# Heterogeneity in Host Risk Factors for Incident Melanoma and Non-Melanoma Skin Cancer in a Cohort of US Women

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Heterogeneity in Host Risk Factors for Incident Melanoma and Non-Melanoma Skin Cancer in a Cohort of US Women

Abrar A. Qureshi1,2, Mingfeng Zhang2,3, and Jiali Han1,2,4

1Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
2Department of Dermatology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
3Department of Epidemiology and Biostatistics, Cancer Center, Nanjing Medical University, Nanjing, China
4Department of Epidemiology, Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, USA

ABSTRACT

Background: Melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) are 3 types of skin cancer that have distinct biologic characteristics and prognoses. We evaluated phenotypic differences in the risk of these cancers in US women.

Methods: We conducted a prospective study of 113,139 female nurses from 1984 to 2002. Over the 18 years of follow-up, there were 375 cases of melanoma, 495 cases of SCC, and 9,423 cases of BCC.

Results: Women with melanoma were more likely to have a family history of melanoma (melanoma: RR 1.94, 95% confidence interval [CI] 1.36–2.76; SCC: RR 0.82, 95% CI 0.58–1.37; BCC: RR 1.49, 95% CI 1.38–1.62) and 6 or more moles on the left arm (melanoma: RR 3.66, 95% CI 2.15–6.24; SCC: RR 1.53, 95% CI 0.83–2.79; BCC: RR 1.48, 95% CI 1.28–1.72). Polytomous logistic regression analysis showed that age at diagnosis (P < 0.0001), family history of melanoma (P = 0.016), and number of moles on the left arm (P = 0.007) were significantly different across the 3 cancers.

Conclusions: This prospective observational study demonstrated that known phenotypic factors for skin cancer have a differential impact on the risk of melanoma, SCC, and BCC.

Key words: melanoma; squamous cell carcinoma; basal cell carcinoma; phenotype

INTRODUCTION

Skin cancer incidence is increasing in the Unites States, and better methods to identify at-risk individuals will support improved prevention strategies, especially for melanoma. Sun exposure is a known environmental cause of skin cancer. Established host risk factors for skin cancer include family history of skin cancer, fair skin color, inability to tan, susceptibility to burn, and light hair color. It has been suggested that there are phenotypic variables specific to melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). However, previous research compared findings across studies separately for melanoma, SCC, and BCC, which is problematic due to variations among populations and differences in study design. Therefore, it is worthwhile to conduct a study to evaluate known host risk factors across different histological types of skin cancer within the same population.

Tanning and burning are 2 distinct traits that dictate sun sensitivity and risk of skin cancer. However, they are often grouped in the assessment of Fitzpatrick skin type, a widely used method to determine skin cancer risk that uses a 6-point scale based on an individual’s past burning and tanning response to sun exposure. Recent findings on the differential pathways underlying burning and tanning responses has prompted researchers to ask whether sensitivity to burn and ability to tan are associated with differential risks for non-melanoma skin cancer and melanoma. Little has been reported on the impact of burning and the tanning response to sun exposure on the risks of melanoma, SCC, and BCC.

Hair color is highly correlated with baseline skin pigmentation, the tanning response, freckling, and susceptibility to burn. Two types of melanin pigment, eumelanin and pheomelanin, are recognized as critical determinants of individual photosensitivity (in addition to baseline skin and hair color) and contribute to tanning ability. Light hair color

Address for correspondence. Abrar A. Qureshi, Department of Dermatology and Channing Laboratory, Brigham and Women’s Hospital, 45 Francis Street, 221L, Boston, MA, USA 02115 (e-mail: aqureshi@bics.bwh.harvard.edu). Abbreviations and acronyms: SCC, squamous cell carcinoma; BCC, basal cell carcinoma; RR, relative risk; CI, confidence interval; UV, ultraviolet. Copyright © 2011 by the Japan Epidemiological Association
has been associated with increased risk of melanoma, SCC, and BCC.5

Acquired melanocytic nevi present in sun-exposed areas of the body, such as the extensor aspects of the upper extremities, have been associated with greater time spent in the sun during childhood and a higher risk of melanoma.12 The risk of melanoma in individuals with more than 100 nevi on their entire body has been shown to be 12 times that of individuals with fewer than 10.13 Similarly, multiple atypical nevi, multiple large nevi, and high nevus counts in sun-exposed or sun-protected areas have been associated with a high risk of melanoma. However, the risk of SCC and BCC associated with nevus counts has not been extensively studied.

Family history of melanoma is associated with a higher risk of melanoma, independent of other phenotypic characteristics. Those with multiple primary melanomas tend to have a higher positive family history rate.14 There are few data on the risk of SCC and BCC in people with a positive family history of melanoma. However, a history of previous melanoma is associated with an increased risk of developing SCC and BCC;15 and individuals with prior SCC or BCC are at higher risk of developing melanoma.16

Few studies have evaluated heterogeneity in risk among melanoma, SCC, and BCC cases from a single population.17 In this study, we prospectively examined the associations between phenotypic host factors and the risk of incident melanoma, SCC, and BCC in a cohort of women. The goal was to distinguish the impact of phenotype on the risk of each of these 3 common skin cancers and to replicate previous findings in a unique US population with high follow-up rates.

METHODS

Study cohort
We used data from a prospective cohort study, the Nurses’ Health Study (NHS),3 which was established in 1976 with 121,700 female nurses aged 30 to 55 years in 11 US states. We have ascertained their lifestyle habits and disease history every 2 years since 1976 via mail questionnaires. Skin cancer has been assessed every 2 years since 1984, and skin cancer risk factors were assessed in 1982, 1986, and 1992 (see “Exposure assessment” below). Details of this cohort have been described previously.18,19

Study population
We conducted a prospective study from 1984–2002. A total of 113,139 participants were followed over the 18-year period. Women with a history of any cancer before 1984 were excluded, as were women who had more than 1 type of skin cancer at any point during the 18-year follow-up, as determined by self-report or case confirmation by medical record review (eg, a woman with confirmed melanoma and SCC would have been excluded). Almost all subjects were US non-Hispanic whites. Appropriate research approval for institutional human studies was obtained at the Brigham and Women’s Hospital.

Case ascertainment
Skin cancer confirmation is routinely conducted. For all 3 skin cancers, participants report new cases during each 2-year cycle. For reported SCC and melanoma cases, we reviewed ICD-9 codes in medical records to confirm the diagnosis. SCC in situ, actinic keratoses, SCC of the oral mucosa or genitalia, melanoma in situ, and dysplastic nevi were excluded from this analysis. Medical records are not obtained for self-report of BCC. Colditz et al20 performed a validation study in 1986 and demonstrated that the validity of self-reports of BCC was higher than 90%, as confirmed by histopathologic records, and this high validity of self-reports of BCC was independently confirmed in a subsequent study.21

Exposure assessment
All information on risk factors and exposures was collected via biennial questionnaires. In 1982, the following information was collected: (1) natural hair color at age 20 years (hair color), (2) as a child or adolescent, the reaction the skin had after 2 or more hours in the sun on a bright sunny day after exposure to the sun several times (susceptibility to burn), (3) as a child or adolescent, the kind of tan that developed after repeated sun exposures, eg, a 2-week vacation outdoors (ability to tan), and (4) family history of melanoma in first-degree relatives.22 In 1986, data were collected on the number of nevi measuring 3 mm or larger on the entire body has been shown to be 12 times that of individuals with fewer than 10. Similarly, multiple atypical nevi, multiple large nevi, and high nevus counts in sun-exposed or sun-protected areas have been associated with a high risk of melanoma. However, the risk of SCC and BCC associated with nevus counts has not been extensively studied.

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Statistical analysis
For the age-adjusted (5-year categories) and multivariate regression models, variables were modeled as dichotomous or categorical. We selected the categories based on the original questions asked in 1982 and 1986. Each study participant contributed person-time from the date the 1984 questionnaire was returned to the date of an incident melanoma, SCC, or BCC, or 30 June 2002, whichever came first. The category with the lowest risk of skin cancer was always used as the reference group. Hence, “black hair” was the reference group for the variable “natural hair color at age 20” and “no burn” was the reference category for the variable “susceptibility to burn” (Table 2). We calculated relative risks by using Cox proportional hazards regression to adjust for age and other potential confounders, including family history of melanoma, hair color at age 20 years, number of moles on left upper arm, ability to tan, and susceptibility to burn. To test for trend, we modeled the exposures as ordinal variables.

To test for differences in associations with melanoma, SCC, and BCC, we used polytomous logistic regression. We used a custom software program described by Marshall and Chisholm, which permits formal testing of the differences in
estimating the beta of each risk factor for the separate components of a composite endpoint. It can specify the variables modeled with a common beta estimate for all outcomes and those modeled with distinct values. We modeled 4 outcome categories (non-diseased, melanoma cases, SCC cases, and BCC cases) using polytomous regression. All risk estimates for each exposure variable were allowed to vary between the 4 outcomes in the initial model. Then, a manual stepwise procedure was conducted, each time with 1 risk factor constrained to be uniform across the 4 endpoints while all others were allowed to vary. The likelihood ratio test (LRT) was used to evaluate the appropriateness of modeling each exposure variable as the same for all 4 outcomes. In comparing each successive model with the baseline model, the variable with the highest LRT \( P \)-value was set to have 1 common estimate for melanoma, SCC, and BCC, and we used this as the baseline model for the next set of models. For each of the remaining variables, we repeated this procedure and set more variables to be the same for the 4 outcomes. This was continued until all remaining variables had LRT \( P \)-values less than or equal to 0.05, which indicated that they were likely to have different associations with the 3 outcomes. We simplified the expressions of each variable for the polytomous logistic regression to reduce the complexity of the computations. Age was modeled as a continuous variable (with 1-year increments) and family history as a dichotomous variable (unchanged from the logistic regression models). For number of nevi, susceptibility to burn, ability to tan, and hair color, we used ordinal variables. Because the risk estimates from polytomous logistic models and logistic models cannot be directly compared, the results from the 2 models are presented separately in Tables 2 and 3.

**RESULTS**

During the 18-year follow-up period, there were 375 cases of melanoma, 495 cases of SCC, and 9423 cases of BCC (Table 1). All cases were incident primary skin cancers diagnosed after 1984. Mean age at diagnosis was lowest for the melanoma cases (58.54 years), followed by the SCC (61.40 years) and BCC (63.73 years) cases. The proportion of women with a positive family history of melanoma was highest among those who developed melanoma (9%), followed by BCC (7%) and SCC (4%). For nevus counts on the left arm, 4% of women with melanoma had 6 or more nevi, as compared with 2% each for SCC and BCC cases. Among the melanoma, SCC, and BCC cases, there was no substantial difference in any other risk factor at baseline, including susceptibility to burn and natural hair color at age 20.

| Table 1. Baseline characteristics of study participants (1984–2002) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Melanoma        | Squamous cell carcinoma | Basal cell carcinoma |
| **Person-years**| **Cases** | **Crude incidence rate** | **Cases** | **Crude incidence rate** | **Cases** | **Crude incidence rate** |
| **Total**       | 1814 108 | 375 | 20.67 | 495 | 27.29 | 9423 | 519.43 |
| **Age (years, mean)** | 58.54 | 1725 247 | 341 | 19.77 | 473 | 27.42 | 8746 | 506.94 |
| **Family history of melanoma** | | | | | | | |
| No              | 1725 247 | 341 | 19.77 | 473 | 27.42 | 8746 | 506.94 |
| Yes             | 88 861 | 34 | 38.26 | 22 | 24.76 | 677 | 761.86 |
| **Number of moles on left arm** | | | | | | | |
| 0–2             | 793 854 | 138 | 17.38 | 251 | 31.62 | 4288 | 540.15 |
| 3–5             | 31 859 | 19 | 59.64 | 14 | 43.94 | 243 | 762.74 |
| ≥6              | 23 958 | 15 | 62.61 | 11 | 45.91 | 180 | 751.31 |
| **Childhood/adolescent tanning ability** | | | | | | | |
| Good tan        | 334 653 | 49 | 14.64 | 79 | 23.61 | 1462 | 436.87 |
| Average tan     | 631 873 | 136 | 21.52 | 175 | 27.70 | 3503 | 554.38 |
| Little tan      | 305 274 | 93 | 30.46 | 121 | 39.64 | 2054 | 672.84 |
| Almost none     | 119 761 | 37 | 30.89 | 53 | 44.25 | 849 | 708.91 |
| **Childhood/adolescent burn susceptibility** | | | | | | | |
| No burn         | 288 546 | 46 | 15.94 | 60 | 20.79 | 1072 | 371.52 |
| Some redness    | 613 152 | 124 | 20.22 | 170 | 27.73 | 3247 | 529.56 |
| Burn            | 306 377 | 90 | 29.38 | 129 | 42.10 | 2117 | 690.98 |
| Painful burn    | 130 844 | 36 | 27.51 | 50 | 38.21 | 953 | 728.35 |
| Painful burn with blisters | 69 697 | 26 | 37.30 | 26 | 37.30 | 588 | 843.65 |
| **Natural hair color at age 20 years** | | | | | | | |
| Black           | 60 318 | 8 | 13.26 | 13 | 21.55 | 193 | 319.97 |
| Dark brown      | 601 502 | 112 | 18.62 | 169 | 28.10 | 2966 | 493.10 |
| Light brown     | 532 894 | 139 | 26.08 | 157 | 29.46 | 3170 | 594.87 |
| Blonde          | 157 085 | 43 | 27.37 | 68 | 43.29 | 1172 | 746.09 |
| Red             | 56 347 | 19 | 33.72 | 26 | 46.14 | 476 | 844.77 |

*mean age at time of diagnosis.

*per 100 000 person-years.
Table 2. Age-adjusted and multivariate analyses of risk factors for melanoma, squamous cell carcinoma, and basal cell carcinoma

<table>
<thead>
<tr>
<th>Age-adjusteda</th>
<th>Multivariatea</th>
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<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
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<table>
<thead>
<tr>
<th>Melanoma</th>
<th>Squamous cell carcinoma</th>
<th>Basal cell carcinoma</th>
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<tr>
<td>n²</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Family historyd</td>
<td>34 1.94 (1.36, 2.76)</td>
<td>1.71 (1.20, 2.43)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0002</td>
<td>0.003</td>
</tr>
<tr>
<td>Ability to tanb</td>
<td>Referred ('good tan')</td>
<td>49 1.00 1.00</td>
</tr>
<tr>
<td></td>
<td>Average tan</td>
<td>136 1.46 1.28</td>
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<tr>
<td></td>
<td>Little tan</td>
<td>3.09 1.61</td>
</tr>
<tr>
<td></td>
<td>Almost none</td>
<td>37 2.08 1.55</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.8 0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>Moles on left arm</td>
<td>Referent (none) 138 1.67 1.62</td>
<td>136 1.12 1.10</td>
</tr>
<tr>
<td></td>
<td>1–5 moles</td>
<td>3.47 3.29</td>
</tr>
<tr>
<td></td>
<td>≥6 moles</td>
<td>3.66 3.48</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Susceptibility to burn9</td>
<td>Referent (no burn) 46 1.26 1.10</td>
<td>60 1.12 1.10</td>
</tr>
<tr>
<td></td>
<td>Some redness</td>
<td>1.24 (0.90, 1.77)</td>
</tr>
<tr>
<td></td>
<td>Burn</td>
<td>1.83 1.35</td>
</tr>
<tr>
<td></td>
<td>Painful burn</td>
<td>1.73 1.19</td>
</tr>
<tr>
<td></td>
<td>Painful burn with blisters</td>
<td>2.21 1.52</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hair color³</td>
<td>Referent (black) 8 1.00 1.00</td>
<td>13 1.00 1.00</td>
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<tr>
<td></td>
<td>Dark brown</td>
<td>1.12 (0.71, 2.96)</td>
</tr>
<tr>
<td></td>
<td>Light brown</td>
<td>2.01 1.68</td>
</tr>
<tr>
<td></td>
<td>Blonde</td>
<td>2.09 1.62</td>
</tr>
<tr>
<td></td>
<td>Red</td>
<td>2.58 1.74</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.17 0.06</td>
<td>0.01</td>
</tr>
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Abbreviations: CI, confidence interval; RR, relative risk.

a Number of participants does not sum to total due to missing data.

b Age-adjusted in 5-year categories.

Multivariate models include the following covariates: age, family history of melanoma, hair color at age 20 years, number of moles on left upper extremity, ability to tan, and susceptibility to burn.

c Family history of melanoma (first-degree relative), dichotomous variable with yes/no response.

d Number of moles (size ≥3 mm) on the left arm from the shoulder to the wrist.

Alternate analysis is adjusted for age, family history of melanoma, ability to tan after 2 hours of sun exposure, number of moles on the left arm, susceptibility to burn after 2 hours of sun exposure, and natural hair color at age 20. In age-

Table 2 shows the results of age-adjusted and multivariate analyses of skin cancer phenotypic factors, ie, family history of melanoma, ability to tan after 2 hours of sun exposure, number of nevi on the left arm, susceptibility to burn after 2 hours of sun exposure, and natural hair color at age 20. In age-

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analyses, family history of melanoma and number of nevi on the left arm remained significant for melanoma and nonsignificant for SCC. Regarding susceptibility to burn, a painful burn with blisters was associated with a higher risk of melanoma (RR 2.31, 95% CI 1.43–3.74) as compared with SCC (RR 1.75, 95% CI 1.10–2.77), but this association was nonsignificant in multivariate analyses. The red-hair phenotype was not associated with a higher age-adjusted risk of melanoma (RR 2.58, 95% CI 1.13–5.89) as compared with SCC (RR 2.21, 95% CI 1.14–4.31) and was nonsignificant in multivariate analyses. Blonde hair color did not materially influence the risk of SCC versus that of melanoma.

The findings for melanoma and BCC were similar with respect to the risk of melanoma and family history of melanoma. Age-adjusted and multivariate estimates for number of nevi on the left arm, susceptibility to burn, and lighter hair color were significant for BCC. As compared with women with SCC, those with melanoma and BCC (RR 2.31, 95% CI 2.08–2.55) were equally likely to report painful burns with blisters after sun exposure. Interestingly, women with BCC (RR 2.78, 95% CI 2.35–3.28), melanoma, and SCC were equally likely to have red hair. However, for family history of melanoma, the risk estimates were lower for BCC in both age-adjusted (RR 1.49, 95% CI 1.38–1.62) and multivariate analyses (RR 1.37, 95% CI 1.26–1.48). Unlike melanoma, age-adjusted estimates for “almost no” ability to tan were lower (RR 1.60, 95% CI 1.47–1.74) and remained marginally significant in multivariate models (RR 1.07, 95% CI 1.00–1.14).

Heterogeneity between melanoma, SCC, and BCC was evaluated using polytomous regression (PLR) models, and the results are presented in Table 3. Using PLR, the risk of each type of skin cancer was compared with a common non-cancer control group, and the relative differences between cancers were evaluated. Significant P-values for family history of melanoma (P = 0.016) and nevi on the left arm (P = 0.007) indicate that there were statistically significant differences among melanoma, SCC, and BCC cases in these 2 phenotypic characteristics. Although risk estimates obtained from PLR models cannot be compared directly with the findings in Table 2, estimates for both family history and number of nevi were higher for melanoma as compared with SCC and BCC. There was no significant difference among the 3 skin cancer types in susceptibility to burn or hair color, whereas there was a tendency towards a difference in ability to tan (P = 0.097).
of the 3 skin cancer types. The risk of a high mole count
significantly differed among the 3 groups, which suggests that
there may be common pathways that are associated with
melanoma and BCC development. Interestingly, melanoma,
BCC, and nevi develop in the basal layer of the epidermis,
although melanoma and nevi arise from melanocytes and
BCC arises from keratinocytes. We postulate that a similar
microenvironment in the basal layers of the epidermis
promotes development of these 3 skin lesions: a benign
UV-induced nevus, a malignant melanocyte tumor, and a
malignant keratinocyte tumor. It is plausible that UV radiation
reaching these deeper layers is of a longer wavelength (more
UV-A than UV-B),26,27 that similar types and concentrations of
free radicals are generated in these layers,27 and that
constitutive pigmentation affects the amount of radiation
reaching the deeper layers.28,29 Further study of these
mechanisms may increase our understanding of the risk of
melanoma and BCC and help us to identify individuals before
they develop potentially life-threatening skin cancer.

Ability to tan was not a differentiating risk factor for
melanoma, SCC, or BCC. PLR analysis showed a trend
toward significance in the comparison of the 3 cancer types,
although it did not demonstrate a significant difference
between the 3 skin cancers in susceptibility to burn or hair
color. Interestingly, the red-hair phenotype did not have a
differentially higher effect on the risk of melanoma versus that
of SCC or BCC. Family history of melanoma and nevus
counts emerged as significant risk factors for melanoma as
compared with SCC and BCC in this analysis.

Our study was restricted to an occupational cohort of
women. Hence, we cannot generalize these results to men.
Eye (iris) color was not included as a risk factor in the
analysis, as these data were not available. A major strength of
the study was collection of phenotype information in 1982
(hair color, ability to tan, susceptibility to burn, family history
of melanoma) before development of skin cancer (follow-up
began in 1984); hence, the results are unlikely to be affected
by recall bias, which can occur in retrospective studies.
Another strength of the study is the occupational homogeneity
of the cohort and, hence, the limited variability in occupa-
tional sun exposure. In addition, the study was sufficiently
powered to detect small differences in risk among the factors
studied, as indicated by the narrow confidence intervals.
Although the question regarding number of nevi was asked in
1986, assessment was retrospective for only 2 of the 18 years
of follow-up. All cases of melanoma and SCC were confirmed
via review of medical records, thereby reducing mis-
classification of the outcome. Although BCC was self-
reported, available evidence indicates that the validity of
self-reports of BCC is higher than 90% in this medically
sophisticated cohort.21

These findings suggest that there are modest differences in
risk between the 3 types of skin cancer. The risks associated
with hair color and susceptibility to burn were similar across
the 3 cancers. Risk prediction algorithms and clinicians should
weigh the risk factors differentially, particularly family history
of melanoma and nevus counts. A better understanding of
the different risk profiles of these cancers will permit more
accurate identification of susceptible populations and help
target prevention strategies.

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Conflicts of interest: The authors have no conflict of interest
to declare.

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