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# Host characteristics and risk of incident melanoma by Breslow thickness

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## Abstract

**Background—**Several host characteristics, including pigmentary traits (hair color, sunburn susceptibility and tanning ability), number of common nevi (moles), and family history of melanoma, have been associated with risk of melanoma.

**Methods—**We prospectively examined the associations between host characteristics and risk of incident melanoma by Breslow thickness (≤1mm, thin melanoma; or >1mm, "thicker melanoma") based on the Nurses' Health Study (NHS, n=86,380 women), NHS-II (n=104,100 women), and Health Professionals Follow-up Study (HPFS, n=46,934 men).

**Results—**During 22~30 years' follow-up, a total of 1813 incident melanoma cases were identified with information on Breslow thickness, 1392 (76.8%) of which had thin melanoma. No significant differences were observed for thin and thicker melanoma in associations with hair color, sunburn susceptibility, and tanning ability. However, we found significant differences for the association with family history of melanoma, with a higher risk estimate for thicker melanoma (HR=2.55, 95%CI: 1.91–3.42) than thin melanoma (HR=1.59, 95%CI: 1.21–2.08) (*P*-heterogeneity=0.02). Interestingly, women and men displayed differential associations between

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nevi count and risk of melanoma by Breslow thickness, with the association appearing stronger for thicker melanoma than thin melanoma in men (*P*-heterogeneity=0.01), but not in women.

**Conclusions—**Individuals with family history of melanoma may be more likely to develop thicker melanoma. Men with high number of common nevi may tend to develop thicker melanoma, which was not found for women.

**Impact—**The findings further stress the risk of thicker melanoma for individuals with a family history of melanoma and men with a high nevi count.

### Keywords

common nevi; family history; melanoma; Breslow thickness; hair color; pigmentary traits

## Introduction

Melanoma is the sixth most common cancer in the US, with 76,380 estimated new cases diagnosed in 2016, and the incidence has been rising dramatically in the past decades(1,2). Melanoma carries a poor prognosis. While it comprises 4% of skin cancer cases in the US, melanoma causes 79% of skin cancer deaths, with 10,130 estimated deaths in 2016(1).

Melanoma has a complex etiologic context resulting from the interplays of host, environmental and genetic factors. A number of host risk factors, including pigmentary traits (natural red or blonde hair, tendency to sunburn, and poor tanning ability), high number of common acquired melanocytic nevi (moles), and a family history of melanoma, are well-established risk factors for skin cancer(3–5). However, whether these host factors are associated with melanoma severity and prognosis remains poorly understood. Breslow thickness is a major indicator of melanoma severity and prognosis. Clinical studies have consistently shown the associations between Breslow thickness, which measures the depth of invasion of abnormally proliferating melanocytes, and increased risk of melanoma deaths(6,7). As participants with melanoma risky phenotypes had particularly increased incidence of melanoma, we hypothesized that they may tend to develop thicker melanoma as well. That is, individuals with those risky phenotypes, compared to individuals without such features, may be more likely to develop thicker melanoma than thin melanoma. In our study, we examined the associations between several host characteristics and risk of incident melanoma by Breslow thickness (≤1 mm, thin melanoma; or >1 mm, “thicker melanoma”) based on the Nurses’ Health Study (NHS), NHS II, and Health Professionals Follow-up Study (HPFS).

## Materials and Methods

### Study population

The NHS was established in 1976 when 121,701 U.S. registered nurses aged 30–55 years completed and returned a mailed questionnaire inquiring about medical history and lifestyle practices(3). The NHS II began in 1989 when 116,430 female nurses aged 25–42 years completed a baseline questionnaire on medical history and lifestyle practices. The HPFS began in 1986 when 51,529 US male health professionals aged 40–75 years completed a

baseline questionnaire on medical history and lifestyle practices(8). Biennially, participants received a questionnaire, and a response rate generally exceeding 90% has been achieved during the follow-up. This study was approved by the Human Research Committee of Harvard School of Public Health and Brigham and Women's Hospital (Boston, MA).

### Assessment of melanoma and Breslow thickness

In all three cohorts, participants report diagnoses of melanoma and other cancers on biennial surveys. Whenever a diagnosis of melanoma is reported, we seek permission to obtain medical records; these are reviewed by physicians to confirm the diagnosis. We excluded self-reported melanoma cases that we could not confirm, and included only pathologically confirmed invasive cases based on medical records. We recorded information on Breslow thickness and other major histopathological factors of melanoma at the time of diagnosis during the review process of pathological reports. For our current analysis, Breslow thickness was classified into two categories: ≤1 or >1 mm, based on the recognized cutoff for defining thin melanoma(7).

### Assessment of main exposure (host characteristics)

Information on the main exposure (host characteristics) was collected via the main questionnaires in our study. Information on natural hair color in early adulthood (age 21 years in NHS and 18 years in NHS II and HPFS) was assessed in the main questionnaire (1982 in NHS, 1991 in NHS II and 1988 in HPFS). Participants were asked about their natural hair color in the following categories: red, blonde, light brown, dark brown, and black. Participants were asked about the total number of nevi with 3 mm diameter or larger on different body sites: left arm from shoulder to wrist for NHS (1986), both lower legs from knees to ankles for NHS II (1989), and both forearms between elbow and wrist for HPFS (1987). Participants reported the total number of nevi by selecting one of the following categories: none, 1–2, 3–5, 6–9, 10–14, 15–20, or ≥21. Family history of melanoma in first-degree relatives (parents or siblings) was asked in 1982, 1992, 1996, and 2000 for NHS, in 1989, 1997, 2001, 2005 and 2009 for NHS II, and in 1990, 1992 and 2008 for HPFS. Number of blistering sunburns throughout life (NHS and HPFS) or number of teenage severe sunburns (NHS II) and tendency to sunburn as a child or adolescent were asked in 1982 (NHS), 1989 (NHS II) and 1992 (HPFS).

### Assessment of covariates

Information on smoking, body mass index (BMI), physical examination by a physician (either for screening or for symptoms), alcohol intake, and citrus consumption was asked in the main questionnaire and updated biennially during the follow-up. A new model of average July ambient erythemal UV radiation was developed based on the area-to-point residual kriging method(9). Compared to the state-based time-invariant UV flux measure we had used(4), the new time-varying model provides a finer resolution estimate of ambient UV exposure (1 × 1 km in spatiotemporal resolution) for our cohorts(9).

## Statistical analysis

Participants who do not have data on any examined host factors (hair color, nevi count, family history of melanoma, sunburn susceptibility and tanning ability) were excluded from the analysis. We restricted the analyses to Whites, as populations of European ancestry are at greatest risk for melanoma out of all ethnicities, and comprise the majority of cohort participants (82.6% of the NHS, 91.6% of NHS II and 97.3% of HPFS). To fulfill a prospective study design, baseline for NHS was set at 1986 for the analysis of nevi and 1982 for analyses of other factors. Baseline for NHS II was set at 1989 for all analyses. Baseline for HPFS was set at 1988 for the analyses of hair color and nevi, 1990 for family history, and 1992 for other analyses. Participants reporting a diagnosis of cancer (melanoma and non-skin cancers) at or before the baseline were excluded for each analysis. End of follow-up was set at June 2012 for NHS, June 2011 for NHS II and Jan 2012 for HPFS. Person-years of follow-up were calculated from the return date of the baseline (as defined above) questionnaire to the diagnosis date of melanoma, death, or end of follow-up, whichever came first.

Association analyses were conducted for hair color (black/dark brown, light brown, blonde, or red), nevi count (0, 1–2, 3–5, or ≥6), family history of melanoma (yes or no), tanning ability (NHS only; practically none, little, average, or deep tan), burning susceptibility (none or redness only, burn, painful burn, or painful burn with blisters), and number of sunburns (0, 1–2, 3–5, or ≥6) respectively. We calculated age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each host characteristic and risk of incident melanoma by Breslow thickness (thin melanoma, ≤1mm or “thicker melanoma”, >1 mm) using Cox proportional hazards analysis stratified by age and calendar year of the questionnaire cycle. Although the three cohort studies had selected different ages, we minimized the confounding by age after applying such statistical approach. Multivariate-adjusted analysis for each host factor was conducted adjusting *a priori* for BMI, smoking, alcohol intake, physical examination, citrus consumption, UV exposure, personal history of keratinocyte carcinoma, and other host characteristics. Information on the covariates was updated in each 2-year questionnaire cycle, whenever available. For nevi count and number of sunburns, trend analysis was conducted using continuous measures by assigning the median value to each category of these variables. *P* value for heterogeneity (*P*-heterogeneity) in the associations for thin and thicker melanoma with each host characteristic was evaluated using Q statistics.

Most of the cohort participants had physical examination by a physician as reported in the biennial questionnaires (Table 1). A sensitivity analysis was conducted by excluding those without physical examination. Another *post hoc* sensitivity analysis was conducted for the analysis of nevi by excluding those with a family history of melanoma. We also conducted a sensitivity analysis by including melanoma cases that occurred before the study baseline.

Analyses were conducted in each cohort respectively. For the meta-analysis of cohorts, we pooled the HRs using random-effect models, in which the individual studies (NHS, NHS II and HPFS) were weighted proportionately to the inverse of the sum of the study specific variance plus the common between-studies variance. *P*-heterogeneity between pooled HRs for thin and thicker melanoma was also calculated using Q statistics. Analyses were carried

out using SAS (version 9.2; SAS Institute Inc, Cary, NC). All *P* values were 2-tailed with the significance level set at $P<0.05$.

## Results

A total of 237,414 participants, including 86,380 women from NHS, 104,100 women from NHS II, and 46,934 men from HPFS, were included in the analyses (the maximum sample size when the baseline was set at 1982 for NHS, 1989 for NHS II, and 1988 for HPFS). During the follow-up (1982–2012 for NHS, 1989–2011 for NHS II, and 1988–2012 for HPFS), a total of 2439 incident melanoma cases were identified. Of them, 1813 incident melanoma cases had information on Breslow thickness available (n=782 in NHS, 485 in NHS II, and 546 in HPFS), with 1392 (76.8%, 1392/1813) having Breslow thickness <1 mm (thin melanoma). Cases with Breslow thickness >1 mm (thicker melanoma) tended to be older at diagnosis and had a family history of melanoma. Male (HPFS) cases with thicker melanoma were more likely to have 6 or more nevi, but were less likely to be red or blonde-haired than thin melanoma cases. In contrast, if female (NHS or NHS II) cases with thicker melanoma were compared with thin melanoma, the distribution of nevi count and hair color went to the opposite direction (Table 1).

We did not find significant differences for thin and thicker melanoma in the associations with hair color in any cohort. Combining three cohorts, red hair was associated with increased risk of both thin (multivariate-adjusted HR=2.00, 95% CI: 1.58–2.53) and thicker melanoma (HR=2.30, 95% CI: 1.28–4.15), with similar effect magnitudes (*P*-heterogeneity =0.93, Table 2).

The analysis of family history of melanoma yielded a higher HR for thicker melanoma than thin melanoma in all three cohorts, although statistically significant difference was only found for NHS II (*P*-heterogeneity=0.009). Combining three cohorts, we found significant differences in association with family history of melanoma, with a HR (95% CI) of 2.55 (1.91–3.42) for thicker melanoma and 1.59 (1.21–2.08) for thin melanoma (*P*-heterogeneity=0.02, Table 3).

Male and female melanoma displayed differential associations with nevi count. The association appeared much stronger for thicker melanoma (HR=4.31, 95% CI: 2.41–7.68 for ≥6 nevi) than thin melanoma (HR=1.75, 95% CI: 1.15–2.67 for ≥6 nevi) in men (*P*-heterogeneity=0.01). In contrast, no significant difference in associations was found between thick and thin melanoma in women, and the association between nevi count and melanoma even appeared stronger for thin melanoma than thicker melanoma (Table 4).

We also examined thin and thicker melanoma in association with tanning ability (NHS only), sunburn susceptibility, and number of sunburns. No significant difference in associations was observed for thin and thicker melanoma in each cohort or in combined cohorts (all *P*-heterogeneity>0.10, Supplementary Table S1).

We conducted several sets of sensitivity analyses by excluding those with a family history, excluding those without physical examination, or including the melanoma cases diagnosed before study baseline, which did not change the results appreciably. For example, after

excluding participants with a family history, similar with the primary analyses as above mentioned, we also observed much stronger association with nevi count for thicker melanoma (HR=4.31, 95% CI: 2.41–7.68 for ≥6 nevi) than for thin melanoma (HR=1.75, 95% CI: 1.15–2.67 for ≥6 nevi) in men, but not in women (*P*-heterogeneity=0.01) (Supplementary Table S2).

## Discussion

In our study, women and men with a family history of melanoma were more likely to develop melanoma with Breslow thickness more than 1mm (Table 3). Men with a high number of cutaneous nevi were also at higher risk for thicker melanoma than thin melanoma, which was not found in women (Table 4). We did not find significant differences in the risk of thin and thicker melanomas associated with hair color, sunburn susceptibility, and suntan ability (Table 2 and Supplementary Table S1). To our knowledge, this is the first study that reports a differential risk of developing thick and thin melanoma associated with host characteristics.

Natural red or blonde hair, increased number of melanocytic nevi, family history of melanoma, poor tanning ability, tendency to sunburn and high number of sunburns are known factors associated with increased risk of melanoma(3–5). However, little is understood whether individuals with these high risk phenotypes are more likely to develop more aggressive melanoma than individuals without such features. To fill this knowledge gap, we examined whether several established risk factors of melanoma would be differentially associated with risk of thin and thicker melanomas.

Approximately 10% of melanoma cases occur in a familial setting, with at least one first-degree relative having a diagnosis of melanoma (10). Clustering of melanoma cases within family members may result from both genetic and shared environmental or host factors. Research into familial melanoma has led to the discovery of melanoma-predisposing genes such as *CDKN2A* (9p21), *CDK4* (12q14), and *POT1* (7q31)(11–14). Previous studies found that familial melanoma cases tends to be diagnosed at an earlier age, have thinner tumors and a higher number of in situ melanomas than sporadic cases(15–17), suggesting that familial melanoma patients may have had an increased awareness of risk and early detection of melanoma by practitioners. However, despite this potential benefit of early diagnoses, we found that subjects with a family history of melanoma were at significantly higher risk of developing thicker melanoma than thin melanoma (Table 3). Our findings highlight the extra risk of developing thicker melanoma, suggesting that a family history of melanoma may be an indicator of poor melanoma prognosis. Based on the strong tendency of melanoma toward familial aggregation, future examination into family-history-related genetic loci may offer an opportunity to examine genetic predisposition of melanoma and provide important insights into low-penetrance susceptibility regions for melanoma thickness. Studies are also warranted to agonistically explore the genetic predisposition for Breslow thickness. Thus far, only one genome-wide association study (GWAS) of Breslow thickness has been published, which did not reveal marginal effect of individual loci associated with Breslow thickness, although several enriched pathways were reported(18).

High nevus count is an established risk factor of melanoma(3–5). Two prior cross-sectional studies reported an inverse association between nevi count and Breslow thickness of melanoma(19,20). In contrast, our prospective study found that men with high nevus count had a particularly higher risk for thicker melanoma than thin melanoma, which was not found for women (Table 4). Similarly, our another study found that male melanoma cases with high nevus count tended to have worse survival, which was not found for female cases (W.Q. Li; personal communication). The reason for the sex-based difference is not understood, but the differed anatomic distribution of melanoma by sex may partly help explain the difference. Melanomas of men tend to occur at head and neck or trunk while melanomas of women occur more frequently at extremities. We previously have shown a stronger association with number of moles for melanoma of the trunk than other sites(3). A prior study from others also has reported a poorer survival in head and neck and trunk melanoma compared with other sites in women(21). In addition, a potential androgen basis of melanoma has long been hypothesized(8,22). We have reported an increased risk of melanoma associated with a history of androgen-related diseases, including prostate cancer and severe teenage acne(8,23). It would be interesting to explore whether the differential association by gender in our current study may be linked to the androgen hypothesis of melanoma.

In our study, male cases (HPFS) of thicker melanoma had more nevi but were less likely to be red or blonde-haired than thin melanoma cases (Table 1). In women (NHS and NHS II), the distribution of nevi and hair color in thin and thicker melanoma cases went to the opposite direction (Table 1). Despite our findings on nevi count differentially associated with thin and thicker melanoma in men (Table 4), we did not find significant differences in the risk of developing thin and thicker melanomas associated with hair color in either men or women (Table 2).

In addition to constitutional factors, other factors may also be important in predicting thicker melanoma. For example, low socioeconomic status has been associated with thicker melanoma and a poorer clinical outcome(24,25). Previous studies also reported an association of elevated BMI with poorer outcomes of primary melanoma(26) but improved progression-free survival and overall survival of metastatic melanoma(27). Further efforts are required to examine other characteristics associated with thin and thicker melanoma.

Our study was strengthened by its prospective design, a large sample size, long follow-up, and detailed information on host and environmental factors, which allowed for robust estimates of the associations between host characteristics and risk of melanoma by Breslow thickness, adjusting for potential confounders. Information on family history of melanoma was updated during the follow-up.

We acknowledge several limitations. First, information on host characteristics was collected by self-report, which may have led to misclassification bias. The questionnaire did not differentiate nevi from seborrheic keratoses and lentigines, which may have led to misclassification bias for nevi. However, the high levels of education and familiarity with medical issues among nurses and health professionals allow high-quality information to be collected on self-administered forms. The self-reported pigmentary traits predict skin cancer

risk in our cohorts, with risk estimates comparable to previous reports(3,4). Our GWAS on self-reported pigmentary traits confirmed previously identified human pigmentation loci(28). Previous studies showed that the self-reported categories of nevi on limbs has reasonable agreement with dermatologist-counted nevi(29) and nevus count on the arms serves as a proxy for the total body nevi counts(30).

Second, information on total number of nevi was collected on different body sites in three cohorts, as shown in the Methods. The observed different associations of nevi with Breslow thickness in women (higher HR for thin melanoma) and men (higher HR for Breslow thickness >1mm) may be partly due to the differences in data collection, although it is less likely that such contrasting associations across men and women were completely due to different nevi body sites.

Third, we only had a modest sample size of melanoma cases with Breslow thickness, which restricted the power for analyses of Breslow thickness with finer categories and for subgroup analyses such as by melanoma body sites. For example, we were not able to examine the risk of melanoma thicker than 4mm (the most recognized cutoff for ‘thick’ melanoma) associated with constitutional factors. The heterogeneity tests that did not approach statistical significance may also be partly explained by a low statistical power.

Fourth, this is an epidemiological study, which cannot necessarily speak to cause and effect. Further efforts are required to elucidate the mechanisms underlying the observed associations. It is also worth noting that the tumor depth at melanoma diagnosis may result from unmeasured characteristics of study participants, such as lack of skin self-awareness and accessibility to medical services.

Fifth, study participants were health professionals and the analyses were restricted to Whites. The homogeneity has enhanced the quality of questionnaire response and minimized confounding from socioeconomic factors. However, the three cohorts were initiated with only women or men and with different age distribution. We also had a relatively small sample size of male participants compared with females. Therefore, cases in our study were not based on the randomized selection of melanoma cases in the general population and the extrapolation of our results should be cautious.

In summary, our prospective study based on three established cohorts found that women and men with family history of melanoma were more likely to develop melanoma thicker than 1mm. Men with a high number of cutaneous nevi may tend to develop thicker melanoma, which was not found for women. As melanoma incidence is increasing rapidly worldwide among Whites, our findings holds important public health implications, which may further inform public and general practitioners on the routine skin examination for individuals with a family history of melanoma and men with a high nevi count.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviation:

| | |
|---|---|
| **CI** | confidence interval |
| **HPFS** | Health Professionals Follow-up Study |
| **HR** | hazard ratio |
| **NHS** | Nurses’ Health Study |

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**Table 1.**

Characteristics of melanoma cases by Breslow thickness in the cohorts[a]

| | NHS | | NHS II | | HPFS | |
|---|---|---|---|---|---|---|
| | **Breslow ≤1 mm (n=579)** | **Breslow >1mm (n=203)** | **Breslow ≤1 mm (n=416)** | **Breslow >1mm (n=69)** | **Breslow ≤1 mm (n=397)** | **Breslow >1mm (n=149)** |
| **Age at diagnosis, years, mean (SD)** | 47.6 (7.0) | 49.8 (6.7) | 34.8 (4.5) | 36.7 (4.3) | 55.4 (9.1) | 56.6 (8.5) |
| **Current smoking, %** | 19.4 | 22.4 | 9.7 | 6.0 | 6.1 | 5.7 |
| **Alcohol intake, g/d, mean (SD)** | 7.0 (11.5) | 7.6 (12.7) | 3.3 (4.9) | 4.3 (7.0) | 12.5 (14.8) | 11.2 (16.1) |
| **BMI, kg/m$^2$, mean (SD)** | 24.7 (4.3) | 24.9 (4.9) | 23.8 (4.7) | 24.8 (4.3) | 25.5 (3.1) | 25.7 (3.6) |
| **Physical activity, metabolic equivalents hours/week, mean (SD)** | 15.4 (18.8) | 16.6 (18.8) | 24.9 (34.0) | 23.6 (29.2) | 30.6 (29.8) | 32.9 (33.6) |
| **Physical examination, %** | 85.1 | 85.8 | 92.2 | 89.7 | 79.0 | 67.0 |
| **Family history of melanoma, %** | 5.3 | 8.8 | 7.3 | 10.1 | 4.3 | 6.1 |
| **Red or blonde hair, %** | 21.2 | 28.5 | 30.0 | 34.9 | 20.2 | 15.1 |
| **≥6 moles on the extremity[b] (%)** | 11.8 | 9.3 | 41.7 | 35.1 | 8.4 | 12.8 |
| **Painful burn or blistering skin reaction to the sun (%)** | 21.9 | 16.0 | 31.7 | 36.6 | 39.5 | 33.7 |
| **Childhood tendency to average to deep tanning response (%)** | 55.4 | 56.7 | | | | |
| **History of ≥6 severe or blistering sunburns[c] (%)** | 64.0 | 56.6 | 15.8 | 19.7 | 46.2 | 50.0 |
| **Lifetime average summer time sun exposure ≥6 hrs/wk (%)** | 42.7 | 43.4 | 50.7 | 39.5 | 71.9 | 63.9 |
| **Annual erythemal UV, mW/m$^2$, mean (SD)** | 184.6(22.6) | 190.4(26.7) | 176.4(41.6) | 175.5(42.0) | 191.6(28.0) | 196.9(29.6) |
| **Citrus consumption, serving/d, mean (SD)** | 0.9 (0.7) | 0.9 (0.8) | 0.6 (0.7) | 0.6 (0.5) | 1.0 (0.9) | 0.9 (0.9) |
| **Personal history of keratinocyte carcinoma (%)** | 1.8 | 3.5 | 0 | 0 | 4.7 | 5.5 |
| **Melanoma Body site (%)** | | | | | | |
| **Head and neck** | 13.3 | 10.7 | 8.3 | 10.2 | 29.1 | 32.9 |
| **Trunk** | 31.0 | 24.2 | 36.1 | 38.1 | 46.1 | 42.2 |
| **Extremities** | 55.6 | 65.1 | 55.6 | 51.7 | 24.8 | 24.9 |

[a]All values were shown for the information at the time of melanoma diagnosis or at the questionnaire cycle closest to melanoma diagnosis except otherwise noted. All values other than age were age-adjusted.

[b]The total number of cutaneous nevi with 3 mm diameter or larger was asked for the left arm in NHS, for both forearms in HPFS, and for both lower legs in NHS II.

[c]NHS and HPFS asked the lifetime number of sunburns while NHS II asked the number of teenage severe sunburns.

**Table 2.**

Hair color and risk of melanoma by Breslow thickness

| | Person-years | Melanoma with Breslow ≤1 mm | | | Melanoma with Breslow >1 mm | | | P for heterogeneity |
|---|---|---|---|---|---|---|---|---|
| | | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | |
| **Nurses' Health Study (82–12)** | | | | | | | | |
| Black/dark-brown | 1020326 | 199 | 1.00 | 1.00 | 73 | 1.00 | 1.00 | |
| Light-brown | 866636 | 230 | 1.36 (1.12, 1.64) | 1.20 (0.99, 1.46) | 66 | 1.06 (0.76, 1.48) | 0.98 (0.70, 1.37) | 0.30 |
| Blonde | 256506 | 64 | 1.28 (0.97–1.70) | 1.01 (0.76, 1.34) | 32 | 1.68 (1.11, 2.55) | 1.43 (0.93, 2.18) | 0.19 |
| Red | 92634 | 52 | 2.90 (2.14, 3.94) | 1.96 (1.41, 2.74) | 21 | 3.08 (1.89, 5.00) | 2.37 (1.38, 4.06) | 0.56 |
| **Nurses' Health Study II (89–11)** | | | | | | | | |
| Black/dark-brown | 764163 | 101 | 1.00 | 1.00 | 16 | 1.00 | 1.00 | |
| Light-brown | 774835 | 170 | 1.67 (1.30, 2.13) | 1.56 (1.22, 2.00) | 25 | 1.57 (0.84, 2.94) | 1.43 (0.76, 2.69) | 0.80 |
| Blonde | 321773 | 90 | 2.16 (1.62, 2.87) | 1.85 (1.39, 2.47) | 12 | 1.94 (0.91, 4.10) | 1.59 (0.74, 3.40) | 0.71 |
| Red | 76570 | 28 | 2.79 (1.83, 4.23) | 2.36 (1.52, 3.65) | 8 | 5.15 (2.21, 12.1) | 3.80 (1.55, 9.35) | 0.35 |
| **Health Professionals Follow-up Study (88–12)** | | | | | | | | |
| Black/dark-brown | 404189 | 136 | 1.00 | 1.00 | 49 | 1.00 | 1.00 | |
| Light-brown | 256736 | 126 | 1.45 (1.14, 1.85) | 1.26 (0.99, 1.61) | 56 | 1.83 (1.25, 2.69) | 1.60 (1.09, 2.36) | 0.31 |
| Blonde | 84481 | 50 | 1.74 (1.26, 2.41) | 1.39 (1.00, 1.93) | 16 | 1.56 (0.88, 2.74) | 1.28 (0.72, 2.26) | 0.80 |
| Red | 20287 | 17 | 2.46 (1.49, 4.08) | 1.64 (0.98, 2.76) | 3 | 1.21 (0.38, 3.87) | 1.01 (0.31, 3.29) | 0.46 |
| **Meta-analysis** | | | | | | | | |
| Black/dark-brown | 2188678 | 436 | - | 1.00 | 138 | - | 1.00 | |
| Light-brown | 1898207 | 526 | - | 1.32 (1.13, 1.53) | 147 | - | 1.27 (0.90, 1.79) | 0.84 |
| Blonde | 662760 | 204 | - | 1.37 (0.96, 1.97) | 60 | - | 1.40 (1.03, 1.92) | 0.93 |
| Red | 189491 | 97 | - | 2.00 (1.58, 2.53) | 32 | - | 2.30 (1.28, 4.15) | 0.66 |

CI: confidence interval; HR: hazard ratio

[a]Stratifying by age and questionnaire cycle, and adjusting for BMI (<25, 25–29.9, or ≥30 kg/m$^2$), smoking (never, past, or current smokers), alcohol intake (0, 0–4.9, 5–9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2-≤4 times/wk, >4 times/wk-<1 time/d, or ≥1 time/d), physical examination (yes or no), erythemal UV radiation (in quintiles), personal history of keratinocyte carcinoma (yes or no), and other host characteristics, including family history of melanoma, nevi count, tanning ability (NHS only), burning susceptibility, and number of sunburns.

**Table 3.**

Family history of melanoma and risk of melanoma by Breslow thickness

| | Person-years | Melanoma with Breslow ≤1mm | | | Melanoma with Breslow >1mm | | | P for heterogeneity |
|---|---|---|---|---|---|---|---|---|
| | | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | |
| **Nurses' Health Study (82–12)** | | | | | | | | |
| No family history | 2208276 | 496 | 1.00 | 1.00 | 172 | 1.00 | 1.00 | |
| With family history | 125129 | 72 | 2.21 (1.72, 2.83) | 1.93 (1.50, 2.48) | 30 | 2.60 (1.76, 3.85) | 2.42 (1.63, 3.58) | 0.34 |
| **Nurses' Health Study II (89–11)** | | | | | | | | |
| No family history | 1744100 | 344 | 1.00 | 1.00 | 44 | 1.00 | 1.00 | |
| With family history | 184278 | 57 | 1.43 (1.08–1.91) | 1.30 (0.97–1.73) | 17 | 3.45 (1.94, 6.14) | 3.10 (1.73, 5.54) | 0.009 |
| **Health Professionals Follow-up Study (90–12)** | | | | | | | | |
| No family history | 470142 | 200 | 1.00 | 1.00 | 72 | 1.00 | 1.00 | |
| With family history | 24506 | 18 | 1.71 (1.05–2.77) | 1.57 (0.85–2.88) | 10 | 2.62 (1.35–5.09) | 2.32 (1.19–4.52) | 0.33 |
| **Meta-analysis** | | | | | | | | |
| No family history | 4422518 | 1040 | - | 1.00 | 288 | - | 1.00 | |
| With family history | 333913 | 147 | - | 1.59 (1.21–2.08) | 57 | - | 2.55 (1.91, 3.42) | 0.02 |

CI: confidence interval; HR: hazard ratio

[a]Stratifying by age and questionnaire cycle, and adjusting for BMI (<25, 25–29.9, or ≥30 kg/m$^2$), smoking (never, past, or current smokers), alcohol intake (0, 0–4.9, 5–9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2-≤4 times/wk, >4 times/wk-<1 time/d, or ≥1 time/d), physical examination (yes or no), erythemal UV radiation (in quintiles), personal history of keratinocyte carcinoma (yes or no), and other host characteristics, including hair color, nevi count, tanning ability (NHS only), burning susceptibility, and number of sunburns.

**Table 4.**

Nevi count and risk of melanoma by Breslow thickness

| | Person-years | Melanoma with Breslow ≤1mm | | | Melanoma with Breslow >1mm | | | P for heterogeneity |
|---|---|---|---|---|---|---|---|---|
| | | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | n | Age-adjusted HR (95% CI) | MV-adjusted HR[a] (95% CI) | |
| **Nurses' Health Study (86–12)** | | | | | | | | |
| 0 | 1093963 | 226 | 1.00 | 1.00 | 93 | 1.00 | 1.00 | |
| 1–2 | 414208 | 123 | 1.43 (1.15, 1.79) | 1.36 (1.09, 1.70) | 39 | 1.13 (0.78, 1.65) | 1.11 (0.76, 1.61) | 0.35 |
| 3–5 | 136421 | 71 | 2.52 (1.93, 3.30) | 2.33 (1.78, 3.05) | 26 | 2.28 (1.48, 3.53) | 2.17 (1.40, 3.35) | 0.78 |
| ≥6 | 78253 | 57 | 3.56 (2.66, 4.76) | 3.15 (2.35, 4.22) | 15 | 2.34 (1.36, 4.04) | 2.28 (1.32, 3.96) | 0.31 |
| P for trend | | | $3.99\times10^{-23}$ | $9.06\times^{-19}$ | | 0.0001 | 0.0003 | 0.32 |
| **Nurses' Health Study II (89–11)** | | | | | | | | |
| 0 | 1061892 | 127 | 1.00 | 1.00 | 26 | 1.00 | 1.00 | |
| 1–2 | 403850 | 68 | 1.41 (1.05, 1.89) | 1.37 (1.02–1.84) | 10 | 1.00 (0.48, 2.08) | 0.98 (0.47, 2.04) | 0.41 |
| 3–5 | 217184 | 41 | 1.57 (1.11, 2.24) | 1.53 (1.08, 2.18) | 7 | 1.31 (0.57, 3.03) | 1.30 (0.56, 3.00) | 0.72 |
| ≥6 | 456479 | 170 | 3.09 (2.46, 3.89) | 2.90 (2.30, 3.65) | 21 | 1.89 (1.06, 3.36) | 1.83 (1.02, 3.27) | 0.15 |
| P for trend | | | $1.98\times10^{-25}$ | $2.40\times10^{-22}$ | | 0.03 | 0.04 | 0.14 |
| **Health Professionals Follow-up Study (88–12)** | | | | | | | | |
| 0 | 444624 | 170 | 1.00 | 1.00 | 43 | 1.00 | 1.00 | |
| 1–2 | 128308 | 64 | 1.30 (0.97, 1.73) | 1.26 (0.94, 1.68) | 29 | 2.33 (1.45, 3.73) | 2.23 (1.39, 3.57) | 0.04 |
| 3–5 | 48326 | 35 | 1.86 (1.29, 2.67) | 1.74 (1.21, 2.50) | 20 | 4.16 (2.45, 7.08) | 3.79 (2.22, 6.47) | 0.02 |
| ≥6 | 33825 | 25 | 1.89 (1.24, 2.88) | 1.75 (1.15, 2.67) | 16 | 4.82 (2.71, 8.57) | 4.31 (2.41, 7.68) | 0.01 |
| P for trend | | | $6.46\times10^{-5}$ | 0.0004 | | $2.44\times10^{-10}$ | $6.22\times10^{-9}$ | 0.01 |
| **Meta-analysis** | | | | | | | | |
| 0 | 2600479 | 521 | - | 1.00 | 162 | - | 1.00 | |
| 1–2 | 946366 | 250 | - | 1.33 (1.15–1.55) | 78 | - | 1.38 (0.83, 2.29) | 0.89 |
| 3–5 | 401931 | 146 | - | 1.88 (1.45, 2.44) | 53 | - | 2.35 (1.38, 4.00) | 0.46 |
| ≥6 | 568557 | 249 | - | 2.63 (1.96, 3.52) | 52 | - | 2.62 (1.59, 4.29) | 0.99 |
| P for trend | | | - | $7.61\times10^{-14}$ | | - | 0.0001 | 1.00 |

CI: confidence interval; HR: hazard ratio

[a] Stratifying by age and questionnaire cycle, and adjusting for BMI (<25, 25–29.9, or ≥30 kg/m$^2$), smoking (never, past, or current), alcohol intake (0, 0–4.9, 5–9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2-≤4 times/wk, >4 times/wk-<1 time/d, or ≥1 time/d), physical examination (yes or no), UV radiation (in quintiles), personal history of keratinocyte carcinoma (yes or no), and other host characteristics, including hair color, family history of melanoma, tanning ability (NHS only), burning susceptibility, and number of sunburns.