Risk Factors for Melanoma by Body Site for Whites

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Abstract

It has been hypothesized that cutaneous melanoma at different anatomic sites develops through divergent pathways. We examined this hypothesis prospectively. We followed 152,949 women and 25,204 men free of cancer at baseline from up to 14 years in three large prospective studies. We examined risk factors for melanoma by anatomic location (head or neck, trunk, upper extremity, and lower extremity). Polytomous logistic regression was used to test the difference among risk factors by location of melanoma. A total of 511 incident cases of invasive melanoma (49 head or neck, 188 trunk, 98 upper extremity, and 176 lower extremity) were included in the analysis. Compared with females, males had a higher risk of developing melanoma on the head or neck and trunk. History of severe and painful sunburn was most strongly related to melanoma of upper extremity; individuals with >10 burns had a 6.86-fold (95% confidence interval, 2.62-18.00) higher risk of melanoma of upper extremity compared with those with no burns (P for trend < 0.0001; P for difference by body site = 0.04). Number of moles was most strongly related to melanoma of the trunk; the multivariate relative risk for having >10 moles was 4.67 (95% confidence interval, 3.07-7.11) compared with having no moles (P for trend < 0.0001; P for difference by body site = 0.04). Age, family history of melanoma, and hair color did not statistically differ by anatomic site of the cancer. These data support divergent etiologic pathways of melanoma development by anatomic sites. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1241–4)

Introduction

Incidence of cutaneous malignant melanoma has been increasing in the United States (1). However, the etiology of melanoma has not been fully understood, except that sun exposure is a risk factor. It has been hypothesized that melanoma develops through multiple etiologic pathways. Previous studies have found that traditional melanoma risk factors have different associations with melanoma by body sites (2). However, there has been no prospective study to examine this hypothesis.

We have reported that higher age, male sex, family history of melanoma, higher number of nevi, history of severe sunburn, and light hair color were each associated with elevated risk of melanoma using data from three large cohort studies of women and men (3). Using the same data set, we examined these risk factors for melanoma by location of cancer. Although we have previously examined self-reported mole counts and melanoma by site in one of the cohorts, that analysis included cases from only the first 8 years of follow-up (head or neck, trunk, upper extremity, and lower extremity). Polytomous logistic regression was used to test the difference among risk factors by location of melanoma. A total of 511 incident cases of invasive melanoma (49 head or neck, 188 trunk, 98 upper extremity, and 176 lower extremity) were included in the analysis. Compared with females, males had a higher risk of developing melanoma on the head or neck and trunk. History of severe and painful sunburn was most strongly related to melanoma of upper extremity; individuals with >10 burns had a 6.86-fold (95% confidence interval, 2.62-18.00) higher risk of melanoma of upper extremity compared with those with no burns (P for trend < 0.0001; P for difference by body site = 0.04). Number of moles was most strongly related to melanoma of the trunk; the multivariate relative risk for having >10 moles was 4.67 (95% confidence interval, 3.07-7.11) compared with having no moles (P for trend < 0.0001; P for difference by body site = 0.04). Age, family history of melanoma, and hair color did not statistically differ by anatomic site of the cancer. These data support divergent etiologic pathways of melanoma development by anatomic sites. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1241-4)

Materials and Methods

Study Population. The Nurses’ Health Study (NHS) enrolled 121,700 female registered nurses ages 30 to 55 years in 1976. NHS II enrolled 116,671 female registered nurses ages 25 to 42 years in 1989. The Health Professionals Follow-up Study (HPFS) included 51,529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) ages 40 to 75 years in 1986. These participants responded to a questionnaire about their medical histories and lifestyles. We have sent follow-up questionnaires to the cohorts biennially to collect and update information regarding individual characteristics, behaviors, and diagnosed diseases. Deaths were reported by family members or by the postal service in response to the follow-up questionnaire or through the National Death Index for nonresponders (5).

To conduct a completely prospective analysis, we used 1986 as a baseline for the NHS and 1992 for the HPFS because the information on several risk factors for melanoma was collected in these years. Participants who reported diagnosis of cancer other than nonmelanoma skin cancer were excluded at baseline and censored at time of diagnosis during follow-up. Cases of melanoma in situ were also excluded at baseline and during follow-up. Because most of the participants were Caucasians and melanoma is rare in other races, we excluded other races. We included only those who answered questions on traditional melanoma risk factors, including age, family history of melanoma, number of nevi (moles), hair color, and history of severe sunburn. A total of 178,153 participants (62,755 in the NHS, 90,194 in the NHS II, and 25,204 in the HPFS) were included in the analysis.

The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women’s Hospital.

Assessment of Melanoma Risk Factors. Each cohort collected information on age, family history of melanoma, number of acquired melanocytic nevi on arms (legs in the NHS II) larger than 3 mm in diameter (as a proxy for the total body nevi count), natural hair color, and history of severe sunburn.

Melanoma Case Confirmation. Within the study populations over the periods of follow-up for these analyses, 536 NHS, 414 NHS II, and 282 HPFS members reported a diagnosis of melanoma. Medical records were obtained for 451 of the NHS, 311 of the NHS II, and 203 of the HPFS and reviewed by a dermatologist. We excluded in situ melanomas (171 NHS, 103 NHS II, and 82 HPFS). Information on anatomic location of
melanoma was collected in most of the cases. Our analyses included only melanoma on the head or neck, trunk, upper extremity, and lower extremity and excluded a few cases with melanoma at other sites or at unknown sites. A total of 511 confirmed cases of invasive melanoma (237 NHS, 188 NHS II, and 86 HPFS), which included superficial spreading and nodular types, were included in the analyses. Cases with lentigo maligna melanoma were not included in the analyses.

**Statistical Analysis.** We examined age, family history of melanoma, number of moles on arms or legs, natural hair color, and history of severe sunburn because these were predictors of melanoma in our previous analyses (3). We calculated incidence rates of melanoma for each site according to categories of the risk factors. Baseline information was used for all of the potential risk factors except age, which we updated in each questionnaire cycle. Participants contributed person-time from the date of return of the baseline questionnaire until a confirmed diagnosis of melanoma (invasive or in situ), a report of another cancer other than nonmelanoma skin cancer, date of death, or date of end of follow-up (June 1, 2000, for NHS; June 1, 1999, for NHS II; and January 1, 2000, for HPFS), whichever came first. Relative risk was calculated as the rate for a given category compared with the reference category. Pooled logistic regression (6) was used to adjust for age and other risk factors simultaneously. Because the duration of follow-up was different across the cohorts, we chose this method to make the three studies comparable. It has been shown that pooled logistic regression is asymptotically equivalent to the Cox proportional hazard regression with time-varying covariates (6). The necessary conditions for this equivalence include relatively short time intervals and small probability of the outcome in the intervals, both of which are satisfied here (7). Tests for trend for variables with >2 categories (history of sunburn, number of moles, and hair color) were conducted by assigning a number to each category (e.g., 1, 2, 3, 4, or 5) and treating the number as a continuous variable.

To test for differences in associations among four anatomic locations of melanoma, we used polytomous logistic regression (8). In particular, we used a custom software program described by Marshall and Chisholm (9) that includes a formal test of the differences in magnitude of the \( \beta \) estimate of each risk factor for the separate components of a composite end point. This program allows the user to specify which variables are modeled with a common \( \beta \) estimate for all outcomes and which are modeled with four distinct \( \beta \)s. Because modeling different outcomes is extremely computationally intensive and to simplify the interpretation of the estimates, we used different expressions of each variable for the polytomous logistic regression compared with those used in the pooled logistic regression models for some of the risk factors. We modeled age as a continuous variable and family history and sex as dichotomous variables in both analyses. For other variables, we used an ordinal variable that was used for analysis for test for trend as described above. We compared a model that allowed all of the risk estimates for each exposure variable to vary between the outcomes with a model constraining a risk factor of interest to be uniform across the end points while allowing all the others to vary. We used likelihood ratio tests for the two models to get the \( P \) value for difference by site for the risk factor obtained by comparing the difference in -2 log likelihood from the respective models with a \( \chi^2 \) distribution with 5 degrees of freedom. We repeated this procedure with each risk factor.

**Results**

We documented 511 incident melanoma cases (237 NHS, 188 NHS II, and 86 HPFS) during up to 14 years of follow-up of women and men in the three cohorts (Table 1). Melanoma on upper extremity included cancers on arm and elbow. Melanoma on lower extremity included cancers on thigh, buttock, leg, and ankle. The mean age of the participants was 50 (SD = 12) during follow-up. The mean age of melanoma cases at diagnosis was 53 (SD = 12).

Table 1 presents traditional risk factors for melanoma in relation to site of melanoma. The \( P \) values, test for difference by site, were significant for sex, history of sunburn, and number of moles. Compared with women, men had a higher risk of having melanoma on the head or neck and the trunk. Although the tests for difference were not statistically significant, age was related to an increased risk of melanoma for the head or neck and the trunk but not for upper or lower extremities. Family history of melanoma was related to at least 2-fold increased risk of melanoma for all body sites (except melanoma on upper extremity) although some of the relative risks were not statistically significant. On the other hand, history of severe and painful sunburn was most strongly related to melanoma of upper extremity. The multivariate relative risks for increasing number of burns (no, 1-2, 3-5, 6-9 and 10+ burns) were 1.00 (reference), 2.88, 3.68, 6.40, and 6.86, respectively (\( P \) for trend < 0.0001; \( P \) for difference by body site = 0.04). Number of moles was more strongly related to melanoma of the trunk than other body sites (\( P \) for difference by body site = 0.04). The test for difference by body site for hair color was only borderline significant (\( P = 0.08 \)). However, there was a suggestion that hair color was most strongly related to melanoma of the trunk than other body sites.

**Discussion**

Using data from three large prospective studies, we examined traditional melanoma risk factors with melanoma risk in different body locations. Associations with sex, history of sunburn, and number of moles and melanoma risk differed by location of the cancer.

It has been hypothesized that melanoma from different body sites may have different etiologies. There have been several case-control studies or case-case comparisons that examined melanoma risk factors with melanoma risk in different body locations (2, 10-18). However, many of them did not test the difference statistically and did not adjust for multiple risk factors. A recent case-control study found that number of moles was more strongly related to melanomas of the trunk than that of the head and neck (2). It was hypothesized that people with an inherent susceptibility for melanoma, as characterized by high mole counts, tend to develop melanoma on the trunk (2). Other case-control studies (11, 15) have reported similar findings that number of moles was more strongly related to melanoma of the trunk than to melanoma of other sites. We also found that number of moles

<table>
<thead>
<tr>
<th></th>
<th>Head or neck</th>
<th>Trunk, shoulder, hip, back, or abdomen</th>
<th>Upper extremity</th>
<th>Lower extremity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHS (women)</strong></td>
<td>17</td>
<td>76</td>
<td>51</td>
<td>93</td>
<td>237</td>
</tr>
<tr>
<td><strong>NHS II (women)</strong></td>
<td>12</td>
<td>69</td>
<td>37</td>
<td>70</td>
<td>188</td>
</tr>
<tr>
<td><strong>HPFS (men)</strong></td>
<td>20</td>
<td>43</td>
<td>10</td>
<td>13</td>
<td>86</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49 (10%)</td>
<td>188 (37%)</td>
<td>98 (19%)</td>
<td>176 (34%)</td>
<td>511</td>
</tr>
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was most strongly related to melanoma of the trunk. In addition, other risk factors representing inherent susceptibility, such as family history of melanoma and hair color, were also most strongly related to melanoma of the trunk than other sites, although the tests for difference were not statistically significant. A case-control study found that family history of melanoma was positively associated with melanoma of the trunk but not with other sites (18). However, a combined analysis of eight case-control studies did not find any relationship between family history of melanoma and primary site of melanoma, although this study did not statistically test for the difference by body site (12). On the other hand, history of multiple sunburns, which may represent the magnitude of environmental exposure rather than individual susceptibility, was least strongly related to melanoma of the trunk. Overall, our findings are in accordance with the hypothesis that melanoma of the trunk may be related to inherent susceptibility for melanoma.

We found that location of melanoma is related to sex. Males had an increased risk of developing melanoma on the head, neck, or trunk, consistent with previous reports (10, 15, 17). Because it has been hypothesized that melanoma on the head and neck has been more strongly related to chronic sun exposure than that of other sites, it is not clear whether the stronger association found among men truly represents gender difference or just a reflection of greater magnitude of sun exposure among males than females. Females had increased risk of melanoma on the lower limb, although it was not statistically significant. Other studies have reported similar findings (10, 17).

We found that age was slightly more strongly related to melanoma of the head or neck than of other sites, also consistent with other studies (14-16), which may reflect the role of cumulative lifetime sun exposure for head and neck melanoma.

It was of interest that melanoma of the upper extremity had the weakest association with family history and strongest association with history of multiple sunburn compared with other body sites. It may suggest that the effect of skin damage due to sunburn (environmental factor) outweighs the effect of genetic influence for this body site. However, in a few studies that examined history of sunburns and location of melanoma, the risk seemed similar across body sites (14, 19).

Although the association between hair color and melanoma risk did not differ by body site, hair color had weaker association with melanoma of the head and neck compared with melanoma of other body sites, which was also found in a case-control study (20).

Our study had strengths. We used data from three large prospective cohort studies, which avoided the possibility of biased recall of exposure information. For each risk factor, we statistically tested the difference of melanoma risk by body site.

As limitations, we had only a modest number of cases of melanoma for some anatomic sites. In addition, because we did not have further details on body site, we were not able to do separate examinations for some body sites that might have different magnitudes of chronic sun exposure. This might have attenuated the overall association for the body sites. However, previous studies have typically used similar method of categorizing cases that we did. Direct measures of cumulative, chronic sun exposure might have been an exposure of interest. This might have different magnitudes of chronic sun exposure. However, this is very difficult to measure and some previous studies with such information have not found strong associations with melanoma risk (21). Because we restricted analysis to Caucasians, the results may not be generalizable to other racial groups, although melanoma is relatively rare in other races (22). We did not have information on the total number of body moles and used the number of moles on the upper or lower extremities as a proxy for the total body mole counts. We
previously examined moles on all four limbs versus one limb in relation to melanoma risk and found that the risks calculated from both calculations were comparable (23). It might have been interesting to examine the associations between risk factors and melanoma risk at different sites by sex. Fewer male (*n* = 86) than female (*n* = 425) cases hampered the analysis by sex. This association should be examined in the future with additional follow-up.

In conclusion, we found that the associations between melanoma and sex, number of nevi, and history of severe sunburn differ by anatomic location of the cancer. Our findings support the hypothesis that melanomas in different body locations may have different etiologies. Future studies may identify the exact mechanisms for divergent developmental pathways of melanomas. Also, studies examining other melanoma risk factors should take into account the location of melanomas.

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**References**

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