Geographic Variation and Risk of Skin Cancer in US Women

Differences Between Melanoma, Squamous Cell Carcinoma, and Basal Cell Carcinoma

Abrar A. Qureshi, MD, MPH; Francine Laden, ScD; Graham A. Colditz, MD, DrPH; David J. Hunter, MBBS, DrPH

Background: Occurrences of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) have been associated with varying geography. Our goal was to evaluate differences in risk of these skin cancers according to residence at varying UV indices at 3 time points.

Methods: Prospective 1984-2002 study of 84,836 female nurses who lived in different UV index regions of the United States at birth and at 15 or 30 years of age. The outcome measure was diagnosis of melanoma, SCC, or BCC.

Results: During the 18-year study, 420 cases of melanoma, 863 cases of SCC, and 8215 cases of BCC occurred. At 30 years of age, age-adjusted risks for SCC were 1.47 (95% confidence interval [CI], 1.22-1.76) and 1.90 (95% CI, 1.51-2.36) for women residing in states with a UV index of 6 (medium) and 7 or more (high), respectively. Although elevated, the age-adjusted risk of BCC at 30 years of age associated with residence in these states was substantially less. Although the risk of melanoma was not elevated for women living in these states at 30 years of age, it was significantly elevated among women living in states with UV indices of 6 at birth and at 15 years of age. There was no material change in risk estimates with multivariate adjustment. For women who reported living in states with UV indices of 7 or more at all 3 time points, the multivariate risk of SCC was highest.

Conclusions: The risk of SCC is independently affected by residence in locations with medium and high UV indices; the gradient of risk is weaker for BCC; and the risk of melanoma does not change significantly across this gradient.

Arch Intern Med. 2008;168(5):501-507

Geographic Location and UV radiation have been implicated as risk-modifying factors for melanoma, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), \(^1\) breast, \(^2\) and colon \(^3\) cancers. That is, UV radiation has been shown to have a beneficial effect postulated via vitamin D for some cancers, with an increasing risk of cancer seen among individuals residing further away from the equator. \(^4\) Sustained sun exposure for long periods results in a higher risk of SCC than of BCC. \(^5\) The incidence of BCC is higher than that of SCC in regions with less sunny climates and intermittent sun exposure (BCC:SCC ratio, 3:1 to 10:1), and SCC incidence increases with migration to sunny regions, resulting in reduction of the BCC:SCC ratio. Unlike SCC and BCC, melanoma does not occur preferentially on exposed body sites, \(^6\) and a history of melanoma in at least 1 first-degree relative is an independent risk factor. \(^7\) Although a north-south gradient for melanoma risk in the United States was seen until the 1960s, the gradient has become attenuated in more recent years, with north-south incidence rates becoming more uniform. \(^8\) The latitude gradient for melanoma
has also been shown to be age dependent, with a slightly higher incidence of melanoma in younger individuals living in regions with a low UV index. In Australia, a decrease in latitude was shown to be associated with an increase in melanoma incidence in 3 states. Similar trends have been found in the United States in some studies for light-skinned but not dark-skinned populations. Hence, there is evidence from case-control studies both for and against the association between geography and melanoma risk.

The United States is the ideal model to study the effect of geography on the risk of skin cancer because of the variation in UV indices between the northern and southern states. Estimated UV radiation exposure as a risk factor for skin cancer has been evaluated by measuring UV levels recorded by Robertson-Berger meters placed at 30 locations across the United States. A criticism of this approach has been the uncertainty of the measurements because these are estimates of real values of UV irradiation measured at specific locations and then modeled with latitude, altitude, and cloud cover. Additional criticisms of the Robertson-Berger meter are that its spectral response curve includes a significant amount of UV-A, which plays no role in vitamin D production, and that the meter is temperature sensitive. Individual sun exposure such as “time spent outdoors” has been even more difficult to measure and less reliable; this measure of sun exposure has been used in case-control studies and is subject to substantial recall bias. At least 1 previous study has shown that UV exposure based on residential history was associated with an increased risk of melanoma compared with time spent outdoors, and another study showed that less sun exposure was a risk factor for melanoma.

Data with long-term follow-up on all 3 types of skin cancer are difficult to obtain for the same group of individuals in the United States. Data on melanoma are collected via the Surveillance Epidemiology and End Results (SEER) database, but no national registries track SCC and BCC. From previous studies, it is not yet clear whether melanoma risk is affected by a north-south UV index gradient compared with SCC and BCC risks in a population at risk of all 3 skin cancers simultaneously. To evaluate the effect of residence at locations of varying UV indices independent of individual behavior, we evaluated risk of melanoma, SCC, and BCC in the same cohort of US women. We hypothesized that SCC and BCC risks would be related to a north-south UV index gradient, and we asked whether risk of melanoma would change significantly with this gradient.

METHODS

STUDY POPULATION

The Nurses’ Health Study (NHS) is an ongoing prospective cohort study that was established in 1976, when 121 700 female registered nurses completed a mailed questionnaire that included items about risk factors for breast cancer and other diseases. At enrollment, study participants were aged 30 to 55 years and resided in the following 11 states: California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas. These states were originally chosen for their size and approval of the study by the respective nursing associations. Since the cohort inception, participants now reside in every US state. The cohort is representative of geographically diverse working women in the United States and has a high follow-up rate. No restrictions were made on the basis of ethnicity or race; however, the participants were 97% white, reflecting the ethnic background of women trained as registered nurses in 1976. They have been followed up since 1984 for skin cancer outcomes and risk factors for skin cancer, eg, natural hair color at 20 years of age, ability to tan, and susceptibility to burn. Residential address changes have also been recorded with every 2-year cycle. Appropriate institutional human studies research approval was obtained at the Brigham and Women’s Hospital.

CASE ASCERTAINMENT

Skin cancer confirmation is performed routinely. For all 3 skin cancers, participants report new cases with each 2-year cycle. Permission is obtained from participants to acquire medical records if SCC or melanoma is reported; these records are reviewed by study physicians. Participants with SCC in situ, actinic keratoses, SCC of the oral mucosa or genitalia, melanoma in situ, and dysplastic nevi have been excluded from this analysis. Participants who self-reported SCC or melanoma before 1976 at the inception of the NHS cohort have also been excluded. Medical records are not obtained for self-report of BCC. For BCC, Colditz et al performed a validation study in 1986 and demonstrated that self-reports of BCC were more than 90% confirmed by histopathological findings. Similar high validity of the self-reports of BCC were documented again.

ASSESSMENT OF GEOGRAPHIC LOCATION

Questionnaires are mailed to each participant in June of each even-numbered year. For each cycle, follow-up is more than 90% on average, and only 4% of the nurses have been nonresponders to 3 consecutive questionnaires since 1986. In 1992, we asked about location of residence (US state) at birth and at 15 and 30 years of age.

The erythemal UV index (referred to as the UV index) is a method to estimate UV radiation reaching the earth’s surface, which is important for effects on human skin on a noncloudy day. When the sun is highest in the sky, UV irradiance is weighted by the action spectrum for erythema (redness) of white skin. Based on the mean UV index in North America for the month of August (by the National Oceanic and Atmospheric Administration), the 50 states (and the District of Columbia) were divided into the following 3 UV index groups: 5 or less (low UV index: Alaska, Maine, Michigan, Minnesota, New Hampshire, Oregon, Pennsylvania, Vermont, Washington, and Wisconsin); 6 (medium UV index: Connecticut, Delaware, Illinois, Indiana, Iowa, Maryland, Massachusetts, Missouri, Nebraska, New Jersey, New York, North Dakota, Ohio, Rhode Island, South Dakota, and West Virginia); and 7 or more (high UV index: Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Montana, Mississippi, Nevada, New Mexico, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Utah, Virginia, Washington, DC, and Wyoming). This grouping for northern, middle, and southern states remains the same for other months throughout the year.

STATISTICAL ANALYSIS

The cohort was restricted to women who answered all 3 questions on lifetime residence on the 1992 questionnaire and had
not been diagnosed as having melanoma, SCC, or BCC before 1984. Participants contributed person-time from the date of return of the 1984 questionnaire. Accumulation of follow-up time ceased at the first report of BCC, the first report followed by confirmation of SCC, the first report followed by confirmation of melanoma, death, or the return of the 2002 questionnaire, whichever came earliest. Women with a history of other cancers were excluded. Each participant’s risk factor status was updated every 2 years on the basis of answers to the follow-up questionnaire. Cox proportional hazards models were run for univariate analyses, and age-adjusted rate ratios were calculated with 95% confidence intervals (CIs). For multivariate models, covariates relevant to skin cancer risk were included in the models, specifically hair color at 20 years of age, ability to tan, and susceptibility to burn. We chose women living in states with a low UV index (UV index, \( \leq 5 \)) as the reference group. To evaluate the skin cancer risk of women who lived at the same location at all 3 time points, we restricted the analysis to women who reported living in the same state at birth and at 15 and 30 years of age.

### RESULTS

#### COHORT CHARACTERISTICS

We found no substantial association between UV indices of the state where participants lived at birth and at 15 and 30 years of age and the ability to tan, the susceptibility to burn, hair color, or the number of moles on the left upper extremity (Table 1). The proportion of women with red or blonde natural hair color at 20 years of age was slightly higher (15%) for states with a UV index of 7 or more than for those with UV indices of 5 or less and 6 (13%). From 1984 to 2002, 420 melanoma cases and 863 SCC cases were confirmed and 8215 BCC cases were self-reported among 84 836 women (Table 2), with approximately 4 million person-years of total follow-up time. Mean age for diagnosis of melanoma (59 years) was less than that for SCC (62 years) or BCC (64 years). There were modest differences among women in each tumor group reporting susceptibility to burn, ability to tan, red or blonde natural hair color at 20 years of age, and 6 or more moles on the left upper extremity (Table 2).

#### RISK OF SKIN CANCER ASSOCIATED WITH AGE AND UV INDEX OF RESIDENCE

RISK OF SKIN CANCER ASSOCIATED WITH AGE AND UV INDEX OF RESIDENCE

Risk of skin cancer associated with residence in states with a UV index of 6 and 7 or more compared with residence in states with a UV index of 5 or less at 3 time points are presented in Table 3. There was no association of melanoma risk with residence in a state with a UV index of 7 or more at birth or at 15 or 30 years of age. Although the risk of melanoma was significantly elevated among women living in states with a UV index of 6 at birth \((1.28 [95\% CI, 1.03-1.06])\) and 15 years of age \((1.32 [95\% CI, 1.05-1.65])\), this became nonsignificant at 30 years of age when adjusting for phenotypic risk factors.

On the other hand, for all 3 age groups, the risks of SCC and BCC were significantly higher for women living in states with a UV index of 6 and 7 or more compared with residence in states with a UV index of 5 or less.
with UV indices of 6 and 7 or more than for women living in states with a UV index of 5 or less, and results of the tests for trend were statistically significant. A trend of increasing risk of SCC was noted for women living in medium (UV index, 6) vs high (UV index, ≥7) UV index locations at all 3 time points (eg, at 30 years of age, for a UV index of 6, 1.47 [95% CI, 1.22-1.76] and, for a UV index of ≥7, 1.90 [95% CI, 1.51-2.36]). A similar gradient was noted with increased risk of BCC when going from medium to high UV index states (eg, at 30 years of age, for a UV index of 6, 1.19 [95% CI, 1.13-1.26] and, for a UV index of ≥7, 1.33 [95% CI, 1.23-1.42]). Multivariate analyses adjusting for natural hair color at 20 years of age, ability to tan, susceptibility to burn, and mole counts on the left upper extremity did not result in any substantial change compared with the age-adjusted estimates (Table 3).

Finally, in models restricted to women who had lived in the same location at all 3 ages to estimate lifetime exposure, the age-adjusted risk of SCC increased from 1.61 (95% CI, 1.31-1.99) to 2.05 (95% CI, 1.54-2.73) in states with UV indices of 6 and 7 or more, respectively (Table 4). The risk of BCC was similar (1.24 [95% CI, 1.17-1.32] and 1.30 [95% CI, 1.18-1.43], respectively) with the same change in UV index. There was no association of UV index with melanoma.

### Table 3. Age-Adjusted and Multivariate Analyses for Melanoma, SCC, and BCC

<table>
<thead>
<tr>
<th>UV index of state where born</th>
<th>Melanoma</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5</td>
<td>115 [Reference]</td>
<td>1 [Reference]</td>
<td>111 [Reference]</td>
</tr>
<tr>
<td>6</td>
<td>247 [1.03-1.60]</td>
<td>1.29 [1.04-1.61]</td>
<td>248 [1.05-1.65]</td>
</tr>
<tr>
<td>≥ 7</td>
<td>42 [0.75-1.52]</td>
<td>1.09 [0.76-1.55]</td>
<td>45 [0.84-1.67]</td>
</tr>
</tbody>
</table>

### Table 4. Age-Adjusted and Multivariate Analyses Restricted to Women Who Reported the Same Location for Birth and Residence at Ages 15 and 30 Years

<table>
<thead>
<tr>
<th>UV Index</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>1.11 (0.72-1.71)</td>
</tr>
<tr>
<td>SCC</td>
<td>1.61 (1.31-1.98)</td>
</tr>
<tr>
<td>BCC</td>
<td>2.05 (1.54-2.73)</td>
</tr>
</tbody>
</table>

**COMMENT**

This prospective study of US women has demonstrated significant geographic variation in incidence rates for SCC and BCC (as previously reported) but not as remarkably for melanoma. The population under investigation was similarly at risk of all 3 skin cancers with respect to sun exposure, sun protection behavior, and occupation. All estimates presented herein were simultaneously adjusted for phenotypic risk factors such as natural hair color, susceptibility to burn, ability to tan, and number of moles on the left upper extremity. The major difference in our study was that melanoma risk was not as dependent as SCC or BCC risk was on residence in locations with a higher UV index (ie, southern states).46
Some previous studies have reported an increased risk of melanoma,47,48 whereas other studies have demonstrated a reduced risk of melanoma with decreasing latitude.49-51 These effects may be region specific; for example, the increased risk with latitude has been well documented in Europe.52 This does not imply that melanoma occurrence is unrelated to sun or UV exposure53,54 because we found increased relative risks that were not statistically significant with residence in locations with a higher UV index. Darker skin pigmentation is a protective factor for melanoma.55,56 Other risk factors, such as intermittent and intense UV exposure as would occur in travel to sunny vacations in the middle of a long winter57,58 or genetic susceptibility, may play a more important role in the pathogenesis of melanoma than that of SCC and BCC, or chronic sun exposure may result in a tan that may be protective for melanoma specifically. A north-south gradient has been shown to have a greater effect on melanoma risk in men compared with women, and this may also explain our results.2,59 In our study, melanoma risk was significantly elevated for women residing in states with medium UV indices at younger ages and became nonsignificant for residence in states with a higher UV index. Darker skin pigmentation was not statistically significant with residence in locations with a higher UV index. The UV index across the United States varies seasonally and, although we chose a particular month (August) to divide the country into low, medium, and high UV index regions, similar UV index trends were noted in other months of the year and did not affect how the United States was divided into northern, middle, and southern states. The reason to use UV indices to divide the United States into 3 regions was that the UV index provides more information about ambient UV radiation than simply latitude of residence. Data were available on state of residence at 3 time points early in life, but we have no information about residence for the 15 years between the time points. However, migration between the UV exposure categories was modest, and our analysis of risk of the 3 skin cancers among women who lived at the same location at all 3 time points demonstrates that the overall trends were the same.44

A major strength of this study was our ability to simultaneously evaluate the risks of melanoma, SCC, and BCC in the same population. The NHS is a cohort study of a defined population of women with high rates of follow-up. The crude incidence rates for melanoma based on the information presented in Table 2 are higher in the NHS compared with the SEER database. We think this has to do with close follow-up and case confirmation for melanoma. However, the NHS population consists only of women, whereas the SEER database tracks men and women, and the areas of the country sampled by the SEER database are somewhat different than the distribution of women in the NHS across the United States. The relatively homogeneous nature of our cohort with regard to education, health awareness, socioeconomic status, and good health care coverage reduces the variation in sun exposure related to occupational or behavioral exposure. Hence, our study evaluated the effect of incidental and recreational exposure as opposed to previous ecologic studies that may have been influenced by differences in occupational exposure in states with different climatic conditions. However, it is also possible that unaccounted variation in recreational and habitual sun exposure may have altered risk specifically for melanoma in this homogeneous population of US women. We were also able to control for individual differences in phenotype such as hair color and susceptibility to burn, which would confound ecologic analyses if these phenotypes varied among states of residence. Diagnosis of melanoma and SCC was confirmed by medical record review, eliminating concern for misclassification of cases. We restricted this analysis to participants with incident primary skin cancers and no history of other cancer to avoid bias resulting from earlier diagnosis of skin cancer due to increased awareness and vigilance among those women. Diagnosis of BCC was by self-report only and may account for a higher BCC:SCC ratio in this study. We previously documented that BCC self-reports are highly valid in this medically sophisticated population.55,56

We did not measure sun exposure directly and used state of residence as an indirect indicator of sun exposure. However, the NHS is a cohort study of a defined population of women with high rates of follow-up. The crude incidence rates for melanoma based on the information presented in Table 2 are higher in the NHS compared with the SEER database. We think this has to do with close follow-up and case confirmation for melanoma. However, the NHS population consists only of women, whereas the SEER database tracks men and women, and the areas of the country sampled by the SEER database are somewhat different than the distribution of women in the NHS across the United States. The relatively homogeneous nature of our cohort with regard to education, health awareness, socioeconomic status, and good health care coverage reduces the variation in sun exposure related to occupational or behavioral exposure. Hence, our study evaluated the effect of incidental and recreational exposure as opposed to previous ecologic studies that may have been influenced by differences in occupational exposure in states with different climatic conditions. However, it is also possible that unaccounted variation in recreational and habitual sun exposure may have altered risk specifically for melanoma in this homogeneous population of US women. We were also able to control for individual differences in phenotype such as hair color and susceptibility to burn, which would confound ecologic analyses if these phenotypes varied among states of residence. Diagnosis of melanoma and SCC was confirmed by medical record review, eliminating concern for misclassification of cases. We restricted this analysis to participants with incident primary skin cancers and no history of other cancer to avoid bias resulting from earlier diagnosis of skin cancer due to increased awareness and vigilance among those women. Diagnosis of BCC was by self-report only and may account for a higher BCC:SCC ratio in this study. We previously documented that BCC self-reports are highly valid in this medically sophisticated population.55,56

We did not measure sun exposure directly and used state of residence as an indirect indicator of sun exposure. The UV index across the United States varies seasonally and, although we chose a particular month (August) to divide the country into low, medium, and high UV index regions, similar UV index trends were noted in other months of the year and did not affect how the United States was divided into northern, middle, and southern states. The reason to use UV indices to divide the United States into 3 regions was that the UV index provides more information about ambient UV radiation than simply latitude of residence. Data were available on state of residence at 3 time points early in life, but we have no information about residence for the 15 years between the time points. However, migration between the UV exposure categories was modest, and our analysis of risk of the 3 skin cancers among women who lived at the same location at all 3 time points demonstrates that the overall trends were the same.

### CONCLUSIONS

In this study, we found that risk of SCC was associated with a north-south UV index gradient and increasing age (as previous studies have reported). Similar trends were seen for BCC, although they were less pronounced. In contrast to SCC and BCC risks, we found that melanoma risk was not significantly associated with the same UV index gradient. These trends remained unchanged after adjusting for phenotypic risk factors such as hair color, ability to tan, number of moles on the left upper extremity, and susceptibility to burn. In this study, we evaluated a population at similar risk of all 3 skin cancers as related to sun exposure–related behavior, yet found differences in risk associated with residence in different geographic areas. More work is needed to better understand the mechanisms behind the observations in this study. Until then we must continue to investigate the role that UV plays in the pathophysiological mechanisms of melanoma vs SCC and BCC. With substantial evidence in the literature of the protective role played by vitamin D in cancer prevention, those recommending sun protection behaviors should also promote vitamin D supplementation.


