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Review

Cutaneous Melanoma: Sheep in Wolves Clothing?

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Abstract. *Cutaneous melanoma incidence in European-origin populations has risen steeply, however, mortality has not, as 73 years of Danish cancer data strikingly show. It has been suggested that such divergent trends in the US are due to overdiagnosis from increasing diagnostic scrutiny and lowering diagnostic threshold. Alternatively, the increase in melanoma incidence may be largely due to increased sun exposure, which would imply that most of these new, sun-caused, melanomas are non-lethal. Consistent with this hypothesis, Icelandic data show an increase in melanoma incidence, predominantly in young women (<50 years), which paralleled increasing sunbed use that remitted after a campaign against sunbeds. Meanwhile, melanoma mortality in young people remained virtually zero. The increase in mortality was mainly in the elderly (>50 years) and dictated by year of birth. This transient excess of melanoma in young people is most likely attributable to skin burns from sunbeds which, like sunburns, carry a high risk of melanoma. High exposure of naevi to UV radiation can induce transient clinical and pathological features of melanoma, which might explain some of the apparent rise in incidence. Ways of distinguishing non-lethal from potentially lethal thin melanomas are sorely needed.*

Global incidence of skin cancers has soared, and increase in melanoma, the most lethal kind, has especially raised alarm. To curb this increase, people have been urged to drastically reduce their sun exposure. Overdiagnosis of cutaneous melanoma, however, appears to be a big, but unacknowledged issue. This should change.

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Welch *et al*. (1) attribute a widening gap between melanoma incidence and melanoma mortality in the US from 1975 to 2016 to overdiagnosis and provide data to substantiate this position. They documented an increased scrutiny of suspicious lesions and a lowering of the threshold in diagnosing melanoma. However, they did not show that these effects could explain the extent of the widening gap. It would be implausible to attribute the long-standing increases in melanoma incidence, which date back to 1935 at least (Connecticut cancer registry data, personal communication to BK Armstrong), to these medical practices alone.

Melanoma incidence and mortality trends. The growing melanoma incidence-mortality gap is not unique to the US; it is very common in Western countries. It is also present in Danish cancer statistics going back to the 1940s (Figure 1). These statistics show that year-by-year, incidence rates for males and females ran close to corresponding mortality rates up to the mid-1950s when incidence began to increase while mortality remained low and more-or-less constant at about 1 per 10^5 person years (PY). This widening gap strongly suggests overdiagnosis.

Overdiagnosis could be increased by campaigning and heightened awareness but, at the time this trend began in Denmark and the USA and for some time afterwards, melanoma was not in the public eye and heightened awareness would therefore appear unlikely to explain these strong trends.

By 2016 the melanoma incidence in Danish males had increased by a factor of 18 and in females by 18.5, whereas mortality had increased by factors of only 3 and 2 respectively. The incidence at ages <50 y was larger in females whereas in >50 y it was slightly higher in men, resulting in an overall higher incidence in females (Figure 1). Mortality occurred mostly at ages >50 y and was persistently higher in men than women. However, for ages <50 y, mortality decreased after 1990, very much in contrast to the still increasing incidence in this age group – emphasizing the low lethality of their melanomas [data on age groups retrievable from (2)]. The other Nordic countries showed similar trends [see also (3)].

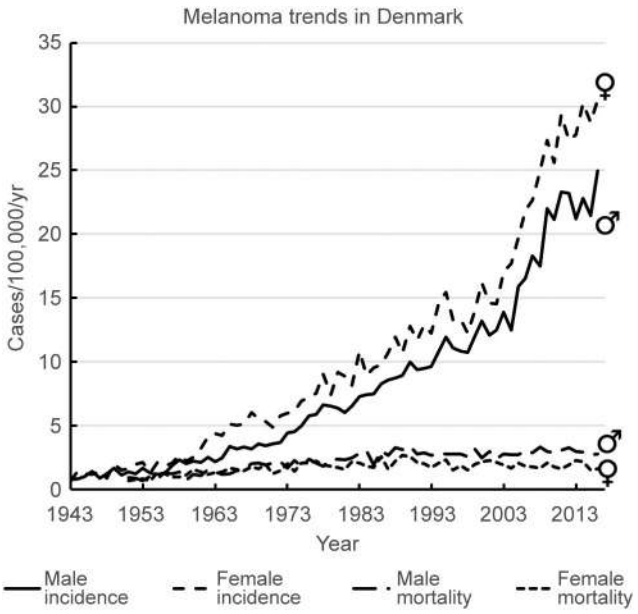

Figure 1. *Trends in cutaneous melanoma incidence (upper 2 lines) and mortality (lower 2 lines) in Danish males and females from 1943 to 2018 (ASR World). Data were obtained from (2).*

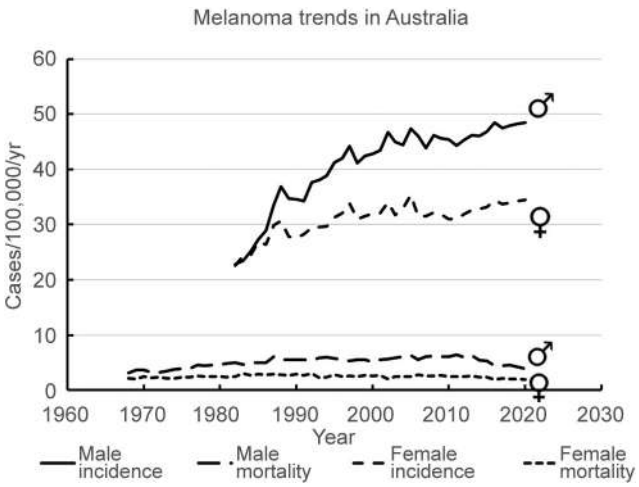

Figure 2. *Trends in cutaneous melanoma incidence (upper 2 lines) and mortality (lower 2 lines) in Australian males and females from 1968 to 2020 (rates from 2017 to 2020 are projected) (ASR World); data were obtained from (4).*

Comparisons of melanoma incidence and mortality trends in Australia since 1982 (when statistics first became available) show a similar difference between incidence and mortality [Figure 2, see also (4)], but with a consistently higher incidence in men (as in the US). Mortality showed a notable drop in males after 2014 while incidence continued to increase.

Birth cohort dominant in mortality trend. Cohort analyses of pre-1977 data showed that melanoma mortality was determined by year of birth (*i.e.*, no period effect), steadily going up from 1870 in the US, UK, Canada, Australia, and New Zealand (5). Mortality also showed a clear latitude gradient over North America, with an increase of about 1 case per million per degree going from 50 to 30˚ North (6). More recently, it was confirmed that melanoma mortality worldwide is mainly determined by year of birth, reaching a peak for birth years between 1938 and 1957 (early in Oceania, US, Northern Europe and later in Western Europe, UK, and Central Europe) (7).

Migration studies showed that moving at a young age from a temperate to a sunny climate resulted in a melanoma risk in adulthood equal to that of the population born in the new country, but there was a 3-to-4-fold lower risk if migration to Australia was after the age of 15 years (8). This observation suggests that the ambient level of solar UV exposure in childhood is particularly important in determining risk of incident melanoma in later life.

Incidence. Melanomas and their explosive growth in incidence are thought to be largely caused by sun exposure, with estimates of 86% caused by sun exposure in South Thames, England, (9) and 68-97% in USA and Australia in a range of plausible comparisons (10). That nearly all cutaneous melanomas display a UV signature in most of their gene mutations strongly supports these epidemiological inferences. Importantly, however, the lack of increases in melanoma mortality of anywhere near the same magnitude to those in incidence logically leads us to infer that these 'UV-related melanomas' are much less lethal than those diagnosed in the 1940s-1950s when mortality amounted to more than 50% of the incidence. A similar inference can be made from melanoma clinical-outcomes studies, which showed that melanoma survival appears to be greater in patients who are highly sun-sensitive, report high personal sun exposure or have signs of sun-induced skin damage (11, 12).

Following age-specific incidence in successive birth cohorts, Diffey & Frank (13) showed that age dependence flattened after birth-year 1930 in GB and the US, *i.e.,* the largest percent increases occurred in adolescence and mid age range (<50 y), but mortality dropped in these younger generations. Further data show that current incidence rates are dominated by thin stage I melanomas, which have had the highest incidence rate increases and now have the highest survival rates, *e.g.*, see (14, 15).

Peak in Icelandic incidence. Unique Icelandic melanoma incidence data add support to these inferences. Between 1992 and 2013 these data show a pronounced increase in melanoma incidence with a peak in 2001 at 25 per 10^5 PY in women and 20 in men (Figure 3A). This trend more-or-less paralleled the growth and decline in numbers of commercial sunbeds in Reykjavik (16). The Icelandic government actively campaigned against sunbed use from 2004.

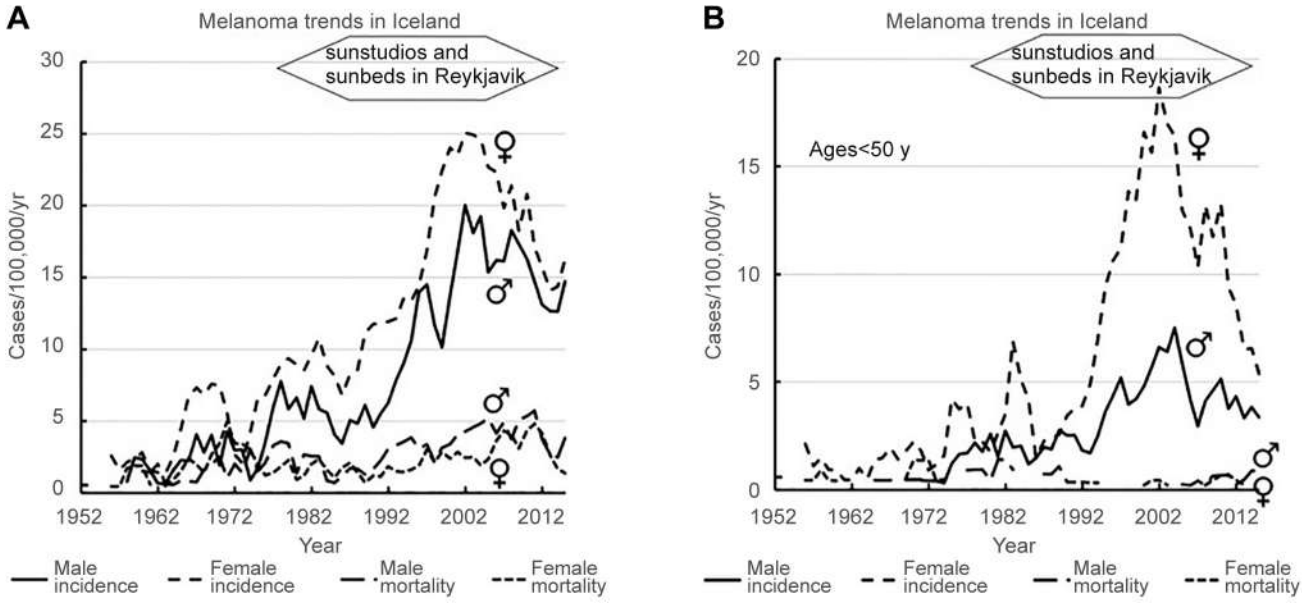

Figure 3. *Trends in cutaneous melanoma incidence (upper 2 lines) and mortality (lower 2 lines) in Icelandic males and females from 1952 to 2016 (ASR World, 3-year moving averages); A) all ages included, B) only ages <50 years. Data were obtained from (2).*

Melanoma mortality remained stable over this period (Figure 3A), and virtually zero in the age group of young women in whom this transient increase in incidence occurred (Figure 3B). The SCHEER report (17) considered this to be important evidence that sunbeds cause melanoma, but these are melanomas of an apparently non-lethal nature. What is more remarkable than the sudden rise in diagnosed melanomas is the almost immediate fall following the campaign against sun parlors and as their numbers dwindled. After discontinuation of exposure to a cancer-initiating carcinogen (mutagen) a protracted effect on incidence in the exposed population is expected, not an immediate drop.

Similarly, a skin cancer prevention campaign that also targeted sunbeds was launched in Denmark in 2007. By 2009 sunbed use was drastically reduced in the age group 15-59 y (OR of being a sunbed user in 2009 *vs*. 2007 equaled 0.6) (18). The effect on the rise in melanoma incidence again appeared to be immediate (Figure 1); more specifically, an abrupt leveling off at ages under 50 y till 2015 [see (2)].

Synthesis. A few papers suggest that diagnosis of melanoma in pigmented naevi may be increased by recent UV exposure. Tronnier *et al*. (19, 20) observed that UV irradiated naevi showed transient morphological and histological changes that could be mistaken for melanoma. The persistence of these features appeared to depend on the UV dose: changes after 4 MEDs lasted longer than after 2 MEDs (1 MED is the threshold dose for visible sunburn, *i.e*., the minimal *erythemal* dose). The effect of repeated high exposures was not assessed. In a later study, Hofmann-Wellenhof *et al*. (21) exposed naevi to 2 MED of UV radiation and examined them dermoscopically at intervals of up to 28 days. Dermoscopic changes, some of which were suggestive of cancer, were observed for up to 14 days after irradiation and darkening could still be observed after 1 year. The relatively short period after UV exposure in which these changes are manifest suggest that they can only be a partial explanation for apparent overdiagnosis of melanoma.

A more robust explanation may lie in intermittent sun exposure (exposing unacclimatised skin) carrying a risk for melanoma (22), which culminates in a higher hazard for melanoma from severe sunburns experienced throughout life: overall a relative risk (RR) of 2 (23). Intermittency is common to (commercial) sunbed use, and not explicitly studied in the large number of studies on melanoma risk in relation to sunbed use. We are aware of only 2 studies that have investigated the risk associated with 'sunbed burns' and confirmed it to confer a high risk of melanoma, RR >2 (24, 25). The case control studies were commonly limited in age range (<60 y) and therefore mainly sampled from incidences in middle aged people, who have relatively low melanoma mortality. That the Icelandic peak in incidence and the halt in the rise in incidence in Denmark immediately followed a campaign against sunbeds indicate that melanomas related to sunburns in adults may form a special category of melanomas with short induction times (<5 y) and low lethality; very different from birth cohort-related lethal melanoma mainly in the middle-aged and elderly, (ages >50 y). It is also material that most of the increase in melanoma incidence in the USA between 1973 and 2012 was in melanoma on the trunk, upper limb and shoulder in men and the lower limb and hip, upper limb and shoulder, and trunk in women (26), sites

intermittently exposed in summer because of their intermittent coverage by clothing or other sunburn protections.

The number of naevi is also a strong predictor of melanoma risk (26). Naevi develop in childhood and are related to sun exposure: level of ambient UV radiation, sun holidays, and most consistently and strongly to sunburns (27, 28). These naevi are markers of early life sun exposure and may thus carry the risk of melanoma into adulthood and underlie the sex difference in later life melanoma risk: the numbers of naevi are significantly higher in boys than girls (28).

Experiments with transgenic mice have proven that a single neonatal UV exposure can be sufficient to cause melanoma in high percentages (>50%) much later in life (29-31), reminiscent of the migration studies in humans. Melanocytes proliferate physiologically only in childhood and early youth, to populate the expanding skin (32). The cell-division underlying this proliferation is the agent that fixes mutations at sites of DNA damage and thus may form the basis for later invasive melanoma right up to the mutational step that causes it to become malignant. Melanocytes in adult skin are indolent and only transiently proliferate following trauma such as wounding or high UV exposure (32), as exemplified by UV exposure of naevi (19, 20). This was also demonstrated in mouse experiments (33) in which high UV doses (6 MEDs) fortnightly gave rise to large numbers of naevi and only a few melanomas (34). Thus, intermittent high UV doses to adult skin appear to exert a tumour-promoting effect by inducing proliferation of melanocytes that have a mutation that could lead to invasive cancer. This promoting effect is temporary and reversible, discontinuation of the intermittent exposure regimen will halt tumour development and possibly reverse it. This difference in the effects of childhood and adult sun exposures provides a biological basis for the widening gap between melanoma incidence and melanoma mortality, with incident, mostly non-lethal, melanomas at younger ages (<50 y) related to contemporary high sun exposure and lethal melanomas in the elderly (>50 y) initiated by UV exposure in their early life.

Conclusion

The observed gap between recent trends in melanoma incidence and mortality suggests there is substantial overdiagnosis of incident melanomas in fair-skinned people who have substantially increased their sun exposure in recent years. Welch *et al*. (1) clearly described the possibly grave repercussions of overdiagnosis and its accompanying overtreatment. They suggest these repercussions might be avoided by not taking a biopsy from suspect lesions "smaller in diameter ... than a pencil eraser (6 mm)". We doubt that these suggestions will settle well with dermatologists who feel responsible for their patients and will be unlikely to accept inferences from broad statistics to guide their management of suspect lesions. Nevertheless, more restraint in diagnosis and treatment (especially of stage I lesions) is called for. Ultimately, however, this 'overdiagnosis dilemma' will only be resolved by advances in histopathological diagnosis or novel molecular analyses that can distinguish between potentially lethal and non-lethal melanomas. To the best of our knowledge there is no such solution in sight.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Both Authors contributed equally to drawing up the outline of this review, data gathering and writing.

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