Table 1. The Australian population and melanoma incidence in selected census years

Year	Total Population, N	Susceptible Population, n	Total Invasive Melanomas, n	Melanoma ASR for Total Population	Melanoma CR for Susceptible Population
1981	14,567,330	13,969,511	Not recorded	—	—
1982	15,178,400	14,107,502	3,534	26.7	25.1
1986	15,602,155	14,663,212	4,711	32.8	32.1
1991	16,850,540	15,396,919	5,959	37.6	38.7
1996	18,224,970	16,184,782	7,824	45.1	48.3
2001	19,274,700	16,607,959	8,965	46.5	54.0
2006	20,450,970	16,988,831	10,397	48.8	61.2
2011	22,340,020	17,722,023	11,570	48.0	65.3

Abbreviations: ASR, age-standardized rate (Australian population year 2000) per 100,000; CR, crude rate per 100,000.

(2000 Australian population) for the entire population shows a recent decline in the incidence of melanoma. Data from the Australian Institute of Health and Welfare (2016) indicate that the age-standardized rate peaked in 2005. The crude rate of melanoma for the susceptible population shows a large increase with no signs of leveling out. The increase in incidence has averaged 9% per year. This is similar to the increase in the number of invasive melanomas, which has averaged 8% per year.

Discussion

When calculating the incidence of melanoma in Australia, researchers must account for the change in the racial composition of the population. Whiteman et al. (2016) dismissed the magnitude of the population change as too small to affect the incidence of melanoma. On the contrary, change in the population has been very large. In the 1981 census, 95% of the population could be considered susceptible to melanoma. In the 2011 census, only 79% could be considered at risk. The change is ongoing. In 1981, 5.6% of children born in Australia had parents at low risk for melanoma; in 2011 this had increased to 19.8% (Czarnecki, 2014). The decrease in the number of Australians susceptible to melanoma will continue; unless it is accounted for, the impression that the incidence of melanoma is decreasing in the country will continue, and the apparent decrease will be greater over time.

There has been no decrease in the incidence of melanoma in the susceptible Australian population, and the crude rate of melanoma is the highest yet reported in the world. Epidemiologists in Australia and other countries with large immigrant populations will also have to adjust their figures to give a true picture of trends in melanoma incidence.

CONFLICT OF INTEREST

The author states no conflict of interest.

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Response to Czarnecki

Journal of Investigative Dermatology (2016) **136,** 1913–1914; doi:10.1016/j.jid.2016.05.096

TO THE EDITOR

We thank Dr. Czarnecki for his interest in our recent article (Whiteman et al., 2016). He asserts that our representation of declining melanoma incidence rates in Australia conveys a misleading summary of the "true" experience because we included all Australians in our denominator instead of the population of "susceptible Australians." We do not dispute the existence of increasing numbers of low-risk people in the Australian population, and we agree that the likely effect of such bias would be to decrease the observed melanoma incidence. However, we believe that Dr. Czarnecki has overestimated the extent of such a bias because of flaws in methods and analysis. Briefly, he estimated the number of "low-risk" Australians and then used those figures to calculate the denominator population of "susceptible Australians" (Czarnecki, 2016). From these, he generated crude incidence rates for melanoma that he then compared with age-standardized rates. There are several problems with the approaches taken. First, the methods for estimating the number of low-risk Australians are not outlined in sufficient detail

Accepted manuscript published online 26 May 2016; corrected proof published online 15 July 2016

to allow independent verification. Second, comparing crude rates with age-standardized rates is invalid. This is because melanoma rates have been increasing in older people but decreasing in younger people during a period in which more Australians are surviving to old age. This means that crude melanoma rates calculated for the year 1982 relate to an entirely different population structure versus those calculated for 2011. Without properly accounting for these changes, the differences between crude and standardized rates are uninterpretable, and no valid comparisons can be made.

We considered the issue of population dilution in our article, and we referenced Dr. Czarnecki's original article positing his hypothesis (Czarnecki, 2014). We also referenced the subsequent paper by Baade et al. (2015) that elegantly disproved it. In their article, Baade et al. modeled melanoma incidence in Australia under the full range of hypothetical scenarios that might explain Australia's population growth between 1982 and 2011—that is, from being 100% attributable to migration to 0% attributable to migration. Regardless of the assumed level of migration, the decline in age-standardized melanoma incidence in Australia was apparent across all scenarios, from which the authors concluded that there is "strong evidence against the hypothesis that the observed decrease in melanoma incidence among young Australians since the mid-1990s can be explained solely by the increasing overseas migration and any resultant lowering of the 'at risk' population in Australia." We agree with their conclusion.

In summary, we agree that population dilution is of interest and may explain some of the decline in the Australian melanoma incidence rates, but we disagree with the assertion that melanoma incidence is rising in young susceptible Australians. As argued by others (Baade et al., 2015), the timing of the changes in melanoma incidence, coupled with the divergent trends among younger and older Australians, are consistent with birth cohort and period effects that are best explained by primary prevention campaigns that commenced nationally in the 1980s.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Association of Melanocortin-1 Receptor Variants with Pigmentary Traits in Humans: A Pooled Analysis from the M-Skip Project

Journal of Investigative Dermatology (2016) **136,** 1914–1917; doi:10.1016/j.jid.2016.05.099

TO THE EDITOR

Skin pigmentation is due to the accumulation of eumelanin, which is brown-black pigment and photoprotective, and pheomelanin, which is yellow-red pigment and may promote carcinogenesis (Valverde et al., 1995). The melanocortin-1 receptor (*MC1R*) gene regulates the amount and type of pigment production and is a major determinant of skin phototype (Garcia-Borron et al., 2005; Valverde et al., 1995). Binding of α-melanocyte stimulating hormone to MC1R stimulates the enzymatic activity of adenylate cyclase enzyme, thereby elevating intracellular cyclic adenosine monophosphate (cAMP) levels. *MC1R* is highly polymorphic, especially in Caucasians: more than 200 coding region variants have been described to date (Garcia-Borron et al., 2014; Gerstenblith et al., 2007; Perez Oliva et al., 2009). Six variants—D84E, R142H, R151C, I155T, R160W, and D294H—have been designated as "R" alleles because of their strong association with the "red hair color" phenotype characterized by red hair, fair skin, freckles, and sun sensitivity. The V60L, V92M, and R163Q variants are found to have a weaker association with the red hair color phenotype and have been designated as "r" alleles (Garcia-Borron et al., 2014; Raimondi et al., 2008).

Previous studies demonstrated that several alleles are associated with phenotypic characteristics and that *MC1R* variants are associated with both

Abbreviations: cAMP, cyclic adenosine monophosphate; MC1R, melanocortin-1 receptor; SOR, summary odds ratio; WT, wild-type

Accepted manuscript published online 29 May 2016