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Article

Incidence of in Situ vs Invasive Melanoma: Testing the "Obligate Precursor" Hypothesis

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Abstract

Background: Melanoma incidence has been rising in populations with predominantly European ancestry (White), speculated to be partly driven by heightened detection of indolent tumors. If in situ melanomas are destined to evolve to invasive cancers, detecting and removing them should deplete the pool of invasive lesions, and people with in situ melanoma should, on average, be younger than those with invasive melanoma. **Methods:** We analyzed long-term incidence trends (1982-2018) for in situ and invasive melanomas in 3 predominantly White populations with high, medium, and low melanoma rates: Queensland (Australia), United States White, and Scotland. We calculated the incidence rate ratio (IRR) of in situ to invasive melanomas and estimated the contributions of age, period, and cohort effects. We compared age at diagnosis of in situ vs invasive melanomas overall and stratified by sex and anatomic site. **Results:** In all 3 populations, the in situ to invasive incidence rate ratio increased statistically significantly from less than 0.3 in 1982 to 1.95 (95% confidence interval [CI] = 1.88 to 2.02) in Queensland, 0.93 (95% CI = 0.90 to 0.96) in the US White population, and 0.58 (95% CI = 0.54 to 0.63) in Scotland in 2018. The mean age at diagnosis of in situ melanomas was the same or higher than invasive melanomas for almost all time periods among men and women and on all body sites except the lower limbs. **Conclusions:** The increasing ratio of in situ to invasive melanoma incidence over time, together with the high (and increasing) mean age at diagnosis of in situ melanomas, is consistent with more indolent lesions coming to clinical attention than in previous eras.

ARTICLE

The incidence of melanoma has increased steadily over the past 5 decades in many susceptible populations (1), whereas mortality has remained largely stable (2). One explanation for these disparate trends is that a concerted effort in secondary prevention has shifted the diagnosis of melanoma toward earlier stages, which, if successfully detecting more cases of biologically aggressive disease, would be expected to decrease the proportion of thick invasive melanomas. Studies reporting an increased incidence of in situ and thin melanoma relative to thick melanoma support this contention (3,4). An alternative explanation (swiftly gaining currency) is that widespread detection efforts are leading to overdiagnosis of melanoma, that is, the diagnosis of indolent lesions that will not cause excess morbidity or death within a person's lifetime (5-7).

Melanoma in situ is recognized histologically by the presence of neoplastic cells resembling those of invasive melanoma but confined to the epidermis, with irregular nested and lentiginous and/or pagetoid growth patterns (8). Detailed microdissection analyses support the notion that a sizeable proportion of invasive melanomas evolve from in situ precursor lesions through the acquisition of successive genetic alterations (9). Of the 9 histological subtypes of melanoma recognized by the World Health Organization, 3 (comprising 80%-90% of cutaneous melanomas) are related to cumulative solar damage and have an in situ stage: superficial spreading melanoma, lentigo maligna melanoma, and desmoplastic melanoma (10). Accepting this paradigm of neoplastic progression, an argument can be made that detecting and excising in situ lesions should reduce the future incidence of invasive melanoma and thereby reduce mortality. Countering this view is the growing acceptance that a proportion (and perhaps the majority) of these in situ lesions are biologically indolent, unlikely ever to progress to invasive disease.

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To understand at a population level the dynamic relationships between these states of melanocytic neoplastic progression, we sought to investigate incidence trends for in situ and invasive melanomas across 3 jurisdictions with high (Queensland, Australia), intermediate (US White population), and low (Scotland, United Kingdom) incidence of melanoma respectively. We focused on the incidence rate ratio (IRR) of in situ to invasive melanomas. We hypothesized that the IRR has increased over time and that the increases will be most marked in those jurisdictions with high levels of melanoma awareness (eg, Queensland) and on more readily visible areas of the body (ie, the head and neck). Further, on the assumption that in situ lesions are biological precursors to invasive melanoma, we hypothesized that, on average, people diagnosed with in situ melanoma will be younger than those diagnosed with invasive melanoma. We sought to test these hypotheses using data from long-standing, population-based cancer registers that have captured information about in situ and invasive lesions.

Methods

Melanoma Incidence Data and Population Denominators

We obtained age-, sex-, and site-specific data on incident invasive and in situ melanoma cases from population-based cancer registries in the United States, Queensland (Australia), and Scotland for the period 1982-2018. We examined 4 anatomic sites: head and neck, trunk, upper limbs, and lower limbs.

We obtained incidence data for the US White population from the Nine Registries Database of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, which covers approximately 9.4% of the US population (11). We accessed the data using SEER*Stat 8.3.9.2 software in September 2021. We obtained incidence data for Queensland and Scotland via direct requests to the respective cancer registries between August and October 2021; each registry approved the release of the data for the purposes of this study.

Statistical Analysis

We fitted joinpoint models to describe trends in age-standardized incidence rates for invasive and in situ melanoma and calculated the average annual percentage rate of change (AAPC) for counts per capita for the period 1982 through 2018 using the Joinpoint Regression Program, Version 4.8.0.1 April 2020 (Statistical Research and Applications Branch, National Cancer Institute). All incidence rates were standardized to the US 2000 population.

We calculated the IRR as the ratio of the age-standardized rates for in situ and invasive disease for each year of the study period and assessed the trend in the age-standardized IRRs using joinpoint regression analyses.

We also conducted age-period-cohort modeling and compared age, period, and cohort effects on in situ and invasive melanoma incidence trends in each of the 3 populations (12). Using this approach, we examined 4 “estimable functions”: longitudinal age curves (using the 1949 birth cohort as referent), cross-sectional age curves (2001 as referent), fitted cohort pattern (reference age 52 years in successive birth cohorts), and fitted temporal trends (reference age 52 years in successive calendar periods). We also examined local drifts (estimated annual percentage changes over time for each age group). Formally, we tested for proportionality using the methods of Rosenberg and colleagues (13). We calculated the corresponding IRRs and local drift differences for in situ vs invasive melanomas in each of the 3 populations.

We calculated mean age (and 95% confidence intervals [CIs]) at diagnosis of in situ and invasive melanoma in 5-year periods from 1984-1988 to 2014-2018. These calculations were based on the standard assumption that the age- and period-specific counts are independent Poisson variates. In any given year, the mean age in the population is a weighted average based on person-years of observation. We obtained variances using the standard delta method. We considered findings to be statistically significant at $\alpha = .05$.

The study was approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (Approval Number P3631).

Results

Trends in Incidence of Invasive and in Situ Melanoma

The age-standardized rate for invasive melanoma increased from 12.94/100 000 in 1982 to 32.20/100 000 in 2018 in the US White population (AAPC = 2.7, 95% CI = 2.5 to 2.9), from 5.88 to 21.04/100 000 in Scotland (AAPC = 3.0, 95% CI = 2.6 to 3.5), and from 43.88 to 73.03/100 000 in Queensland (AAPC = 1.4, 95% CI = 0.5 to 2.4) (Table 1). Although Queensland had the highest incidence of invasive melanoma, the average rate of change in incidence was approximately one-half of that observed in the US White population. The rate of increase was much higher for melanoma in situ and was similar in all 3 populations (AAPC = 8.4 for US White population, 8.5 for Scotland, and 7.1 for Queensland).

By 2018, the incidence in Queensland of melanoma in situ was approximately twofold higher than the incidence of invasive melanoma (142.35 vs 73.03/100 000, respectively), whereas in the US White population, the rates of invasive and in situ melanoma were similar (32.20 vs 30.02/100 000, respectively). In Scotland, the incidence of melanoma in situ was approximately one-half the rate of invasive melanoma (12.26 vs 21.04/100 000, respectively).

In all 3 populations, the AAPC for invasive lesions decreased over time. The AAPC for in situ lesions also decreased over time. Even so, in every year, the AAPC for in situ lesions was greater than that for invasive lesions. For example, in Queensland between 2006 and 2018, the incidence for in situ lesions increased by 7.7%/y but by only 1.2%/y for invasive lesions (Figure 1, A). Consequently, the incidence curves for Queensland crossed over circa 2008; the incidence of in situ lesions was higher than that of invasive lesions for all years subsequently. In contrast, in the US White population, the curves were on a convergent course (Figure 1, B), whereas in Scotland, the curves remain separated (Figure 1, C). Despite these differences, the ratio of in situ to invasive lesions increased over time in all 3 populations (Figure 1, D). The increase in IRR was observed in men and women (Supplementary Figure 1, available online) for melanomas occurring on all body sites and for all age groups (Supplementary Table 1, available online).

Incidence Trends in Invasive and in Situ Melanoma by Age and Calendar Period

The trends in in situ to invasive IRRs for melanoma are subject to the effects of age, period, and birth cohort. To disaggregate

Table 1. Age-standardized incidence of invasive and in situ melanoma in three populations and average annual percent change in rates

Location	ASR 1982		ASR 2018		AAPC for 1982–2018 (95% CI)	
	Invasive	In situ	Invasive	In situ	Invasive[a]	In situ[a]
US White						
Men	14.36	1.98	40.36	38.93	2.9 (2.7 to 3.1)	8.7 (7.4 to 10.1)
Women	12.02	1.79	26.21	23.26	2.5 (2.2 to 2.7)	7.2 (6.7 to 7.6)
Persons	12.94	1.83	32.20	30.02	2.7 (2.5 to 2.9)	8.4 (6.9 to 10.0)
Queensland						
Men	49.54	10.47	89.10	165.66	1.8 (1.4 to 2.1)	7.3 (6.2 to 8.5)
Women	40.68	8.73	62.06	123.87	1.3 (0.5 to 2.1)	7.4 (5.6 to 9.2)
Persons	43.88	9.39	73.03	142.35	1.4 (0.5 to 2.4)	7.1 (6.0 to 8.2)
Scotland						
Men	4.78	0.37	22.46	12.75	3.9 (3.4 to 4.3)	8.6 (7.3 to 10.0)
Women	6.97	0.71	20.51	12.29	2.4 (1.9 to 3.0)	8.2 (7.1 to 9.3)
Persons	5.88	0.59	21.04	12.26	3.0 (2.6 to 3.5)	8.5 (7.5 to 9.5)

[a]All AAPCs were statistically significantly different from zero at the $\alpha = .05$ level. AAPC = average annual percent change; ASR = age-standardized incidence rate; CI = confidence interval.

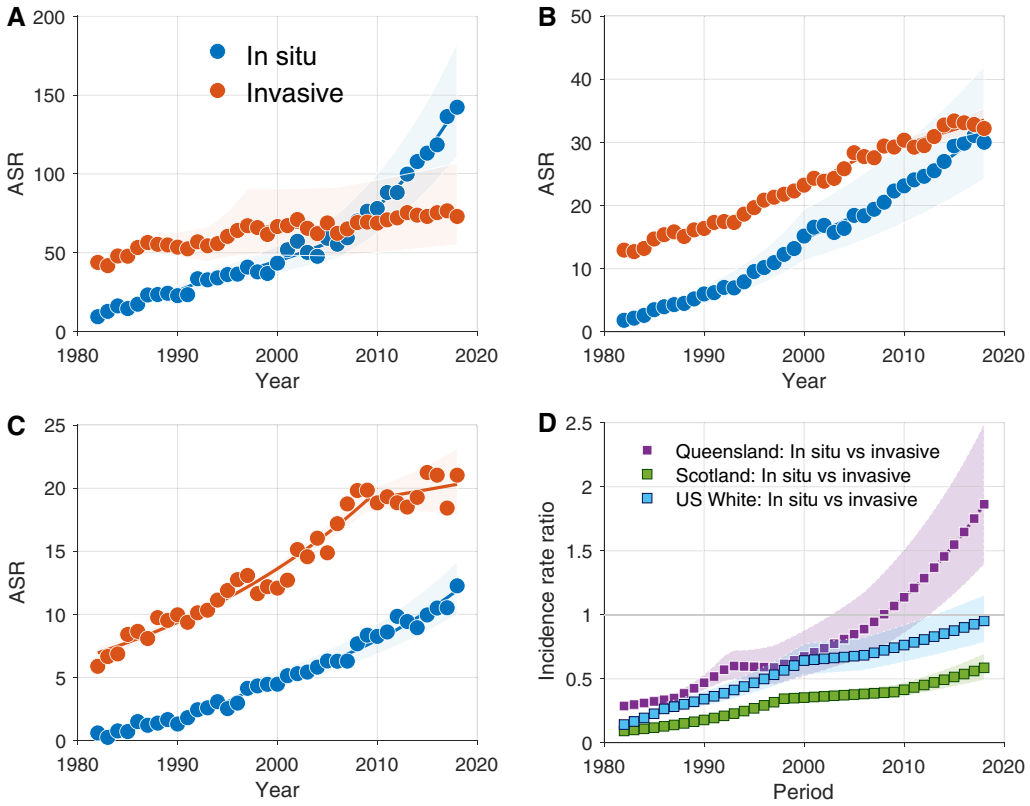

Figure 1. Age-standardized melanoma incidence from 1982 through 2018 in the US White, Queensland, and Scotland populations. Joinpoint regression models for in situ and invasive melanoma: **A**) Queensland, **B**) United States (US) White, **C**) Scotland populations, and **D**) in situ to invasive melanoma incidence rate ratios. ASR = age-standardized rate (US 2000).

and display these effects, we plotted the in situ to invasive IRRs for each age group and calendar period (Figure 2). These 3-dimensional plots show similar age-related patterns in each population: that is, steady increases in the in situ to invasive IRR with advancing age, peaking at age 70-79 years in the US White population and Scotland (Figure 2, B, C) and at age 55-64 years in Queensland (Figure 2, B). However, the effects of calendar period on the IRR differed across the 3 populations. In the US White population, the IRR increased with successively more recent calendar periods for all age groups, with abrupt increases noted in the mid- to late 1990s (Figure 2, B). In Queensland, there were striking increases in the IRR over time for all age groups, especially from the early 2000s, such that by 2014 the IRR exceeded 1 for all age groups. In Scotland, the effects of calendar period on IRR were evident but to a lesser extent than in either the US White or Queensland population.

To further explore the changes in incidence over time, we fitted age-period-cohort models (summarized in Supplementary Figure 2, available online). We focused specifically on the local drift parameters, which estimate the annual percent change in in situ

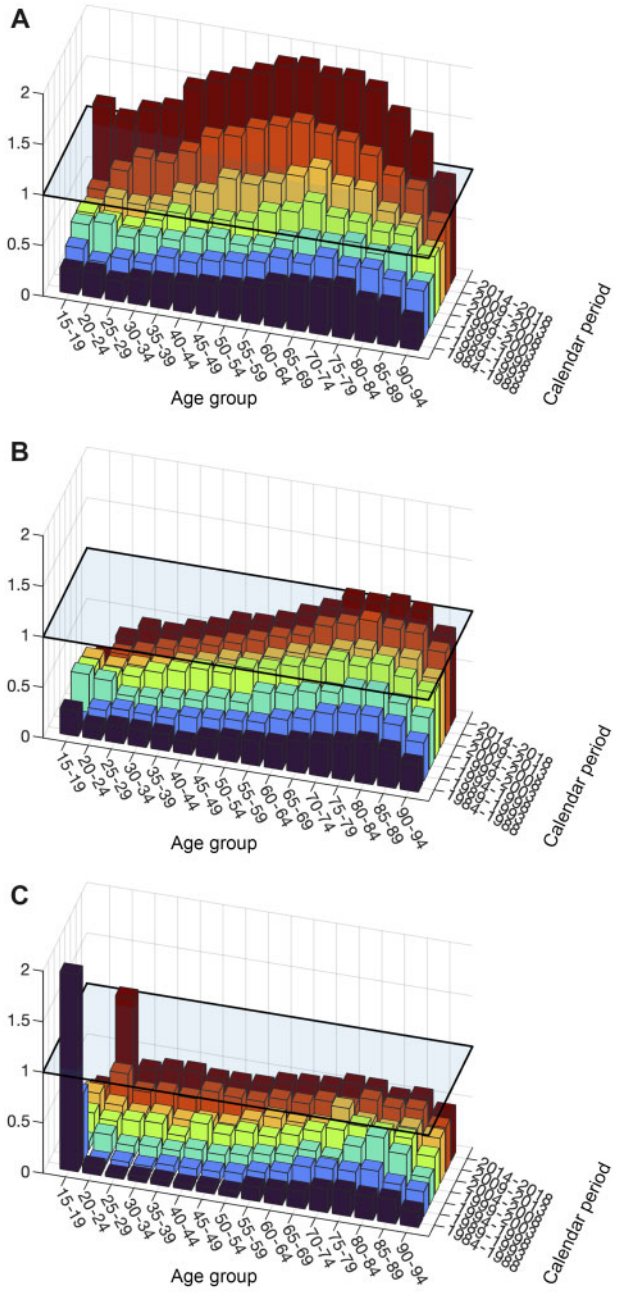

Figure 2. In situ to invasive melanoma incidence rate ratio (IRR) (1982-2018) by calendar period and age: **A**) Queensland, **B**) United States (US) White, and **C**) Scotland populations.

and invasive melanoma incidence over time for each age group after accounting for period and birth cohort effects (Figure 3). In all 3 populations, the local drifts had positive values for in situ melanomas, indicating a steady trend of year-on-year increases in rates of in situ disease in all age groups. In contrast, for invasive melanomas, we observed negative drift values in age groups younger than 25 years in the US White population and Scotland and younger than 40 years in Queensland, indicating declining rates of invasive melanoma in younger people. Notably, the drift difference was statistically significantly positive for all age groups in each population, demonstrating that the rate of change for in situ melanomas exceeded the rate of change for invasive melanomas in all age groups.

Trends in Age at Diagnosis for in Situ and Invasive Melanoma

Figure 4 compares the mean age of diagnosis for in situ vs invasive melanomas for the 3 populations in 5-year periods from 1984-1988 to 2014-2018. Three high-level observations are apparent. Firstly, the mean age at diagnosis of melanoma is higher for in situ compared with invasive lesions in all populations across the period of study (except in Queensland for the 2 most recent time periods). Secondly, the mean age of diagnosis of both in situ and invasive melanomas has been increasing in all populations except for in situ lesions in Scotland, where the mean age has remained steady. Thirdly, the mean age of diagnosis of melanomas in Queensland is younger than in the US White and Scotland populations.

Because in situ lesions occur more frequently among men than women and on sun-exposed sites such as the head and neck, we examined the trend by sex and body site. The mean age at diagnosis of melanoma was higher for in situ compared with invasive lesions for both men and women (Supplementary Figure 3, available online) and for all body sites except for the lower limbs (Supplementary Figure 4, available online).

Discussion

We examined trends in incidence of in situ and invasive melanoma across 3 populations of predominantly European ancestry and found that rates of in situ melanoma have been increasing faster than invasive melanoma in each one. The steepest increases were observed in Queensland. By 2018, more than 2 of 3 melanomas in Queensland were detected in the preinvasive state. Among the US White population, by 2018 almost 1 in 2 melanomas was preinvasive. This shift towards a preponderance of in situ melanomas has occurred on a background of continued increasing incidence of invasive melanomas in all 3 populations, suggesting that the diagnosis of increasing numbers of in situ melanomas in previous years has not appreciably diminished the pool of invasive melanomas. The trend was apparent for men and women and for melanomas on all body sites. The increase in the in situ to invasive IRR was observed across all birth cohorts and age groups. The local drifts indicate that the rate of change of in situ melanoma statistically significantly exceeds that of invasive melanoma in almost every age group. In addition, in all 3 populations, those diagnosed with in situ melanomas were, on average, older than those diagnosed with invasive melanoma.

Our analyses expand on earlier works reporting steeper increases in incidence of in situ and thin melanomas relative to thick melanomas in the United States (14), Europe (4), and Australia (3). Specifically, we calculated the IRRs for in situ to invasive melanoma in 3 populations with different levels of ambient insolation and at different stages in their response to the melanoma epidemic. With respect to the latter, in Australia, for example, multicomponent community-wide prevention campaigns began in the 1980s, aiming to increase awareness about skin cancer and reduce high levels of sun exposure (15), whereas in the United States and United Kingdom, similar campaigns were conducted at least a decade later (16,17), with lower levels of investment and, for the United States, without national coordination (17). Although directly comparable data are not available, it appears that the prevalence of opportunistic skin-screening activities is higher in Australia (18,19) than the United States (20,21) or Scotland. The overall patterns of trends across

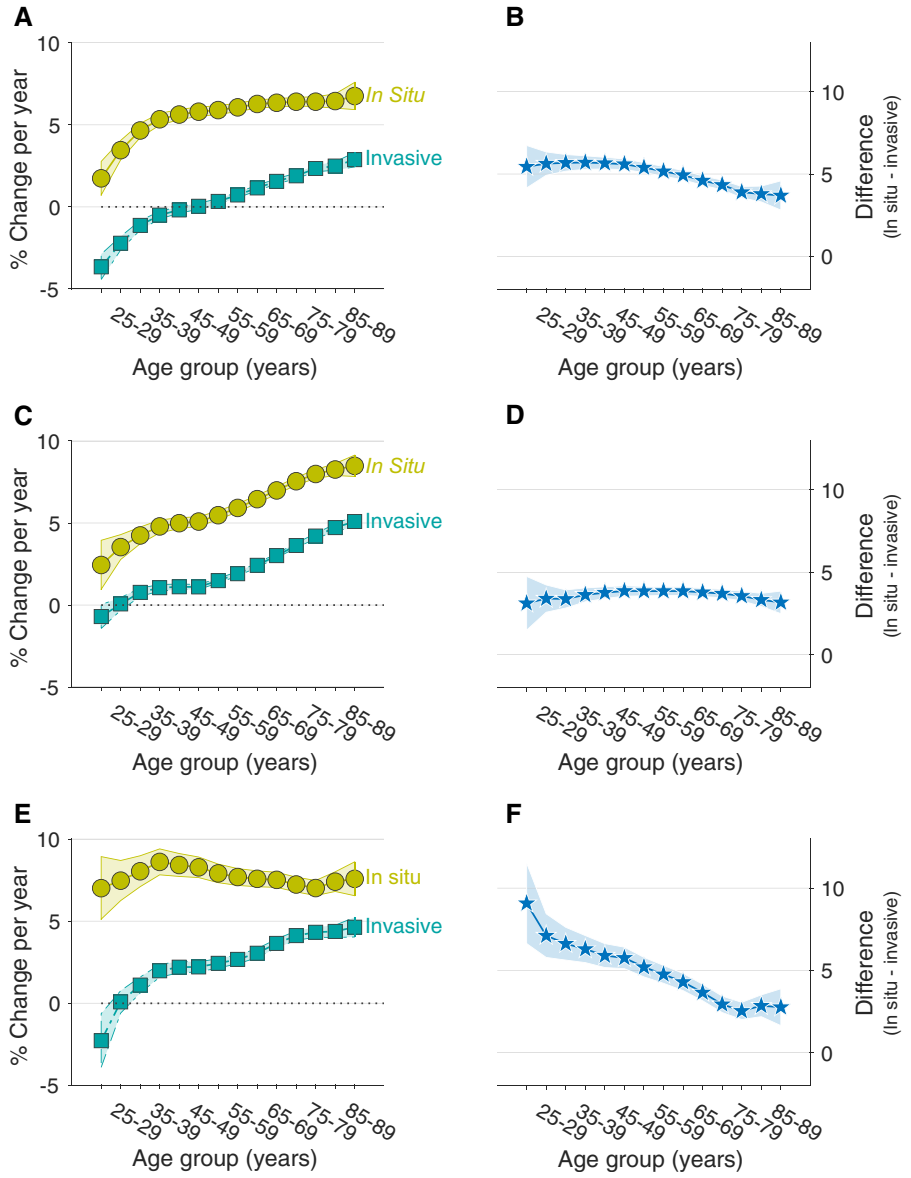

Figure 3. Local drifts for in situ and invasive melanoma incidence from age-period-cohort analyses (1982-2018): **A**) Queensland, **C**) United States (US) White, and **E**) Scotland populations. Local drifts describe the average annual percent change of the expected age-specific rates over time. The difference between local drifts for in situ and invasive melanoma is plotted in the **right panel** for each population (**B**, **D**, and **F**).

time and across birth cohorts were similar in all 3 populations: a steady increase in the IRR for in situ compared with invasive melanomas.

These patterns of diverging incidence trends for a cancer and its precursor might be explained by several different forces. First, there may have been real increases in the incidence of biologically aggressive precursor lesions that harbor the potential to invade and metastasize to distant sites ("new disease, newly diagnosed, newly recorded"). Second, there may have been changes in diagnostic and registration practices such that in situ melanomas that have always been excised in clinical settings have only recently been reported by pathologists or recorded by cancer registries ("existing disease, previously diagnosed, newly recorded") (22-24). Third, it may be that a reservoir of indolent, nonprogressive melanocytic lesions has always existed but previously did not come to clinical attention and has been detected and treated in recent years ("existing disease, newly diagnosed, newly recorded").

It is not possible to disentangle these competing explanations definitively using ecological data; however, one can posit relationships between the 2 states (ie, in situ vs invasive melanoma) that would be expected if in situ lesions are a necessary precursor to invasive disease. First, for any given birth cohort, an increase in the incidence of true precursors should predate any increases seen for biologically aggressive disease. Second, the age of diagnosis for precursor lesions at a given site should be lower than the age of diagnosis for invasive lesions because, under the assumption that in situ lesions are precursors of invasive disease, they necessarily must arise first (10).

Neither hypothesis was supported. Instead, we found that the increase in incidence of in situ melanomas is a relatively recent phenomenon similarly affecting all age groups and birth

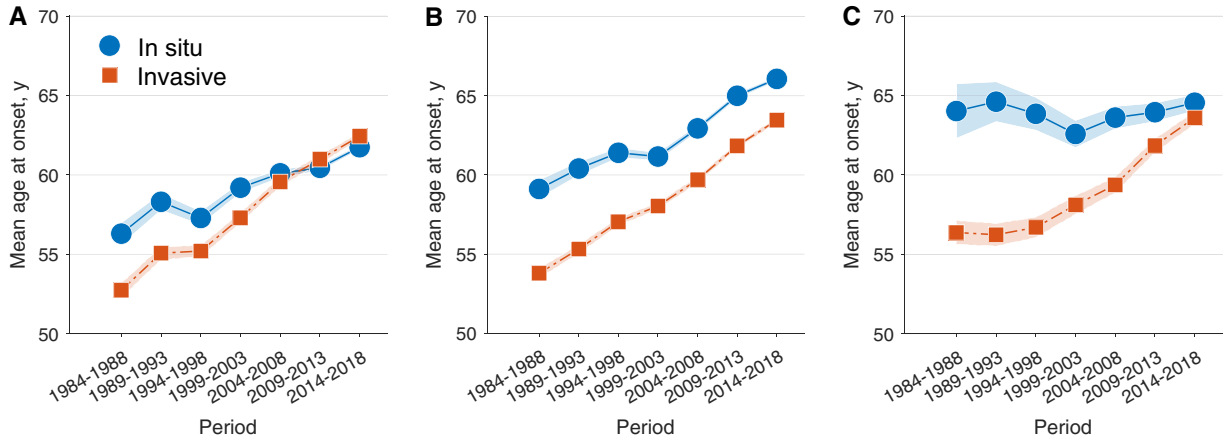

Figure 4. Mean age at diagnosis (and 95% confidence bands) of in situ and invasive melanoma (1982-2018) in **A**) Queensland, **B**) United States (US) White, and **C**) Scotland populations.

cohorts, a pattern consistent with period effects. We also found a higher mean age at diagnosis for in situ melanomas compared with invasive melanomas in all populations.

We are aware of only 1 previous study comparing age at diagnosis for in situ vs invasive melanomas at a population level (25). That study reported trends for the US White population in the interval 1975 to 1997, and hence the underlying data overlap with some of the data reported here. In that study, patients with in situ melanoma were 2 to 3 years older on average than those with invasive melanoma; however, the analysis did not stratify by potential effect modifiers of age at diagnosis, such as sex or anatomic site, and was restricted to only 1 population. We consistently observed older age at diagnosis for in situ melanomas than invasive melanomas across populations and within strata of age, anatomic site and birth cohort. The fact that most people treated for in situ disease are older than those treated for invasive disease suggests that many of the tumors harvested in the former group grow slowly, challenging the proposition that excising greater numbers of in situ lesions will yield meaningful mortality benefits.

We contend that these analyses, using novel statistical techniques applied to high-quality data from diverse populations, provide stronger support than earlier analyses for the contention that the increase in incidence of in situ melanomas likely reflects heightened detection of slow-growing lesions. Our finding that the in situ to invasive IRR was highest in Queensland, where awareness of the importance of early detection and in reducing morbidity and mortality is high and the prevalence of skin checks is also very high (18), provides some support for this notion. The possibility of underreporting of in situ lesions to cancer registries included in these analyses cannot be excluded, although we believe this is unlikely to explain the magnitude of effects observed here. The requirements for reporting in situ lesions to the cancer registries under study have not changed over the period examined. For the Queensland and Scottish cancer registries, the coding classifications (International Classification of Diseases for Oncology) have changed over the years and several new morphologies for in situ melanoma have been introduced; however, these changes improved specificity of type of melanoma in situ and did not influence rates of diagnosis. The completeness and accuracy of registration of melanoma in situ in Scotland is very high (26). For the US SEER registries, the completeness of reporting of melanoma (both in situ and early invasive) has decreased over time because of the decentralization of melanoma pathology (27-29); the extent of the impact on our findings is difficult to determine, but it seems likely that the magnitude of change in the ratio of in situ relative to invasive melanoma incidence over time may be underestimated. We also acknowledge the limitation of ecological data in distinguishing between the influences of etiologic and diagnostic factors.

These analyses need to be interpreted in context. It would be wrong to infer that most invasive melanomas arise de novo without a preexisting in situ component. Microdissection studies with genomic sequencing clearly demonstrate that invasive melanomas evolve from different types of precursor lesions—including in situ melanomas—that can be recognized through acquired somatic mutations in different classes of genes (30). It would also be wrong to infer that early detection of melanoma has no value; the very low long-term mortality for people undergoing surgical excision for thin invasive melanomas and, conversely, the higher risks of metastasis and death associated with thicker lesions provide powerful arguments in favour of early detection. Moreover, thin melanomas can be lethal; we have shown previously that thin melanomas account for more melanoma deaths overall than thick melanomas (31). On the other hand, the harms of overdiagnosis are not trivial and include overtreatment, stigma, anxiety, costs, and treatment-related adverse events (32,33).

In conclusion, these analyses, spanning more than 3 decades of observations across 3 populations with different melanoma trajectories, suggest the existence of a large pool of "noninvasive" melanocytic tumors that are being diagnosed as melanoma in situ with increasing frequency. These lesions are typically detected at older ages than invasive melanomas, and their rate of detection has climbed steeply in recent years. By necessity, our inferences here are limited to registry data comparing in situ with invasive tumors, but it remains possible that there also exists a pool of indolent melanomas that display dermal invasion but lack the capacity for metastasis ("radial growth phase melanomas") (8). The challenge remains as to how to reliably discriminate those lesions that have malignant potential from those that do not. New approaches, perhaps involving novel technologies, may be needed to help clinicians at the point of care identify those tumors most likely to harm their patients.

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Author contributions: Conceptualization: DCW, CMO; Data curation: CMO; Formal analysis: CMO, NP, PSR; Writing—Original draft: CMO, DCW; Writing—Review & editing: DCW, CMO, NP, PSR.

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Data Availability

All data used in this work are publicly available. The US data can be obtained from the US Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Specifically, this work used data from the SEER-9 registries database. These data can be downloaded using the software SEER*Stat, which may be downloaded from https://seer.cancer.gov/seerstat/. The data from the Queensland Cancer Registry (QCR) and the Scottish Cancer Registry are available by direct request to the respective registries.

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