Re: A Prospective Study of Pigmentation, Sun Exposure, and Risk of Cutaneous Malignant Melanoma in Women

The results obtained in at least 24 case-control studies that have examined the association between indoor tanning and melanoma are largely inconclusive (1). The study by Veierød et al. (2) is important because it provides the first prospective evidence for an association between indoor tanning and melanoma and it includes data reflecting recent exposures to modern tanning devices. The authors reported on women who were aged 30–50 years when they completed questionnaires in 1991 or 1992 about their use of tanning devices during 10-year age periods, up to age 49 years. The authors presented an analysis stratified by the age periods and reported that the strongest associations between melanoma and indoor tanning were among women who reported using a tanning device when they were between the ages of 20 and 29. We would like to suggest that Veierød et al. perform an analysis in which they consider the calendar year of use of tanning devices.

For example, in the United States, indoor tanning devices that emitted greatly reduced UVB relative to UVA radiation became available around 1980 (3). These devices allowed users to have longer exposures with less burning and gave rise to the indoor tanning industry that operates today. Although UVB is thought to be more carcinogenic than UVA because the observed action spectra for direct DNA damage (erythema in humans and skin cancer in mice) are in that range, UVA exposure may also be an important factor in melanoma development (4). To date, only one case-control study has included subjects with substantial exposure to these modern tanning devices; that study (5) reported an odds ratio for melanoma of 1.8 (95% confidence interval [CI] = 1.2 to 2.7) for regular users of tanning devices. In a population survey conducted in Minnesota in 2002, we found that 10% of individuals who had tanned indoors reported doing so prior to 1980 and, even among those who were age 30 or older in 1980, the majority initiated indoor tanning after 1980 (Lazovich D, Sweeney C, Forster J; unpublished data). We suspect that a similar period effect may be operating in the study by Veierød et al. because of the low prevalence of exposure reported by women for the 10–19 and 20–29 age periods. Veierød and colleagues observed an estimated relative risk of 2.58 (95% CI = 1.48 to 4.50) associated with the use of tanning devices at least once per month relative to no use among women when they were 20–29 years old; their study population included a substantial proportion of women who attained that age prior to 1980. Thus, assuming that the availability of modern tanning devices in Sweden and Norway parallels that in the United States, an examination of the data by calendar year of use would allow readers to consider whether the estimated relative risk of 2.58 reflects exposure to higher UVB-emitting devices in the more distant past among older women or exposure to higher UVA-emitting devices more recently among younger women.

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Results of the prospective cohort study of host and environmental factors and risk of cutaneous melanoma recently reported by Veierød et al. (1) not only suggest that solarium use is a risk factor for melanoma but may also provide evidence in support of current hypotheses of melanoma etiology. On the one hand, it has been suggested that sun exposure and host susceptibility factors play different roles in the etiology of melanoma depending on the age at which an individual develops melanoma. For example, melanomas that arise in individuals younger than 50 years are preferentially localized to body sites that are the most likely to be intermittently exposed to sunlight (i.e., the trunk and legs) and are superficial spreading type, whereas melanomas that arise in individuals older than 50 years are frequently located on body surfaces that are chronically exposed to sunlight (i.e., the face and neck) and are of the lentigo maligna type, which are widely accepted as being caused by chronic sunlight exposure (2). Host susceptibility factors are likely to promote the development of melanoma at an earlier age. For example, the median age at diagnosis of invasive melanoma is 11–16 years younger for members of families prone to cutaneous malignant melanoma or dysplastic nevus syndrome than it is for sporadic melanomas (3). Furthermore, pigmentation factors (i.e., skin phototype, hair color) are more strongly associated with melanomas that arise in individuals younger than 50 years than those that arise in individuals older than 50 years (4), whereas individual susceptibility to UVB radiation is manifest only in patients younger than 40 years (5). On the other hand, it has recently been postulated that cutaneous melanomas may arise through two pathways: one pathway is associated with melanocyte proliferation and melanocytic nevi, and the other pathway is associated with chronic exposure to sunlight but not with nevi (6).
We hypothesize that individuals who had an initial exposure to UV radiation in childhood and/or adolescence and have high susceptibility to UV radiation will develop melanomas at a relatively young age and typically on the trunk following intermittent UV exposure as an adult. Such a susceptibility to UV radiation could be associated with a high nevus count. By contrast, we hypothesize that individuals without high susceptibility to UV radiation will develop melanomas only after chronic, cumulative UV exposure and, hence, at a more advanced age, on a part of the body that is chronically exposed to sunlight (i.e., head and neck), and that those melanomas will be of the lentigo maligna type and not associated with nevi.

UV exposure via solarium use is typically an intermittent exposure. Thus, it would be of interest to test the hypothesis that melanomas that develop in solarium users are more frequently associated with a higher nevus number than melanomas that develop in nonusers by analyzing the study cohort described by Veierod et al. (1), which included nearly a million person-years of a relatively young population with a complete follow-up and histopathologic confirmation of all incident melanoma cases. We further predict that melanomas in solarium users would be preferentially localized to anatomic sites that are usually intermittently exposed (i.e., the trunk).

Our hypothesis, if confirmed, would have a major public health impact because it predicts that the risk of melanoma associated with solarium use would be greatest among young populations with high individual susceptibility to UV radiation. It would therefore be important to discourage the use of a solarium or any device that emits artificial UV light by people with host susceptibility factors such as melanocytic nevi.

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RESPONSES

The proposal put forward by Boniol et al. to further investigate the role of solarium use in the development of cutaneous melanoma is interesting from an etiologic as well as a public health perspective. They hypothesize that solarium users will be more likely than nonusers to develop melanomas at habitually covered sites (such as the trunk) and will have higher nevus counts overall.

The correspondence by Boniol et al. highlights the nature and intermittency of UV exposure as a driving force underlyng the development of melanoma at anatomic sites. By contrast, we have approached this important issue from the perspective of personal susceptibility (1). Although the importance of UV exposure in the development of melanoma is well documented (2,3), the majority of Australians never develop melanoma despite considerable (and, in many cases, extraordinary) exposure to intense UV radiation, which underscores the importance of individual susceptibility. Clearly, these two views are not mutually exclusive and may ultimately be reconciled as our understanding of melanoma development unfolds.

We wish to correct an apparent misconception in the correspondence of Boniol et al., that lentigo maligna melanoma is the only type of melanoma that occurs on the head and neck in association with chronic sun exposure. We found that patients with lentigo maligna melanoma and patients with head and neck melanomas other than lentigo maligna melanoma have very similar risk factor associations (1). Given that approximately 50% of head and neck melanomas are histologic types other than lentigo maligna melanoma (4), it is important to recognize that they are likely to share a similar causal pathway.

We endorse the suggestion of Boniol et al. that further analyses of the Norwegian–Swedish Women’s Lifestyle and Health Cohort Study (5) should be conducted, even though that large, well-conducted prospective study has the following limitations. First, the cohort is quite young and follow-up is short, and thus the full melanoma burden of the cohort is yet to be realized. This limitation is particularly important with respect to the anatomic distribution of melanomas in the cohort, as we predict that women with low nevus propensity (putative “UV-resistant” women) will have had insufficient exposure time to develop melanoma at routinely exposed sites. Second, the cohort is restricted to women, for whom patterns of dress, sun exposure, and the anatomic distribution of melanomas differ substantially from those of men. Finally, in that study, nevus counts were self-reported, and only asymmetrical nevi larger than 5 mm on the legs were counted. If theories about the genesis and evolution of large nevi through components of UV radiation hold true (6), such a selective measure of nevus burden will be biased toward identifying women with particular sun exposure histories. Despite these limitations, we support the approach suggested by Boniol et al. for stratified analyses according to the nevus counts of study participants, and we agree with them that the findings would be of considerable interest to melanoma researchers and public health policy makers.

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We are also grateful for the constructive comments and suggestions from Lazovich et al. in Norway and Sweden (as in the United States), tanning devices that used fluorescent tube lamps with high levels of UVA relative to the levels of UVB were introduced in the late 1970s, and commercial tanning salons became common around 1980 (Saxebøl G, Wester U: personal communications). However, the sale of medium-pressure mercury lamps (i.e., lamps with high levels of UVB relative to UVA) for tanning purposes was banned in 1983 in Norway and Sweden (Saxebøl G, Wester U: personal communications). Thus, as suggested by Lazovich et al., we evaluated whether women who used solaria before 1983 had a higher risk of melanoma than women who used solaria after 1983, after adjusting for age and other variables.

To determine solarium use before and after 1983, we considered how solarium exposure was recorded in the Norwegian-Swedish Women’s Lifestyle and Health Cohort Study. Women born between 1943 and 1962 were recruited to our study in 1991 and 1992 and asked to report their frequencies of solarium use when they were 10–19, 20–29, 30–39, and 40–49 years old. We thus focused our analysis on the women who reported solarium use (≥1 time/month) when they were 20–29 years of age, because solarium use was rare among women when they were 10–19 years old and because only 12% of the women were 30–39 years old in or before 1983 and very few of them reported solarium exposure one or more times per month.

We previously reported that the estimated relative risk (RR) of cutaneous malignant melanoma associated with the use of a solarium one or more times per month relative to no use at age 20–29 was 2.58 (95% confidence interval [CI] = 1.48 to 4.50) (1).

Women who were 29 years old before or during 1983 were 20–29 years old from 1963 through 1983 (i.e., before a ban on the sale of tanning lamps with high levels of UVB relative to UVA), whereas women who were 29 years old after 1983 were 20–29 years old from 1975 through 1991. Thus, none of the women in the cohort lived the whole 20–29 age decade after 1983. After close inspection of the relationship between age and calendar year, we constructed a variable for calendar year of exposure comprising three categories: women aged 29 before or during 1983 (i.e., women exposed from 1963 through 1983), women aged 29 after 1983 and aged 25 before or during 1983 (i.e., women exposed from 1975 through 1987), and women aged 25 after 1983 (i.e., women exposed from 1979 through 1991). Lazovich et al. reported that only 10% of individuals who had tanned indoors were doing so prior to 1980. Among women in our study who used a solarium one or more times per month at age 20–29, only 18% had all of their exposure before or in 1983.

We also constructed a new exposure variable by combining solarium use at age 20–29 and the variable for calendar year of exposure (Table 1). For solarium use, we included only the categories ‘Never’ and ‘≥1 time/month’ (i.e., women who reported that they rarely used a solarium were excluded). We found that women who used a solarium one or more times per

### Table 1. Relative risks (RRs) and 95% confidence intervals (CIs) of cutaneous malignant melanoma according to solarium use at age 20–29 and calendar years lived in that age group, n = 77 524*

<table>
<thead>
<tr>
<th>Solarium use at age 20–29</th>
<th>Calendar years during which women were 20–29 years old</th>
<th>No. of women (%)</th>
<th>No. of cases</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never (referent)</td>
<td></td>
<td>71 133 (91.8)</td>
<td>123</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>≥1 time/mo</td>
<td></td>
<td>2795 (3.6)</td>
<td>7</td>
<td>2.81 (1.11 to 7.13)</td>
<td>3.19 (1.22 to 8.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2464 (3.2)</td>
<td>4</td>
<td>1.19 (0.43 to 3.31)</td>
<td>1.28 (0.46 to 3.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1132 (1.5)</td>
<td>7</td>
<td>3.43 (1.60 to 7.39)</td>
<td>3.75 (1.73 to 8.13)</td>
</tr>
</tbody>
</table>

*Poisson regression analysis.
†Multivariable model included attained age, region of residence, hair color, number of sunburns at age 20–29, and number of sunbathing vacations at age 20–29.
month at ages 20–29 years before 1983 had a statistically significantly higher risk of melanoma than women who had never used a solarium at ages 20–29 years (RR = 3.75, 95% CI = 1.73 to 8.13). However, we also found that women who used a solarium one or more times per month at ages 20–29 years mainly after 1983 (i.e., from 1979 through 1991) had a statistically significantly higher risk of melanoma than women who had never used a solarium at ages 20–29 (RR = 3.19, 95% CI = 1.22 to 8.32) (Table 1). However, because there were so few cases in each of these categories, firm conclusions cannot be made until we have a larger number of incident cases.

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