See related commentary on pg 1765

An Epidemiologic Analysis of Melanoma Overdiagnosis in the United States, 1975–2017

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The primary cause of the increase in melanoma incidence in the United States has been suggested to be overdiagnosis. We used Surveillance, Epidemiology, and End Result Program data from 1975 to 2017 to examine epidemiologic trends of melanoma incidence and mortality and better characterize overdiagnosis in white Americans. Over the 43-year period, incidence and mortality showed discordant temporal changes across population subgroups; trends most suggestive of overdiagnosis alone were present in females aged 55–74. Other groups showed mixed changes suggestive of overdiagnosis plus changes in underlying disease risk (decreasing risk in younger individuals and increasing risk in older males). Cohort effects were identified for male and female mortality and male incidence but were not as apparent for female incidence, suggesting that period effects have had a greater influence on changes in incidence over time in females. Encouraging trends included long-term declines in mortality in younger individuals and recent stabilization of invasive incidence in individuals aged 15–44 years and males aged 45–54 years. Melanoma in situ incidence, however, has continued to increase throughout the population. Overdiagnosis appears to be relatively greater in American females and for melanoma in situ.

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INTRODUCTION

Overdiagnosis refers to the detection of asymptomatic disease that would not have otherwise become clinically apparent during a patient's life. It can occur because of more sensitive or intensive screening or from changing the disease classification threshold or nomenclature (Brodersen et al., 2018). Overdiagnosis is problematic because the patient derives no benefit and can be potentially harmed from both the diagnosis and resultant treatment. Growing evidence suggests that overdiagnosis may be particularly common for some cancers in the United States (US) (Welch and Black, 2010). Welch et al. (2019) examined incidence and mortality trends of common cancers and identified epidemiologic signatures that may indicate overdiagnosis. In particular, the discordant combination of rising incidence and stable mortality, which was identified in thyroid cancer, kidney cancer, and cutaneous melanoma, was interpreted to primarily indicate overdiagnosis. This has also led to a re-evaluation of the potential causes of the increase in melanoma incidence as well as the efficacy of prevention efforts on mortality (Welch et al., 2021).

There are few published reports examining epidemiologic trends of melanoma in the US through the lens of overdiagnosis considering demographic factors, period effects, and cohort effects. Such an analysis is particularly relevant to melanoma because UVR exposure, dermatologic care, and public awareness have changed over time and are heterogenous throughout the population. In addition, effective therapies for metastatic disease have only been available since 2011. We present an analysis of incidence and mortality trends in melanoma stratified by age and sex and consider period and cohort effects to help elucidate relative differences in overdiagnosis among subgroups of the population. These data might allow appropriate changes in prevention strategies that could improve the benefit-to-harm trade-off.

RESULTS

Patient characteristics

The nine Surveillance, Epidemiology, and End Result Program (SEER) registries reported 268,109 first cases of melanoma in white individuals (55.2% male) from 1975 to 2017. There were 175,442 first cases of invasive melanoma (55.3% male) and 105,385 first cases of in situ melanoma (56.3% male). During this same period, there were 291,214 deaths (63.0% male) among white individuals across the entire US attributed to melanoma.

Overall period trends

Melanoma incidence increased 41.6 per 100,000 (+459.0%) from 1975 to 2017; invasive and in situ incidence increased 20.1 per 100,000 (+235.8%) and 25.4 per 100,000 (+4,675.0%), respectively (Figure 1 and Supplementary Table S1). Mortality increased 0.8 per 100,000 (+34.2%)

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Abbreviations: SEER, Surveillance, Epidemiology, and End Result Program; US, United States

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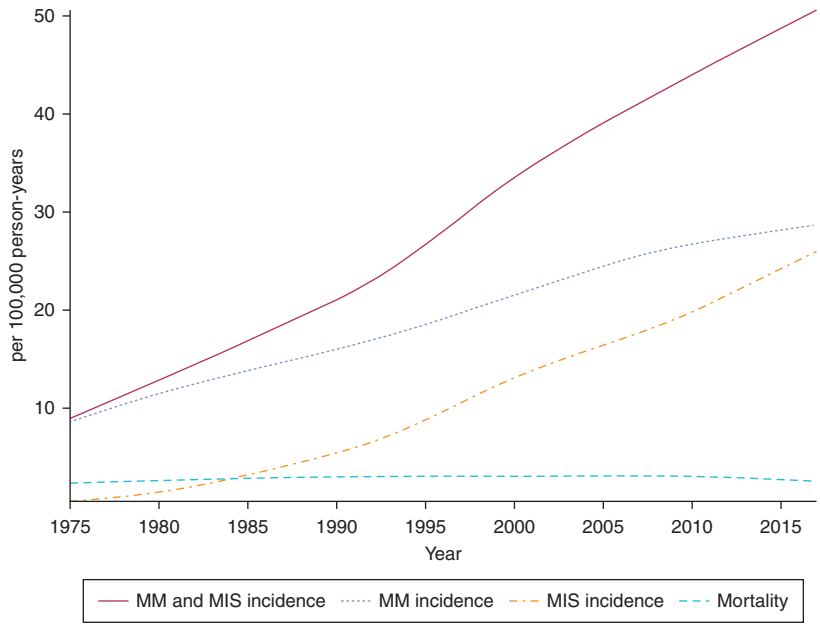

Figure 1. Age-adjusted rates of melanoma incidence and mortality in the US, 1975–2017. Incidence data are from the SEER Program, SEER 9 Registries (five states [Connecticut, Hawaii, Iowa, New Mexico, and Utah] and four metropolitan areas [Atlanta, Detroit, San Francisco, and Seattle]). All ages are included, and all rates are age-adjusted to the 2000 US standard population. Mortality data are from the National Vital Statistics System maintained by the National Center for Health Statistics. Incidence represents cases of invasive and in situ melanoma. MM incidence represents cases of invasive melanoma. MIS incidence represents cases of in situ melanoma. Mortality represents cases of melanoma death. MIS, melanoma in situ; MM, invasive melanoma; SEER, Surveillance, Epidemiology, and End Result Program; US, United States.

from 1975 to 2010 and decreased 0.6 per 100,000 (−20.0%) from 2010 to 2017.

Discordant age–sex trends in incidence and mortality

Not all age–sex groups (Supplementary Figure S1 and Supplementary Table S1) demonstrated rising incidence and stable mortality from 1975 to 2017 evident in the population-level overall period analysis. Three distinct signatures were identified: (i) rising incidence and stable mortality (for example, females aged 55–74 years), (ii) a disproportionate rise in incidence compared with an increase in mortality (for example, males aged 75+ years), and (iii) a rise in incidence and a decrease in mortality (for example, females aged 15–44 years) (Figure 2).

Trends in incidence by Breslow thickness from 1988 to 2017 across age–sex groups showed that most of the increase in incidence occurred in diagnoses of in situ and thinly invasive (≤1 mm) disease (Supplementary Figure S2). The only age–sex group with a decline in >1–2 mm and >2 mm melanoma incidence occurred in males aged 15–44 years. In all other age–sex groups, it either remained stable or increased. The greatest increase in thick melanoma incidence occurred in males aged 55+ years and females aged 65+ years.

Although invasive incidence continuously increased from 1975 to 2017 in the overall population, it has plateaued in some age–sex groups: males aged 15–44 years (beginning in 1985), males aged 45–54 years (beginning in 1995), males aged 55–64 years (beginning in 2005), and females aged 15–54 years (beginning in 2005). The melanoma in situ incidence rate, however, has not stabilized in any age–sex group.

Age- and sex-related effects on mortality, incidence, and the incidence-to-mortality ratio

Mortality rates increase exponentially with age (Figure 3). These rates are similar in magnitude in males and females until age 25 years, after which rates are higher in males. Incidence rates also increase with age; however, incidence increases exponentially in males and linearly in females. Unlike mortality, incidence is higher in females than males until age 50 years. After 50 years, incidence sharply increases in males and is double that of females by age 70 years. Thus, the ratio of incidence to mortality in females is two to three times as high as in males from ages 20 to 40 years; the difference in ratios becomes smaller with increasing age until it is approximately equal in males and females age 80+ years. Age effects were similar over stratified time periods and for melanoma in situ and invasive melanoma separately, respectively (data not shown).

The incidence-to-mortality ratio increased from 3.9 to 14.0 (+261.4%) from 1975 to 2010. From 1975 to 1995, this ratio increased at a similar rate in females (4.7 to 11.0 [+132.5%]) and males (3.3 to 7.4 [+126.2%]) (Supplementary Figure S1). From 1995 to 2010, the incidence-to-mortality ratio increased more in females (11.0 to 19.1 [+73.9%]) than in males (7.4 to 11.5 [+53.8%]). This disproportionate temporal increase in the incidence-to-mortality ratio was driven by a comparatively greater increase in melanoma incidence in females versus males aged 15–54 years, despite similar declines in the mortality rate.

Birth cohort effects on incidence and mortality

Nonparallel changes in age-specific incidence and mortality rates plotted by sex across years of birth suggested that age and period effects alone do not fully account for the trends in these rates and that the variation includes cohort effects (Supplementary Figure S3). The birth cohort residuals and estimated rate ratios for the effect of birth cohort on melanoma incidence and mortality are shown in Figure 4 and Supplementary Table S2. Strong cohort effects on mortality rates among males and females were observed, but the effects were relatively greater in males. After removing the effects of age and period, cohorts born during 1890–1920 and 1960–2000 had lower mortality

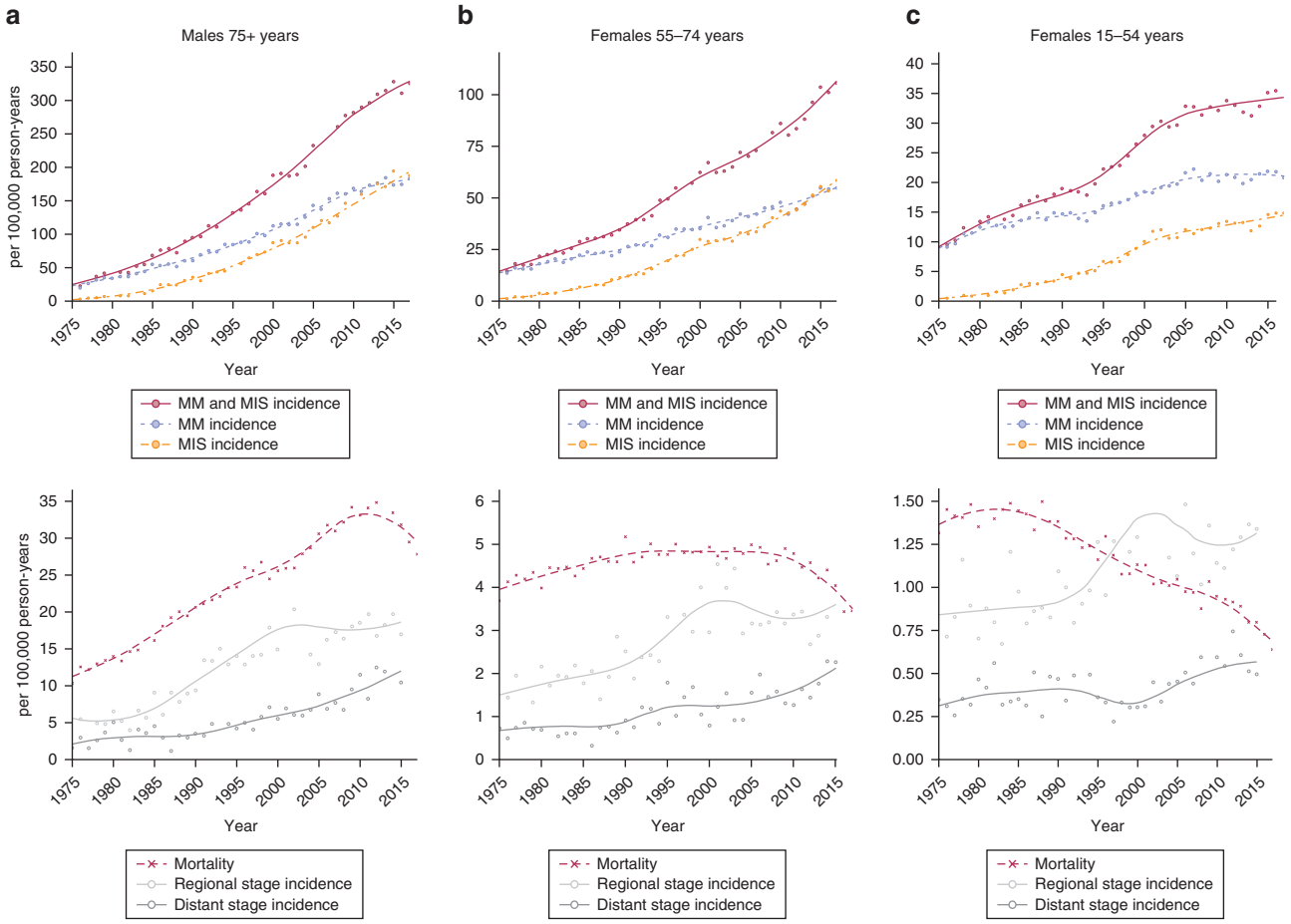

Figure 2. Representative epidemiologic signatures in age–sex groups. (**b**) The age–sex group that showed trends most suggestive of melanoma overdiagnosis alone were in females, aged 55–74 years. Other groups showed mixed effects, suggestive of overdiagnosis plus changes in underlying disease risk. (**a**) For example, males aged 75+ years had a disproportionate increase in incidence compared with the increase in mortality (increase in true melanoma risk plus overdiagnosis). (**c**) Females aged 15–44 years had rising incidence but declining mortality (decrease in true melanoma risk plus overdiagnosis). Changes in the incidence of regional and distant cases over time are most likely caused by differences in staging practices over time (that is, upstaging owing to increased use of imaging and sentinel lymph node biopsy). MIS, melanoma in situ; MM, invasive melanoma.

than those born from 1920 to 1960, with the highest risk being those born in 1950. Cohort effects were also evident for male incidence. Female incidence showed less pronounced evidence of cohort effects until generations beginning with 1990, at which the risk of diagnosis had declined (independent of age/period effects) compared with those born in 1950.

DISCUSSION

We present an analysis of trends in melanoma incidence and mortality rates in the US from 1975 to 2017. Overall, there were complex patterns in the trends of these rates. We identified evidence to suggest overdiagnosis, which appeared relatively greater in middle-aged and younger females. We also identified evidence of a true epidemic of disease, which was most apparent in older males. Positive findings include the success in reducing deaths in contemporary cohorts and stabilization of invasive incidence in younger age groups. Of concern, the increase in melanoma in situ incidence was particularly high, and it has not yet stabilized or decreased in any age–sex group.

From 1975 to 2011, females aged 55–74 years most clearly demonstrated rising incidence and stable mortality. Overdiagnosis alone could account for these discordant trends, because a true increase in cancer occurrence should be accompanied by an increase in mortality. For mortality to remain stable, a synchronous annual counterbalancing of improved treatment and/or detection would be required to prevent additional deaths. Because there was no effective systemic therapy for melanoma before 2011 and fewer than 20% of US adults have ever received a screening total body skin examination in their lifetime (Lakhani et al., 2014), a true rise in cancer occurrence appears unlikely. Although the rise in incidence of regional and distant metastatic cases in these individuals could be interpreted as a true increase in cancer occurrence, upstaging is a more likely cause owing to temporal changes in staging (i.e., use of sentinel lymph node biopsy and whole-body imaging with computed tomography).

Before 2011, males aged 75+ years had both rising incidence and mortality, suggesting an increase in true cancer occurrence. In line with this observation, the incidence of thicker tumors ≥1 mm also substantially increased in older

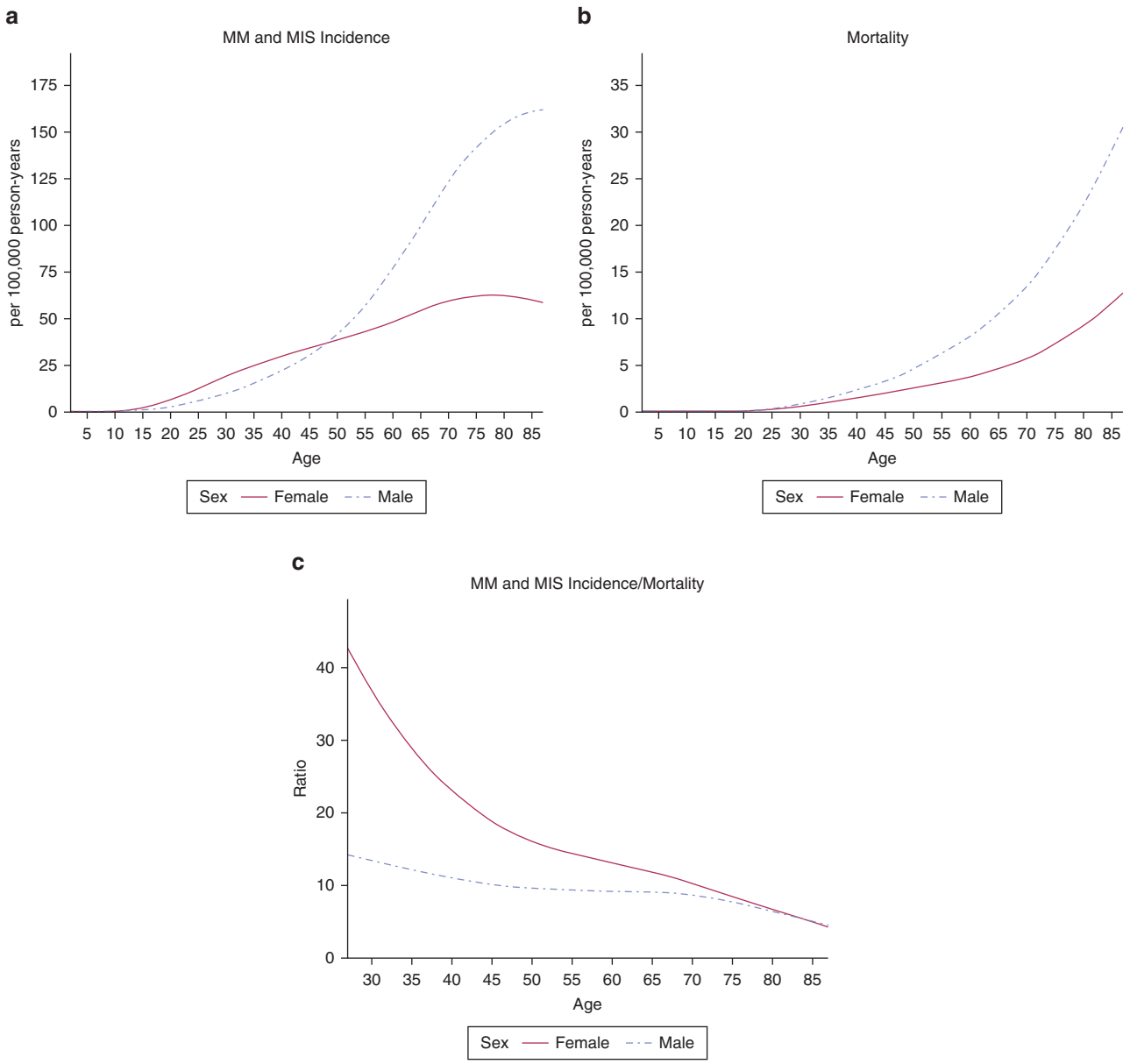

Figure 3. Effect of age on average melanoma incidence and mortality rates from 1975 to 2017. (**a**) Incidence rate, (**b**) mortality rate, and (**c**) incidence-to-mortality ratio stratified by sex and 5-year-grouped age categories, averaged from 1975 to 2017. Curves fit with LOESS regression. LOESS, locally estimated scatterplot smoothing; MIS, melanoma in situ; MM, invasive melanoma.

males. However, the relative increase in incidence compared with mortality was disproportionate, suggesting additional overdiagnosis. Although an incongruent rise in incidence versus mortality over time might be due to an increase in true cancer occurrence plus effective secondary prevention mitigating the rise in observed mortality or causing lead time bias, these factors appear unlikely. First, the penetrance of screening total body skin examinations in the population remains low. Second, the efficacy of physician-based melanoma screening examinations in reducing melanoma-related deaths remains unproven. Although low-to-moderate quality data (Aitken et al., 2010; Schneider et al., 2008; US Preventive Services Task Force et al., 2016) suggests that screening could reduce melanoma mortality, this has not yet been proven through a randomized trial, and at present the United States Preventive Task Force considers there to be insufficient evidence to support physician-based screening in the general population.

Females aged 15–54 years had rising incidence but declining mortality. Such a relationship is most commonly found after introduction of effective screening, but young Americans are the least likely to have ever received a total body skin examination (Lakhani et al., 2014). In addition, the magnitude of the decline in mortality (~50%) parallels or surpasses mortality declines found in cancers with widely implemented and effective screening (i.e., breast cancer in women aged >40 years, colon cancer in individuals >50 years of age) (Welch et al., 2019). If effective secondary prevention was the primary factor leading to a decrease in mortality, one would additionally expect a decrease in the

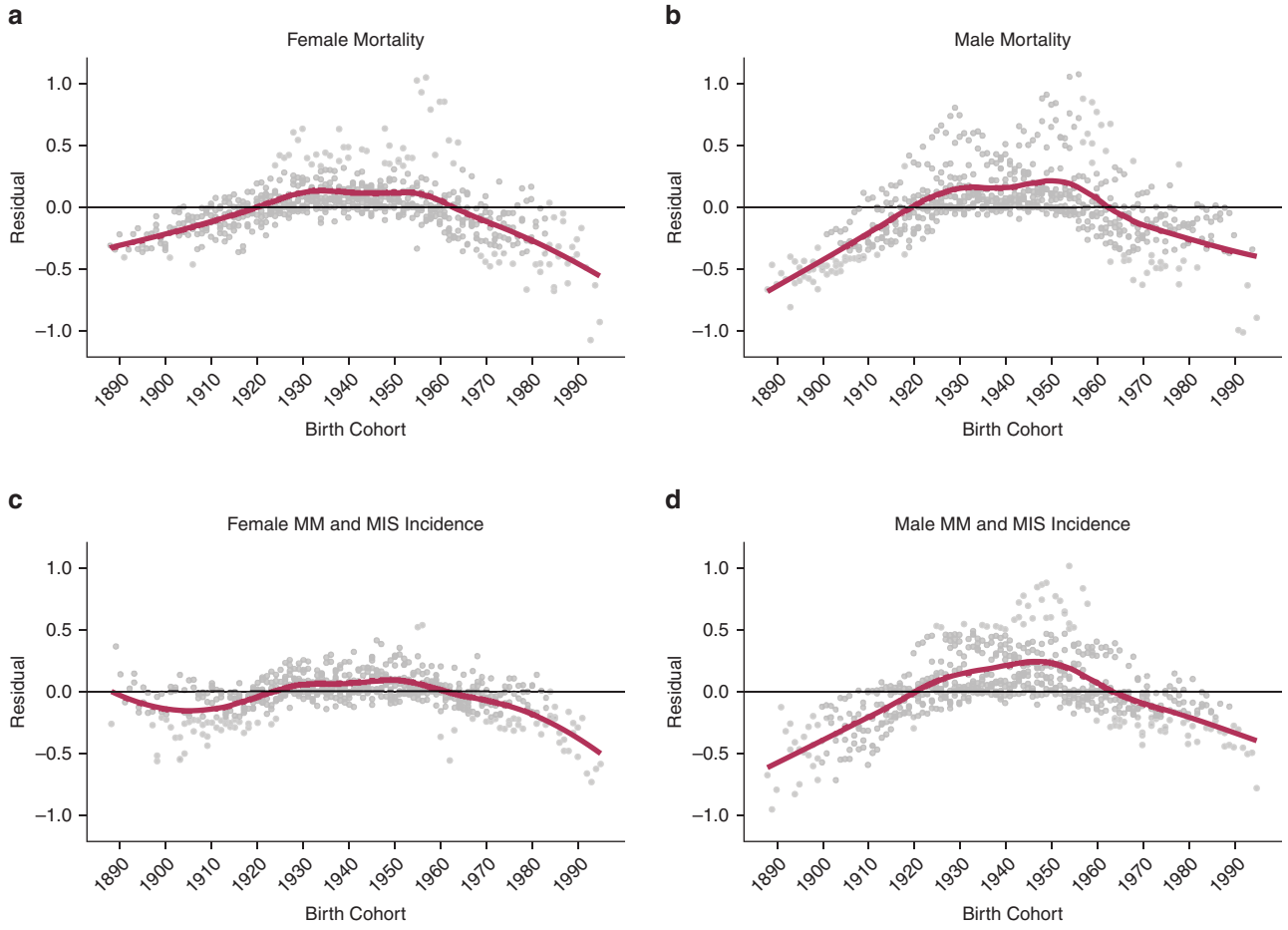

Figure 4. Birth cohort residuals of the median polish analysis. Dots represent the residuals from the median polish procedures plotted against year of birth. (**a, b**) Four median polish procedures modeled absolute age-adjusted male and female mortality, and (**c, d**) incidence by adult (≥20 years) 5-year-grouped age categories and year of occurrence from 1975 to 2017. The curve fit of the residuals is produced from LOESS regression. Rates were transformed by taking natural logarithms before fitting the median polish models to analyze the interaction of age and period on the multiplicative scale. Systematic deviation from 0.0 suggests the presence of a birth cohort effect. LOESS, locally estimated scatterplot smoothing; MIS, melanoma in situ; MM, invasive melanoma.

incidence of thicker melanomas because of earlier diagnoses. Among females aged 15–54 years, however, the incidence of thicker melanomas increased. Young females may be at particular risk of having a Spitz nevus/tumor be misdiagnosed as melanoma, which could contribute to overdiagnosis of thicker tumors. These lesions are most prevalent in younger females, present as dermal nodules, and are associated with false-positive melanoma diagnoses (Dika et al., 2017; Orchard et al., 1997). The absence of improving medical therapy suggests that a decrease in true occurrence risk plus overdiagnosis may be the most likely explanation for these discordant trends. A decline in true occurrence risk could be due to effective primary prevention and possibly the successful removal of potential melanoma precursors (that is, congenital and dysplastic nevi).

The nonconcordant temporal changes in incidence and mortality in older and younger individuals suggested that the variance included cohort effects (that is, factors that uniquely affect a birth generation through age-specific exposure or susceptibility). After removing the effects of age and period, male and female generations born in the US from 1920 to 1960 were found to be at a relatively increased risk of melanoma mortality, consistent with previous analyses (Roush et al., 1992; Scotto et al., 1991). Autier et al. (2015) identified that cohort effects explained changes in melanoma mortality over time better than period effects and postulated that excessive UVR exposure of children and adolescents from 1900 to 1960 was probably responsible for the epidemic of fatal melanoma (Albert and Ostheimer, 2003). In particular, the 1920s–1940s were characterized by a zealous enthusiasm for UVR exposure as a panacea for health (Albert and Ostheimer, 2003; Sorene, 2015), and the skin of young children was not uncommonly exposed to UVR lamps by the medical community (Sorene, 2015). Childhood is thought to be a particularly susceptible window for the long-term harmful effects of UVR on melanoma risk (Green et al., 2011).

Cohort effects were similarly present for incidence in males but were not apparent for incidence in females until generations born after 1980. The presence of cohort effects on female mortality and absence of cohort effects on female incidence suggests that changes in female incidence over time are predominantly explained by period effects (that is, factors that affect the entire population during the same period of time). A possible explanation is that there is a greater degree of overdiagnosis in females versus males,

which would appear as a period effect. This could result from more scrutiny for melanoma owing to higher rates of overall health care use, total body skin examinations, and skin self-examinations in females (Berwick et al., 1996; Lakhani et al., 2014; Manuel, 2018; Xu and Borders, 2003).

The incidence-to-mortality ratio was higher in younger women than men; with increasing age, the ratios became more similar until equivalency at ages 80+ years. The primary reason for this discrepancy is a higher incidence but lower mortality in younger females versus younger males. Multiple factors could contribute to these observations. First, there may be a paradoxical age-dependent sex difference (Natale et al., 2018) in melanoma risk and survival. Indeed, higher overall melanoma survival in females compared with males (Hieken et al., 2020; Scoggins et al., 2006) has been suggested to be related to intrinsic biologic sex differences (Natale et al., 2018). Unique age-related differences in melanoma risk by sex could be due to indoor tanning, which is more prevalent in young females (Centers for Disease Control and Prevention, 2012). An alternative explanation is that there is a greater degree of overdiagnosis in females versus males.

There are likely multiple contributing factors to the disproportionate rise of in situ melanoma. First, the diagnostic criteria used by pathologists have changed over time (Goldsmith et al., 1992, Davis and Little, 1977; Dubow and Ackerman, 1990; Elder et al., 2020; Hirst, 1977). Second, population-based ecological studies have shown that increased skin biopsies are associated with increased diagnoses of in situ, but not invasive, melanoma (Weinstock et al., 2017; Welch et al., 2005). Third, newer diagnostic technologies have allowed detection of clinically featureless tumors (Brouha et al., 2021; Carli, 2007; Kittler et al., 2006). Concerningly, a large study of pathologists in the US demonstrated that the diagnosis of in situ melanoma is neither reproducible nor accurate (Elmore et al., 2017).

There are limitations to this study. First, mortality and incidence data were drawn from unique datasets that differ in geographical coverage of the country. To mitigate race/ethnicity accounting for disparate trends in incidence and mortality, we limited analyses to white individuals. Analyses assumed that the completeness of case reporting has been similar over time. Reporting of incident cases of melanoma to registries has previously shown to be suboptimal, and there has been a recent trend toward electronic reporting (Cockburn et al., 2008; Raji et al., 2015). If the reporting of incident melanoma cases to registries improved over time, it could lead to the appearance of an artificial rise in incidence and the false interpretation of overdiagnosis. Inferences made from examining trends in incidence and mortality should be cautiously interpreted; because this study was descriptive, we can only speculate about potential explanations for the observed melanoma trends. Ultimately, the most reliable method to identify overdiagnosis is through a randomized trial (Carter et al., 2015; Duffy et al., 2010).

In conclusion, long-term trends in melanoma incidence and mortality vary among subsets of the population, suggesting an interplay of age, sex, period, and cohort effects. There is evidence to suggest overdiagnosis throughout the population. Time-varying factors, however, make it challenging to precisely quantify overdiagnosis, but it appears greater in females. Further research is needed to identify how to limit overdiagnosis. A re-evaluation of the benefits and harms of diagnosing and treating melanoma in situ may be a starting point. Taken together, these data argue for the need to refocus detection pressure to groups at highest risk of death from melanoma and to improve diagnosis of potentially lethal disease, perhaps through the use of more objective triage and diagnostic tests (Fried et al., 2020; Marchetti et al., 2021). Refining the ability to risk-stratify patients diagnosed with melanoma may also limit overtreatment (Grossman et al., 2020; Marchetti et al., 2020).

MATERIALS AND METHODS

The study was exempt from Institutional Review Board review under federal regulation because the data were publicly available. All data were obtained from SEER. Incidence data were drawn from SEER 9, which includes the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the cities of Detroit, Atlanta, San Francisco-Oakland, and Seattle-Puget Sound (~9.8% of the US population). New instances of cutaneous melanoma were defined from International Classification of Diseases-0-3 histology codes 8720–8799 with in situ or malignant behavior codes and primary sites C44.0–C44.9, and only those with a known patient age were included. Distinctly for each reported outcome, if a patient had more than one instance in the registry, only the first record was included. Data for mortality attributed to melanoma of the skin is provided by the National Center for Health Statistics and covers the entire US population. Year-, age-, and sex-specific incidence and mortality rates were extracted and age-adjusted to the 2000 US standard population. Additionally, for each recorded case of melanoma, the year and age (19-category in 5 year age groups) at diagnosis, sex, tumor staging, and Breslow thickness were extracted. Tumor staging was defined according to SEER historic stage A, which is derived from various schemas used during the period. Breslow thickness data were not available before 1988. Instances of in situ melanoma by International Classification of Diseases-0-3 codes were considered in situ even when a thickness of >0 mm was indicated (2.2% of cases). The analyses were limited specifically to white individuals, the more susceptible population, to account for potential racial-demographic shifts in the overall US population (Crombie, 1979; Hobbs and Stoops, 2002).

Relationships between melanoma incidence rates (invasive, in situ, and combined invasive and in situ), mortality rates, and the combined incidence-to-mortality ratio were assessed over the period of 1975–2017. Estimated rates were stratified by sex and five age classes as recommended (Corazziari et al., 2004) for standardized cancer survival analysis (15–44, 45–54, 55–64, 65–74, and 75+ years). Rates are reported in terms of per 100,000 individuals per year. The presence of overdiagnosis was estimated by qualitatively examining temporal trends in incidence and mortality for previously described epidemiologic signatures attributed to cancer (Oke et al., 2018; Welch et al., 2019). In addition, 5-year recorded ages were used to analyze birth cohort effect as well as continuous age-specific effects. Given the identification problem with age-period cohort analyses, birth cohort effects were conceptualized as a partial interaction between age and period rather than an independent effect (Keyes and Li, 2010). Median polish was used to remove the log-additive components of age and period effects (Keyes and Li, 2010). The resulting residuals were modeled by 10-year period birth

cohorts using linear regression (ordinary least squares). Relative birth cohort rate ratios were derived by exponentiating the resulting coefficients from the linear regression model.

Breslow thickness was undefined for 6.6% of cases in SEER (ranging from 19% of cases in 1988 to <4% of cases in 2017) and imputed using multivariable imputation with chained equations. Similar imputation methods were used for regional and distant staging (undefined in 12% of cases in 1975 to <2% of cases in 2015). Both tumor staging and thickness were defined as ordinal categorical variables, and a proportional odds model was selected as the multivariable imputation with chained equations imputation method, which controlled for year, sex, and age (19-category in 5-year age groups) as independent factors.

Data were exported from SEER and statistical analyses were performed in R using base, stats, dplyr, tidyr, readxl, ggplot2, mice, wesanderson, extrafont, grid, gridExtra, and reshape2 packages. Periodic trend was approximated with locally estimated scatterplot smoothing, using a smoothing parameter of $^1/_2$, and reported rates and relative rates were estimated from the smoothed trends.

Data availability statement

All data used in the preparation of this manuscript are publicly available.

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CONFLICT OF INTEREST

RIH: Funding for other research projects from the Melanoma Research Foundation and the Veterans Affairs Integrated Service Network 1. Scientific Officer, Evereden (makes personal care products, including sunscreen). VMR: Expert Advisor, Inhabit Brands, Inc. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: MAM; Data Curation: NRK; Formal Analysis: NRK, SWD; Funding Acquisition: ACH, AAM, MAM; Methodology: NRK, SWD, ACH, RIH, ACG, AAM, VMR, MAM; Project Administration: ACH, AAM, MAM; Resources: ACH, AAM, MAM; Software: NRK; Supervision: ACH, AAM, MAM, ACG; Validation: NRK, SWD, MAM; Visualization: NRK; Writing - Original Draft Preparation: NRK, SWD, MAM; Writing - Review and Editing: NRK, SWD, ACH, RIH, ACG, AAM, VMR, MAM

Disclaimer

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2021.12.003.

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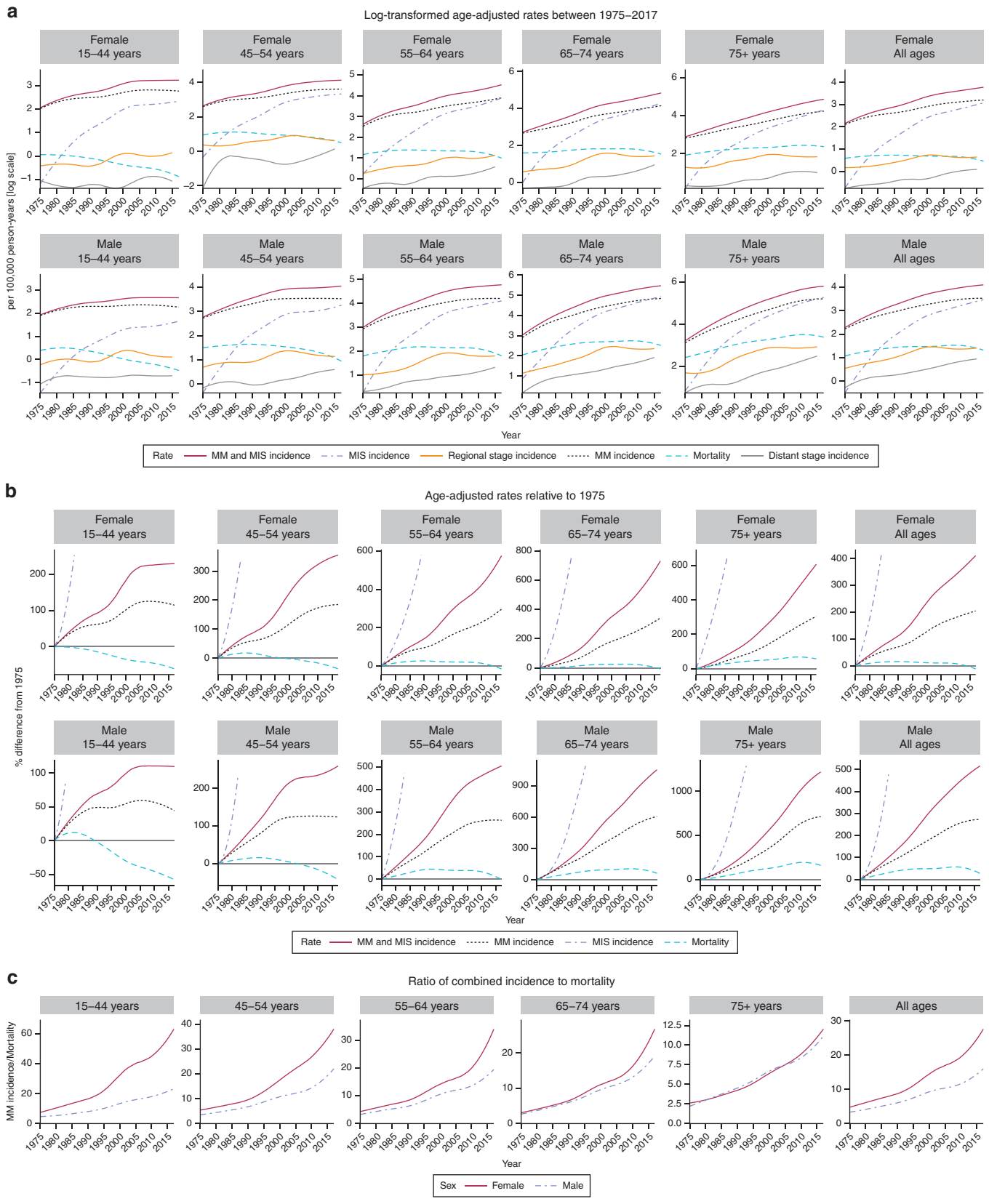
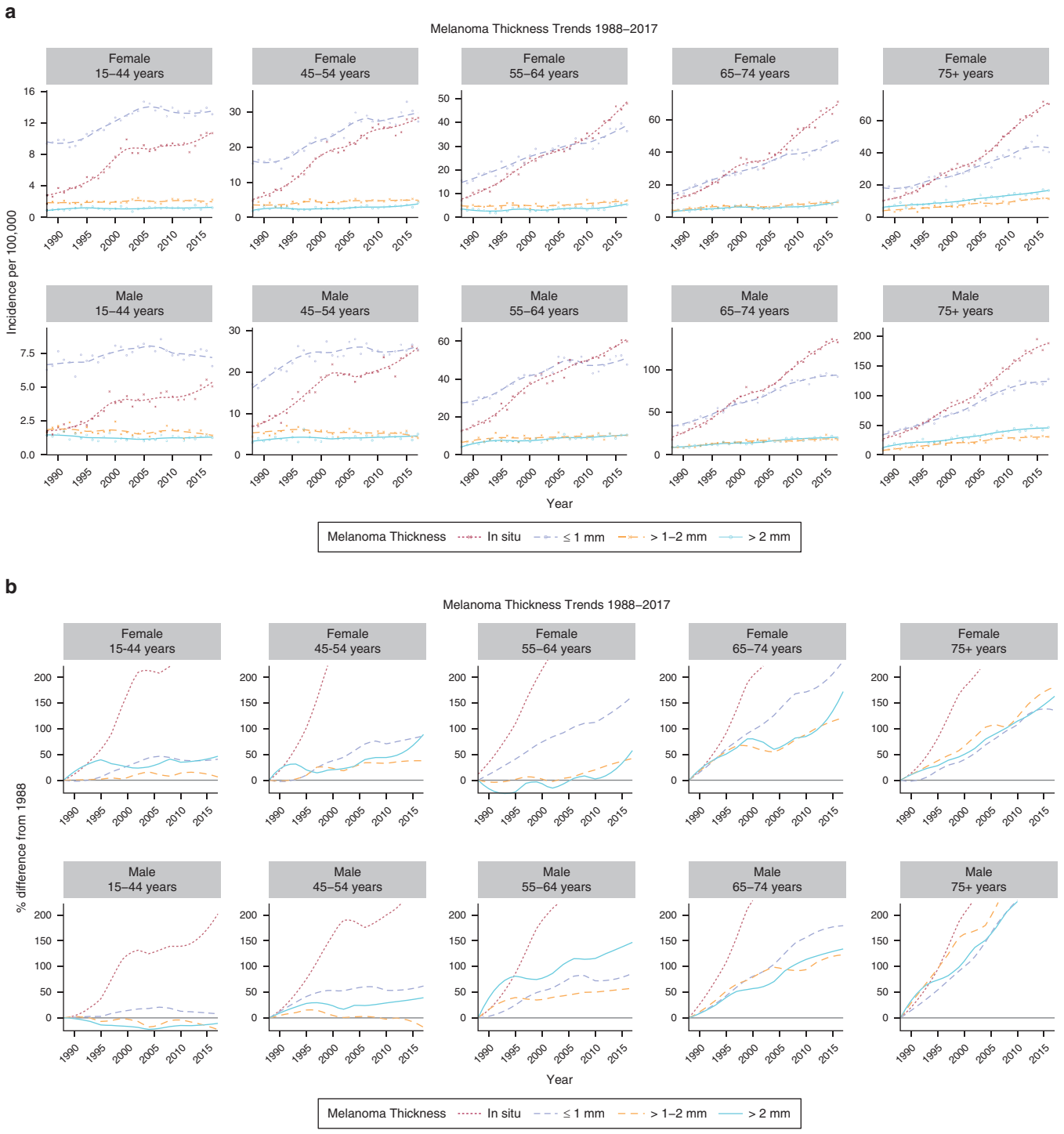
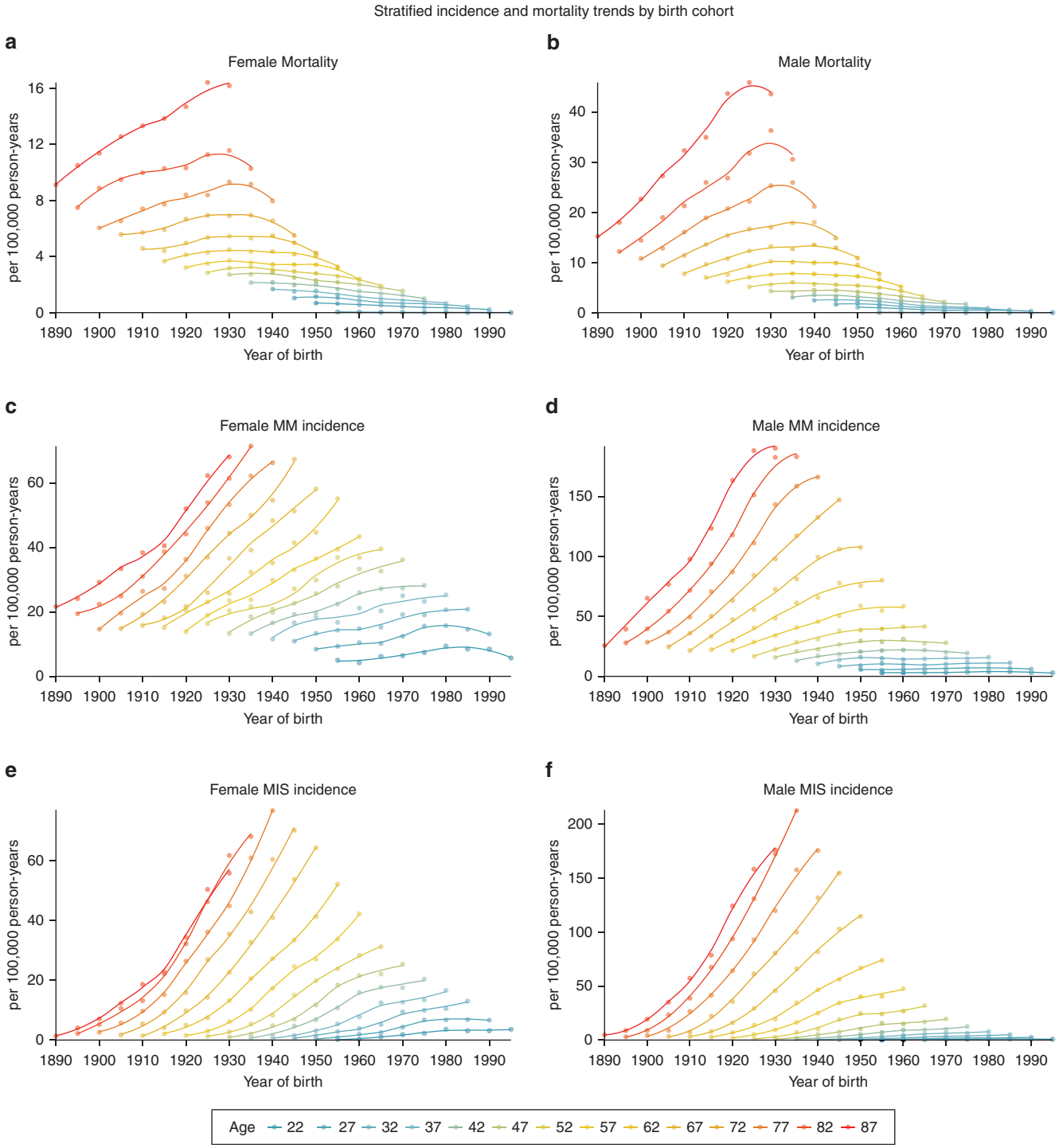


Supplementary Figure S1. Age-adjusted melanoma incidence and mortality rates, relative rates, and ratio of rates stratified by age and sex. The top two rows (**a**) show the trended age-adjusted rates of melanoma incidence (overall incidence, in situ incidence, invasive incidence, regional stage incidence, distant stage incidence) and melanoma mortality from 1975 to 2017 in females and males, stratified by age group. The middle two rows (**b**) show the trended age-adjusted rates in terms of percent change from 1975 baseline rates. The bottom row (**c**) shows the trended combined incidence-to-mortality ratio from 1975 to 2017. MIS, melanoma in situ; MM, invasive melanoma.



Supplementary Figure S2. Trends in melanoma incidence stratified by Breslow thickness, 1988–2017. The top two rows (**a**) show trends in melanoma incidence by Breslow thickness and stratified by age and sex. The bottom two rows (**b**) show trends in terms of percent change from 1988 baseline rates, stratified by age and sex. MIS, melanoma in situ; MM, invasive melanoma.



Supplementary Figure S3. Age-specific melanoma incidence and mortality rates by birth cohort. (**a, b**) Age-specific melanoma mortality (top panels), (**c, d**) invasive incidence (middle panels), and (**e, f**) in situ incidence (bottom panels) rates stratified by sex and plotted across years of birth. Each line represents a unique 5-year age group, with points along the lines reflecting data from 1975 (left) to 2017 (right). The points vertically above each year of birth on the x axis show that cohort's age-specific rates. If age-specific rates change over time in a parallel way, the variation is best described as a period effect. If age-specific rates change in significantly different ways among age groups (i.e., nonparallel lines), the variation is best described as including cohort effects. MIS, melanoma in situ; MM, invasive melanoma.

Supplementary Table S1. Trends in Melanoma Incidence and Mortality Rates in White Americans, 1975–2017

				10-Year Trend				10-Year Trend				10-Year Trend				12-Year Trend				42-Year Trend	
Outcome	Sex	Age	1975	Absolute Change	Percent Change	AAPC	1985	Absolute Change	Percent Change	AAPC	1995	Absolute Change	Percent Change	AAPC	2005	Absolute Change	Percent Change	AAPC	2017	Absolute Change	Percent Change
Mortality	Females	15–44	1.1	−0.1	−5.7	−0.6%	1.0	−0.2	−19.7	−2.2%	0.8	−0.2	−22.6	−2.5%	0.6	−0.2	−35.4	−3.6%	0.4	−0.7	−62.2
		45–54	2.6	0.5	18.1	1.7%	3.0	−0.4	−13.2	−1.4%	2.6	−0.3	−11.1	−1.2%	2.3	−0.7	−31.3	−3.1%	1.6	−1.0	−37.4
		55–64	3.2	0.7	23.4	2.1%	3.9	0.0	−1.0	−0.1	3.9	−0.1	−2.7	−0.3%	3.8	−1.1	−30.1	−2.9%	2.6	−0.5	−16.9
		65–74	4.9	0.3	7.0	0.7%	5.3	0.8	15.6	1.5%	6.1	0.1	1.1	0.1%	6.2	−1.6	−26.2	−2.5%	4.6	−0.4	−7.7
		75+	6.9	1.9	27.0	2.4%	8.7	1.3	14.7	1.4%	10.0	0.9	8.7	0.8%	10.9	−0.3	−2.3	−0.2%	10.6	3.8	54.8
		All ages	1.8	0.2	13.6	1.3%	2.0	0.0	−0.2	0.0%	2.0	−0.1	−3.4	−0.3%	2.0	−0.4	−20.7	−1.9%	1.6	−0.2	−13.2
	Males	15–44	1.5	0.1	9.6	0.9%	1.6	−0.4	−23.0	−2.6%	1.2	−0.3	−27.3	−3.1%	0.9	−0.3	−31.4	−3.1%	0.6	−0.8	−57.9
		45–54	4.5	0.6	12.8	1.2%	5.0	−0.1	−1.8	−0.2%	4.9	−0.7	−14.1	−1.5%	4.2	−1.7	−40.6	−4.2%	2.5	−1.9	−43.5
		55–64	6.1	1.8	30.3	2.7%	8.0	0.8	10.7	1.0%	8.8	−0.3	−3.6	−0.4%	8.5	−2.5	−29.8	−2.9%	6.0	−0.1	−2.4
		65–74	7.7	3.8	49.7	4.1%	11.5	3.0	26.2	2.4%	14.5	0.8	5.2	0.5%	15.3	−3.1	−20.3	−1.9%	12.2	4.5	58.5
		75+	11.3	5.6	49.7	4.1%	16.9	7.1	41.8	3.6%	24.0	5.8	24.1	2.2%	29.7	−0.8	−2.8	−0.2%	28.9	17.6	156.0
		All ages	2.9	0.9	30.9	2.7%	3.8	0.5	13.8	1.3%	4.4	0.1	3.1	0.3%	4.5	−0.8	−18.3	−1.7%	3.7	0.7	25.5
MM incidence	Females	15–44	7.5	4.1	54.6	4.5%	11.6	1.3	11.6	1.1%	13.0	3.9	29.9	2.7%	16.9	−0.6	−3.5	−0.3%	16.3	8.7	116.3
		45–54	12.9	7.2	55.6	4.5%	20.1	3.8	19.0	1.8%	23.9	8.9	37.0	3.2%	32.8	4.2	12.8	1.0%	37.0	24.0	186.2
		55–64	12.4	9.9	80.0	6.1%	22.4	5.5	24.7	2.2%	27.9	9.0	32.3	2.8%	36.9	12.6	34.1	2.5%	49.4	37.0	297.9
		65–74	14.3	6.3	43.8	3.7%	20.6	13.3	64.5	5.1%	33.8	11.9	35.2	3.1%	45.7	17.6	38.4	2.7%	63.3	49.0	342.9
		75+	17.2	7.4	43.1	3.6%	24.5	9.6	39.3	3.4%	34.2	15.7	45.8	3.8%	49.9	19.3	38.7	2.8%	69.1	52.0	303.0
		All ages	8.1	4.5	55.6	4.5%	12.6	3.0	24.1	2.2%	15.7	5.4	34.7	3.0%	21.1	3.7	17.6	1.4%	24.8	16.7	205.9
	Males	15–44	6.6	2.8	42.0	3.6%	9.4	0.4	4.3	0.4%	9.8	0.8	8.4	0.8%	10.6	−1.1	−9.9	−0.9%	9.6	3.0	44.6
		45–54	15.2	8.7	57.2	4.6%	23.9	8.3	34.6	3.0%	32.1	2.2	6.8	0.7%	34.3	−0.3	−0.9	−0.1%	34.0	18.8	124.1
		55–64	18.4	15.2	82.7	6.2%	33.7	15.8	46.9	3.9%	49.5	14.2	28.8	2.6%	63.7	3.6	5.7	0.5%	67.3	48.9	265.4
		65–74	18.0	25.0	138.4	9.1%	43.0	27.6	64.1	5.1%	70.6	29.3	41.5	3.5%	99.9	26.9	26.9	2.0%	126.7	108.7	602.8
		75+	22.3	25.6	114.8	7.9%	47.9	36.6	76.4	5.8%	84.5	51.4	60.8	4.9%	135.9	44.2	32.6	2.4%	180.2	157.9	707.5
		All ages	9.1	6.9	75.9	5.8%	16.0	6.7	41.8	3.6%	22.7	7.0	30.7	2.7%	29.7	4.3	14.4	1.1%	33.9	24.8	272.8

(*continued*)

Supplementary Table S1. Continued

				10-Year Trend				10-Year Trend				10-Year Trend				12-Year Trend				42-Year Trend	
Outcome	Sex	Age	1975	Absolute Change	Percent Change	AAPC	1985	Absolute Change	Percent Change	AAPC	1995	Absolute Change	Percent Change	AAPC	2005	Absolute Change	Percent Change	AAPC	2017	Absolute Change	Percent Change
MIS incidence	Females	15–44	0.3	1.5	461.8	18.8%	1.8	2.7	150.6	9.6%	4.6	4.4	95.9	7.0%	8.9	1.7	18.8	1.4%	10.6	10.3	3,174.5
		45–54	0.7	3.4	483.3	19.3%	4.0	6.6	163.5	10.2%	10.7	10.5	98.2	7.1%	21.1	6.7	31.5	2.3%	27.8	27.1	3,904.6
		55–64	1.2	4.2	339.0	15.9%	5.5	10.1	184.5	11.0%	15.5	12.7	81.8	6.2%	28.2	20.4	72.4	4.6%	48.7	47.4	3,813.5
		65–74	0.9	6.3	667.5	22.6%	7.3	13.5	186.1	11.1%	20.8	16.6	79.8	6.0%	37.3	33.4	89.6	5.5%	70.8	69.8	7,384.7
		75+	1.1	6.3	584.6	21.2%	7.4	11.7	157.9	9.9%	19.1	17.8	93.2	6.8%	36.9	35.4	96.0	5.8%	72.3	71.2	6,587.1
		All ages	0.5	2.3	485.1	19.3%	2.8	4.6	165.4	10.3%	7.3	6.6	90.4	6.6%	13.9	7.7	55.6	3.8%	21.7	21.2	4,500.7
	Males	15–44	0.2	0.9	360.4	16.5%	1.1	1.4	126.8	8.5%	2.6	1.4	56.3	4.6%	4.0	1.2	30.7	2.3%	5.2	5.0	2,033.6
		45–54	0.8	3.7	464.3	18.9%	4.5	7.5	167.3	10.3%	12.0	7.6	63.6	5.0%	19.6	6.4	32.4	2.4%	26.0	25.2	3,166.8
		55–64	1.2	7.9	652.8	22.4%	9.1	15.0	164.1	10.2%	24.1	20.0	83.2	6.2%	44.1	16.3	37.0	2.7%	60.5	59.3	4,890.2
		65–74	2.7	10.7	393.6	17.3%	13.4	30.7	229.6	12.7%	44.1	37.4	84.7	6.3%	81.5	56.6	69.5	4.5%	138.1	135.4	4,992.5
		75+	2.6	14.1	551.2	20.6%	16.7	36.0	215.8	12.2%	52.8	54.3	102.9	7.3%	107.1	84.5	78.9	5.0%	191.5	189.0	7,364.6
		All ages	0.7	3.1	477.3	19.2%	3.8	7.2	188.9	11.2%	10.9	9.2	83.7	6.3%	20.1	11.64	57.9	3.9%	31.7	31.1	4,737.6

Abbreviations: AAPC, average annual percent change; MIS, melanoma in situ; MM, invasive melanoma.

Supplementary Table S2. Estimated Rate Ratios for the Effect of Birth Cohort on Melanoma Incidence and Mortality in White Adults in the United States, 1975–2017

Birth Cohort	Mortality				MM and MIS Incidence				MM Incidence				MIS Incidence			
	Female		Male		Female		Male		Female		Male		Female		Male	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
1890	0.65	(0.57 – 0.74)	0.45	(0.38 – 0.53)	0.93	(0.86 – 1.02)	0.46	(0.40 – 0.53)	0.94	(0.86 – 1.03)	0.46	(0.40 – 0.53)	0.84	(0.69 – 1.03)	0.70	(0.57 – 0.87)
1900	0.71	(0.66 – 0.77)	0.52	(0.47 – 0.57)	0.77	(0.73 – 0.81)	0.55	(0.50 – 0.59)	0.76	(0.72 – 0.80)	0.59	(0.55 – 0.64)	0.93	(0.84 – 1.03)	0.60	(0.53 – 0.68)
1910	0.77	(0.72 – 0.83)	0.65	(0.59 – 0.71)	0.80	(0.77 – 0.84)	0.62	(0.58 – 0.67)	0.83	(0.79 – 0.87)	0.66	(0.61 – 0.71)	0.84	(0.77 – 0.91)	0.74	(0.67 – 0.83)
1920	0.86	(0.81 – 0.91)	0.79	(0.74 – 0.86)	0.87	(0.84 – 0.91)	0.79	(0.74 – 0.84)	0.88	(0.85 – 0.92)	0.83	(0.78 – 0.88)	0.94	(0.87 – 1.01)	0.86	(0.78 – 0.94)
1930	1.00	(0.92 – 1.04)	1.00	(0.87 – 1.02)	1.00	(0.94 – 1.02)	1.00	(0.86 – 0.97)	1.00	(0.96 – 1.04)	1.00	(0.90 – 1.01)	0.95	(0.88 – 1.03)	0.96	(0.88 – 1.06)
1940	0.98	(0.92 – 1.04)	0.93	(0.87 – 1.00)	0.98	(0.95 – 1.02)	0.97	(0.91 – 1.03)	0.99	(0.95 – 1.03)	0.99	(0.93 – 1.05)	0.95	(0.88 – 1.02)	1.00	(0.91 – 1.09)
1950		reference		reference		reference		reference		reference		reference		reference		reference
1960	0.92	(0.87 – 0.98)	0.87	(0.81 – 0.94)	0.93	(0.90 – 0.97)	0.84	(0.79 – 0.90)	0.93	(0.90 – 0.97)	0.86	(0.81 – 0.91)	1.00	(0.93 – 1.08)	0.91	(0.83 – 1.00)
1970	0.74	(0.69 – 0.79)	0.66	(0.60 – 0.72)	0.85	(0.82 – 0.89)	0.71	(0.66 – 0.76)	0.89	(0.85 – 0.93)	0.73	(0.68 – 0.78)	0.95	(0.88 – 1.04)	0.83	(0.74 – 0.92)
1980	0.70	(0.65 – 0.75)	0.66	(0.60 – 0.72)	0.82	(0.78 – 0.86)	0.69	(0.64 – 0.74)	0.88	(0.83 – 0.92)	0.75	(0.70 – 0.81)	0.93	(0.85 – 1.02)	0.78	(0.70 – 0.87)
1990	0.58	(0.52 – 0.64)	0.54	(0.47 – 0.62)	0.60	(0.56 – 0.65)	0.57	(0.50 – 0.64)	0.67	(0.62 – 0.72)	0.64	(0.58 – 0.72)	0.67	(0.58 – 0.77)	0.64	(0.54 – 0.76)
2000	0.34	(0.24 – 0.50)	0.33	(0.20 – 0.53)	0.51	(0.40 – 0.66)	0.36	(0.24 – 0.54)	0.44	(0.34 – 0.56)	0.48	(0.32 – 0.70)	0.89	(0.55 – 1.43)	0.35	(0.20 – 0.64)

Abbreviations: CI, confidence interval; MIS, melanoma in situ; MM, invasive melanoma; RR, rate ratio.

The primary purpose of an age-period cohort analysis is to estimate the presence of the cohort effect, which is defined as variance in the incidence or mortality rates over time specific to a birth cohort. The cohort effect was considered to be a partial multiplicative interaction between age and period. Median polish was used to remove the log-additive components of age and period effects, and linear regression of residuals was modeled to quantify the relative magnitude of the cohort effect. Each cohort can be compared with the referent cohort to obtain a relative estimate of the size of the cohort effect. The generation born in 1950 was chosen as the referent because it contributed the highest adjusted male and female mortality risk, independent of age/period effects. For example, after removing the effects of age and period, males born in the 1990 cohort had an estimated 46% relative lower risk of death, 36% relative lower risk of invasive melanoma, and 36% relative lower risk of melanoma in situ compared with males born in 1950. These rate ratios should not be interpreted to signify an absolute reduction in incidence or mortality for these cohorts.