Anne Cust's sub-study protocol titled 'Risk of a new primary melanoma or other cancer after a diagnosis of melanoma in NSW'

The following documentation is included in this approval:

- REGIS Amendment Request form, dated 8 August 2022
- Project Specific Protocol 2022UMB0902 version 1.1, dated 11 July 2022

The following sub study has been approved:

Cancer Institute NSW sub-study reference: 2022UMB0902
Sub Study Title: Risk of a new primary melanoma or other cancer after a diagnosis of melanoma in NSW

Please take note of the reference number of the approved sub-study: 2022UMB0902. This reference number will need to be quoted in all Annual Reports for the Program of work.

The NSW Population and Health Services Research Ethics Committee is constituted and operates in accordance with the National Statement on Ethical Conduct in Human Research (NH&MRC, 2007).

This email constitutes ethical and scientific approval only.

For NSW authorised sites (listed in REGIS): A Site General Amendment form will need to be submitted to each affected site. You are not required to upload this form or the ethics approved documents into the site form but you will need to identify this approved amendment form ID (101670).

Please contact us if you would like to discuss any aspects of this process further, as per the contact details below.

Yours Sincerely,

Secretariat on behalf of David Roder, Chairperson, NSW Population and Health Services Research Ethics Committee
T (02) 8374 5689 / 8374 3610 F (02) 8374 3600 E cinsw-ethics@health.nsw.gov.au

Cancer Institute NSW
Level 4, 1 Reserve Road, St Leonards NSW 2065
Locked Bag 2030 St Leonards NSW 1590
cancer.nsw.gov.au

We acknowledge the traditional custodians of the lands on which we work and live,
and pay our respect to Elders past, present and future.
Please consider the environment before printing this email.

D.2. Enduring Cancer Data Linkage (CanDle) Study Protocol

CanDLe Sub-Study Protocol Application Form

Approved Umbrella Project
Title: **Enduring Cancer Data Linkage (CanDLe) for health services research in New South Wales**
CINSW Reference Number: **2019/ETH12584**
Co-ordinating Principal Investigator: **Sarah McGill, Cancer Institute NSW**

Title of Sub-study

Title: **Risk of a new primary melanoma or other cancer after a diagnosis of melanoma in NSW**
Version: **1.1**
Date: 11/07/2022
Sub study Reference Number ***(To be assigned by CanDLe secretariat)**:*

Lead Researcher

Title / First Name / Surname: Professor Anne Cust
Institution: Melanoma Institute Australia and University of Sydney/Faculty of Health and Medicine
Site: Melanoma Institute Australia
Institutional Email: anne.cust@sydney.edu.au
Lead Researcher Reference Number ***(To be assigned by CanDLe secretariat)***:

Other study personnel *Please list all researchers and people who will have access to the study data for this sub-study (including key research group members previously noted on the Lead Researcher Expression of Interest).*

Full Name	Institution	Site	Position	Email Address	Role in Project	Researcher category
Associate Professor Serigne Lo	Melanoma Institute Australia & University of Sydney	Melanoma Institute Australia & University of Sydney	Head, Research and Biostatistics Group, Senior Biostatistician	serigne.lo@melanoma.org.au	Lead researcher, sub study protocol development, statistical analysis, interpretation and manuscript writing	**Established Researcher**
Professor Anne Cust	University of Sydney & Melanoma Institute Australia	Daffodil Centre	Deputy Director, Professor of Cancer Epidemiology	anne.cust@sydney.edu.au	Sub study protocol development, interpretation and manuscript writing	**Established Researcher**
Associate Professor Alex Varey	Melanoma Institute Australia and Westmead Hospital	Melanoma Institute Australia and Westmead Hospital	Plastic surgeon	alex.varey@melanoma.org.au	Specialist consultant, interpretation and manuscript writing	**Established Researcher**

Full Name	Institution	Site	Position	Email Address	Role in Project	Researcher category
Dr Caroline Watts	University of Sydney	Daffodil Centre	Research Fellow	caroline.watts@sydney.edu.au	Sub study protocol development, interpretation and manuscript writing	**Early Career Researcher**
Yuan Ni	University of Sydney & Melanoma Institute Australia	Daffodil Centre	PhD student	yuni5219@uni.sydney.edu.au	Sub study protocol development, statistical analysis, interpretation and manuscript writing	**PhD Student**
						Choose an item.
						Choose an item.

Add new rows as required.

For all researchers that are students, please provide further details:

First Name / Surname: Yuan Ni
Commencement date of study (e.g., PhD, Masters):PhD
Anticipated completion date of study: 30/06/2024
Supervisor/(s) and Institution: A/Prof Serigne Lo, Prof Anne Cust, The University of Sydney
Institutional Email: serigne.lo@melanoma.org.au anne.cust@sydney.edu.au
If the supervisor will not have access to CanDLe data, please describe how supervision and oversight will be conducted: N/A

Add additional tables as required.

Contents

1. Sub Study Overview

Please provide a lay synopsis of your project (75–100 words).

Patients with a personal history of melanoma have a higher risk of developing subsequent primary melanoma, and possibly some other cancers. This study will examine the risk of developing subsequent primary melanomas following an initial diagnosis of melanoma, as well as the risk of developing other types of cancer. We will estimate the absolute and relative risk associated with risk of subsequent primary melanoma and other types of cancers after an initial diagnosis of melanoma, estimate the association and risk of developing subsequent melanomas and first primary melanoma.

2. Background and Rationale

Provide an introduction to the study including a brief literature review, outline of knowledge gaps, how the study will address these, and the intended contribution to the field.

Melanoma is a major public health issue in Australia, and it is the most common cancer affecting young adult Australians, as well as the third most invasive cancer in Australia for both men and women [1]. In the lifetime of Australians, it is roughly estimated that two thirds of them will be diagnosed some form of skin cancer [1]. Although melanoma accounts for only 3% of skin cancer cases, it accounts for 65% of skin cancer mortality [1]. Each year, 17,000 incident invasive melanomas and 28,000 incident in situ melanomas are diagnosed in Australia (Australian Institute of Health and Welfare) .

People who have developed one melanoma are at high risk of developing a second primary melanoma, but the individual risk varies substantially according to patient and lesion characteristics, and this risk is not very well understood or communicated [2]. There is also relatively little guidance in Australian and international clinical practice guidelines regarding the optimal surveillance for people with single versus multiple primary melanomas or for people at different levels of risk [3].

This study aims to estimate the risk of developing subsequent primary melanoma and other primary cancers after an initial diagnosis of invasive or in situ melanoma. We will estimate relative and absolute risks for people according to different patient and lesion factors, for different time periods, and for different types of cancers. We will also assess the impact on survival for people who develop multiple primary melanomas. The findings will help guide the follow-up for patients newly diagnosed with primary melanoma.

3. Aims

Provide a statement of primary and secondary aims/objectives, key research questions, and/or a clearly defined hypothesis (where appropriate).

Primary aims: To estimate the risk of developing a subsequent primary melanoma after the diagnosis of a first primary in situ or invasive melanoma.

Secondary aims:

1) To examine the risk of developing other types of cancers (other than melanoma) after a first primary in situ or invasive melanoma.

2) To examine the risks of developing a subsequent primary melanoma or other cancer according to different patient and lesion factors (e.g. age, sex, SES, body site, Breslow thickness, histopathological subtype, location of residence), for different time periods, and for different types of cancers.

3) To assess the impact on survival for people who develop multiple primary melanomas.

4. Research Plan

Please provide information about your study design.

This will be a retrospective cohort study using linked administrative datasets during the period of 1988-latest available. The NSW Cancer Registry (NSWCR), NSW Registry of Births, Deaths and Marriages Death Registrations (RBDM) and Australian Coordinating Registry Cause of Death Unit Record File (COD URF), will be used to define the study participants and covariates, and examine the associations.

5. Study Population

Please describe your cohort, specifying any inclusion and exclusion criteria.

The analysis data set consists of all adults aged 18+ years with a first in situ or invasive primary melanoma diagnosis from 1st January 1988 to latest available data, and without a personal history of another cancer (except non-melanoma skin cancer) at the date of the first melanoma diagnosis. Diagnosis of melanoma will be determined from the NSW Cancer Registry, ICD-O-3 C44.0-C44.9 or C80 M872-M879 with behaviour code /3 (invasive) or /2 (in situ). **As our outcome is development of subsequent primary cancer (including subsequent primary melanomas, which often occur at the same site/topography as the first melanoma) it is important that the separate 'multi' file is included in the analysis dataset, if available.** *The team has used the multi data in a previous linked data project and understands that the multi data may not have been subject to the same quality review by registry staff.*

6. Data Sources

Please select the CanDLe data assets and datasets that will be used for this sub-study.

☒ CanDLe 1 Data Assets: *A primary cohort of people diagnosed with or treated for cancer in NSW from the NSW Cancer Registry and a subset of the NSW Admitted Patient Data Collection with a malignant condition in the diagnosis code.*

☐ CanDLe Women Screen Data Assets: *All women in NSW who were invited to participate in either breast or cervical cancer screening and all women who were diagnosed with or treated for cancer in NSW from the NSW Cancer Registry and all women in a subset of the NSW Admitted Patient Data Collection with a malignant condition in the diagnosis code.*

The following datasets will be used for this sub-study:

☒ NSW Cancer Registry (NSW CR)

☐ NSW Pap Test Register (NSW PTR)

☐ BreastScreen NSW

☐ NSW Admitted Patient Data Collection (APDC)

☐ NSW Emergency Department Data Collection (EDDC)

☒ NSW Registry of Births Deaths and Marriages Death Registrations (NSW RBDM Deaths)

☒ Cause of Death Unit Record File (COD URF)

7. Analysis Plan

Describe the study outcome measures (primary and secondary) and include information on study exposure/s, covariates, and other factors and how these are defined based on the data (200 word minimum).

The outcomes of interest are incident primary melanomas, incident other cancers (after a first melanoma diagnosis) and survival. Study factors of interest include patient and lesion characteristics and time period. Individuals diagnosed with cancer types of interest will be ascertained in the NSWCR.
Cause of death information will be taken from the NSWCR where available, otherwise it will be from CODURF.

Valuables to be included in analysis:

Outcome/Covariate	Dataset	Variable name	Details
Patient ID	NSWCR		
Tumour ID	NSWCR		To measure incidence of multiple melanomas and other cancers
Cancer diagnosis	NSWCR	Cancer type (ICD-O-3 codes)	Cancer types will be defined using ICD-O-3 codes based on Cancer Institute NSW "cancer type" ICD-O-3 definitions (https://www.cancer.nsw.gov.au/glossary#term-cancer-type) for any incident cancers (combined) as well as specifically for (where numbers allow): Melanoma: C44 8720–8790 or C80.9

			Non-melanoma skin cancer (reportable) (C44 and not M872-M879 Colon: C18 Rectum: C19-21 Lung: C33, C34 Breast: C50 Prostate: C61
Cancer diagnosis	NSWCR	Number of primary sites	
Cancer diagnosis	NSWCR	Topography code (ICD-O-3)	Anatomical site of origin (or organ system) of the cancer at diagnosis.
Cancer diagnosis	NSWCR	Morphology code (ICD-O-3)	Histological subtype
Cancer diagnosis	NSWCR	Registry derived stage (STaR)	Only available for breast cancer, colorectal cancer, lung cancer, prostate cancer and melanoma cases diagnosed in 2011.
Cancer diagnosis	NSWCR	Behaviour code	Invasive or in situ (note that in situ only available from 2002)
Cancer diagnosis	NSWCR	Degree of spread at diagnosis	
Cancer diagnosis	NSWCR	Breslow thickness of melanoma	
Cancer diagnosis	NSWCR	Laterality	
Cancer diagnosis	NSWCR	TNM staging group	Where available
Cancer death	NSWCR, CODURF	Cause of Death Diagnosis Code	Cancer types will be defined using ICD-O-3 codes, based on Cancer Institute NSW "cancer type" definitions.
Age at diagnosis	NSWCR	Age at diagnosis	
Age at death	RBDM, CODURF	Age at death	Where age at death differs between datasets, the RBDM will be preferred.
Date of diagnosis	NSWCR	Year of diagnosis, Month of diagnosis, and day of diagnosis	Full date requested to analyse incidence and survival relative to diagnosis.
Date of death	RBDM, CODURF	Date of death	
Gender	NSWCR	Gender	
Country of birth	NSWCR	Country of birth	
Remoteness of residence at diagnosis	NSWCR	Remoteness	ARIA+ categories
Socioeconomic position of residence at diagnosis	NSWCR	Socioeconomic position	IRSAD deciles, IRSD deciles

Limitations: We are aware that subsequent primary melanomas recorded after the first primary are considered multiple primary cancers and have not been subject to the same review by Registry staff. Also, if the melanoma is on the same body site (topography), this is likely to be excluded from the current CanDLe dataset as approximately 50% of subsequent primary melanomas are likely to be at the same site as the initial primary melanoma. **As this multi file is typically not included in the Cancer Registry CanDLe extract, we specifically request inclusion of the 'multi' file for this analysis, if available, to ensure that we generate scientifically valid results.**

Provide a statistical analysis plan outlining how the aims/objectives will be met, the statistical methods to be used, and who will be carrying out the analysis (200 word minimum).

For analysis of outcomes, we will analyse 1) all melanomas combined (invasive and in situ), 2) invasive and in situ melanoma separately, 3) reportable non-melanoma skin cancers, 4) all other cancers combined, 5) individual cancer types where numbers allow. Analyses that include in situ melanomas will be from 2002 only, based on availability of these data in the cancer registry dataset.

Descriptive statistics will be used to describe the characteristics of patients and the first melanoma lesion, and the crude incidence of melanomas and other cancers. Means and standard deviation will be used to describe continuous variables and frequency tables for categorical variables. Differences between categorical variables will be assessed using chi-square tests, and differences in means between groups will be examined by t-tests and ANOVAs.

Logistic regression (e.g., single versus multiple primary within a 10-year timeframe) and Cox regression models (e.g. time to develop a subsequent primary melanoma or other cancer [or censoring at time of death or end of follow-up] using the maximum available follow-up available) will be used to estimate relative and absolute risks and hazard ratios, and identify pathological, patient and socio-demographic factors and year of diagnosis associated with outcomes. For the use of Cox regression analysis, the proportional hazard assumptions will be checked graphically (crossing Kaplan-Meier curves) and using the Schoenfeld residuals. If the proportional assumption does not hold, alternative methods including the restricted mean survival time (RMST) or the proportional baselines landmark supermodel (PBLS) will be used[4]. Variables that show p-value of 0.2 from the univariable analysis will be considered as potential confounders and included in the multivariable models. In addition to standard Cox model and logistic regression, graphical modelling will be used wherever possible to describe any patterns observed for development of multiple primary cancers.
For the evaluation of melanoma-specific mortality from the time of their first melanoma for single vs multiple primary melanomas, we will use multivariable logistic regression including pathological features from the thickest tumour (if there are multiple primary melanomas).

Subgroup analyses will be conducted examining risks and survival according to: age-group, gender, SES, body site, Breslow thickness, histopathological subtype, location of residence [rural, regional, metro]), and time period of first melanoma diagnosis.

The analysis will be conducted by Yuan Ni using SAS software 9.4 under the supervision of A/Prof Serigne Lo and Prof Anne Cust.

8. Informed Consent and Privacy Considerations

Please specify if there are any special considerations as to why this sub-study would not meet the waiver of consent and privacy considerations which have been previously described in the approved CanDLe program protocol (*2019/ETH12584, Protocol version 2, 25/10/2019, p.9-12*) and NSW Privacy Addition to HREA Form, and summarised below. In particular, *where the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them*.

CanDLe Program Considerations

The results from research studies using CanDLe will be made available only in aggregate form (i.e., reporting on sufficiently large cell sizes to ensure that no individual can be identified, suppressing cell sizes <5) in peer review

publications, conference presentations and the public domain. The Cancer Institute NSW and Lead Researchers will be responsible for communicating findings arising from use of CanDLe that may have significance for individuals, communities, non-government and government organisations to inform prevention, screening, clinical practice and policy development related to cancer control.

In addition, all researchers wishing to use CanDLe are required to enter into a Data Access Declaration to ensure appropriate use of the data to better ensure for patient confidentiality.

Special considerations, if any: N/A

9. Data Governance

Please list any special considerations as to why this sub-study would not meet the overarching data governance from the approved protocol (*2019/ETH12584*) as summarised below:

CanDLe Program Considerations

1. Data Collection: No data will be explicitly collected as part of this project. The project will utilise the CanDLe existing linked health data collections.

2. Data transfer & security: The CanDLe datasets are stored in secure data environments , (i.e., SURE or ERICA). CHeReL's Data Linkage Unit will prepare the datasets and securly transfer the data to the appropriate platform. The linkage and secure transfer process will be carried out annually, or more frequently if agreed.

3. Data access, use and disclosure: The Researchers listed on this sub-protocol will be provided with dedicated virtual computing environments. Each Lead Researcher will have their own remote virtual environment where their teams will access and use the data for their sub-studies.

4. Data storage: Unit record data will be stored on secure data storage workplaces on SURE's secure servers or on ERICA's secure cloud computing environment.

5. Data Retention: Following the completion of this sub-study, all data files and coding created will be digitally archived and retained for 5 years from the completion of the study.

6. Data disposal: At the end of the 5 year archiving period, all research study data files and coding will be permanently deleted rendering the data unrecoverable.

Modifications that will be made at this site, if any:N/A

The SURE/ERICA workspace number:

10. Outcomes and Significance

This research project will provide information to patients and health professionals about risk of future cancers and prognosis after the diagnosis of a first primary melanoma, and whether there are shared underlying risks for different cancer types. This research project will also inform follow-up recommendations in clinical practice guidelines.

11. Funding

Please outline how this sub-study will be funded.

The study is supported by Melanoma Institute Australia, a not-for-profit organisation supporting clinical care, education and research. Funding support is also obtained from a National Health and Medical Research Council (NHMRC) Investigator Grant to AEC (2008454).

12. Aboriginal Data

a. Will Aboriginal peoples be reported as a group in the results? Yes ☐ No ☒

If yes, please complete b and c below.

b. Provide a summary that demonstrates how the NSW Aboriginal Health Impact Statement has been considered.

c. List sub-study personnel who have received any cultural compentancy training

Name	Details of training	Date

(Add more rows as necessary)

13. References

1. Insight Economics. State of the Nation - A Report into Melanoma, A National Health Priority. Sydney,Australia; 2022.

2. Peek G, Olsen CM, Baade P, Youlden DR, Aitken JF, Green AC, et al. Survival in patients with multiple primary melanomas: Systematic review and meta-analysis. J Am Acad Dermatol. 2020;83(5):1406-14.

3. Vale L, Kunonga P, Coughlan D, Kontogiannis V, Astin M, Beyer F, et al. Optimal surveillance strategies for patients with stage 1 cutaneous melanoma post primary tumour excision: three systematic reviews and an economic model. Health Technol Assess. 2021;25(64):1-178.

4. Li L, Yang Z, Hou Y, Chen Z. Moving beyond the Cox proportional hazards model in survival data analysis: a cervical cancer study. BMJ Open. 2020;10(7): e033965.

14. Principal Investigator's/Lead Researcher's Declaration

I certify that the above information is accurate and that the project will continue to be carried out in accordance with the original PHSREC approved protocol and any approved amendments.

Name:

Date: 11/07/2022

Signature: _____Anne Cust_____
**Electronic signature accepted*

Appendix E. Supplementary material for Chapter 4

F.1. Cancer Registries Ethics Approval letters

Anne Cust

From: Patrick Borzycki (Cancer Institute NSW) <Patrick.Borzycki@health.nsw.gov.au> on behalf of CINSW-Ethics <CINSW-Ethics@health.nsw.gov.au>
Sent: Monday, 1 March 2021 3:37 PM
To: Anne Cust
Cc: Anne Cust; CINSW-Ethics; Amelia Smit
Subject: RE: 2020/ETH03109: Application HREA - Approved

Date of Decision Notification: **27 Jan 2021**

Dear Professor Anne Cust,

Thank you for submitting the following Human Research Ethics Application (HREA) for HREC review;

2020/ETH03109: A national risk-stratified melanoma screening program in Australia: a modelling study of the benefits, harms, cost-effectiveness and resource implications

This Application was reviewed as a **Greater than low risk review pathway** and was initially considered by the **NSW Population and Health Service Research Ethics Committee** at its meeting held on **9th December 2020**.
The project was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED**.

This email constitutes ethical and scientific approval only.
This project cannot proceed at any site until separate research governance authorisation has been obtained from the Institution at which the research will take place.

This project has been Approved to be conducted at the following sites:
- The University of Sydney NSW
- Cancer Council NSW

The following documentation was reviewed and is included in this approval:

- Cover Letter, dated 26 November 2020
- Letter of Response, dated 19 January 2021
- Human Research Ethics Application 2020/ETH03109 version 2, dated 21 December 2020
- PHSREC Protocol version 2, dated 19 January 2021
- NSW Privacy Form
- Data Variables Requested from Cancer Registries version 2, dated 19 January 2021
- AIHW Data Specifications
- NSW CR Data Custodian Correspondence, dated 27 November 2020
- WA CR Data Custodian Email Confirmation, dated 6 November 2020
- NT CR Data Custodian Email Confirmation, dated 7 October 2020
- QLD CR Data Custodian Email Confirmation, dated 16 September 2020
- ACT CR Data Custodian Email Confirmation, dated 12 October 2020
- SA CR Data Custodian Email Confirmation, dated 16 September 2020
- VIC CR Data Custodian Email Confirmation, dated 9 October 2020
- TAS CR Data Custodian Email Confirmation, dated 8 October 2020
- Anne Cust CV
- Karen Canfell CV
- Amelia Smit CV
- Yoon-Jung Kang CV
- Gillian Reyes-Marcelino CV

- Michael Caruana CV
- Caroline Watts CV
- Kristie McLoughlin CV
- David Espinoza CV
- Independent Peer Review Report, dated 25 November 2020
- NHMRC Projects Recommendation

The Human Research Ethics Application reviewed by the HREC was:
Version: 2
Date: 21 Dec 2020

The approval is for a period of 5 years from the date of this e-mail **(27 Jan 2021)**

The Committee granted a waiver of the usual requirement of consent for the use of re-identifiable information held by NSW agencies, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW).

The Coordinating Principal Investigator will:
• provide the HREC with an annual report and the final report when the project is completed at all sites. This will be through the submission of a milestone in REGIS.
• immediately report anything that might warrant review of ethical approval of the project.
• submit proposed amendments to the research protocol, including; the general conduct of the research, changes to CPI or site PI, an extension to HREC approval, or the addition of sites to the HREC before those changes can take effect. This will be through a notification of an amendment in REGIS
• will notify the HREC if the project is discontinued at a participating site before the expected completion date, with reasons provided.
• submit any necessary reports related to the safety of research participants in accordance with NHMRC Safety and Reporting Guidance. This will be through the Significant Safety Issue or Third Party Breach form in REGIS.
• Interventional trials must be registered on one of the clinical trial registeries e.g. https://www.anzctr.org.au.

Submission of annual progress/final reports (milestone), amendments and safety reports should be done through the forms provided in REGIS. Guidance on these processes can be found on the REGIS website.

It is noted that the **NSW Population and Health Service Research Ethics Committee** is constituted in accordance with the National Statement on Human Conduct in Research, 2007 (NHMRC).

The processes used by the HREC to review multi-centre research proposals have been certified by the National Health and Medical Research Council.

Please contact us if you would like to discuss any aspects of this process further, as per the contact details below. We look forward to managing this study with you throughout the project lifecycle.

Regards,
Secretariat on behalf of David Roder, Chairperson, NSW Population and Health Services Research Ethics Committee
T (02) 8374 5689 / 8372 3610 **F** (02) 8374 3600 **E**cinsw-ethics@health.nsw.gov.au

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cancer.nsw.gov.au

We acknowledge the traditional custodians of the lands on which we work and live,
and pay our respect to Elders past, present and future.
Please consider the environment before printing this email.