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Host risk factors for the development of multiple non-melanoma skin cancers

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Abstract

Non-melanoma skin cancer (NMSC) is one of the most common cancer in the US, and having multiple lesions conveys substantial cost and morbidity for the individual involved. Although there are data available on risk factors for NMSC, few studies currently identify specific risk factors for development of multiple NMSCs. We evaluated host risk factors for multiple NMSCs among men in the Health Professionals Follow-up Study and women in the Nurses' Health Study. Compared with individuals with a single NMSC, having greater number of sunburns was a risk factor for developing ≥2 NMSCs [≥10 sunburns, cumulative relative risk (RR) = 1.21, 95% confidence interval (CI): 1.07–1.36] and a higher risk of developing ≥11 NMSCs (≥10 sunburns, RR = 2.33, 95% CI: 1.57–3.46). Inability-to-tan was associated with risk of developing ≥2 NMSCs (cumulative RR = 1.29, 95% CI: 1.18–1.40) and a higher risk of developing ≥11 NMSCs (RR = 1.91, 95% CI: 1.50–2.43). Men had an increased risk of developing ≥2 NMSCs (cumulative RR = 1.53, 95% CI: 1.40–1.66). Risk of developing 2–4, 5–10 and ≥11 NMSCs increased with age. Other risk factors for developing ≥2 NMSCs included red natural hair colour (cumulative RR = 1.23, 95% CI: 1.07–1.42), family history of melanoma (cumulative RR = 1.15, 95% CI: 1.03–1.28), and having ≥6 nevi on the left arm (cumulative RR = 1.22, 95% CI: 1.07–1.40). In conclusion, physicians caring for individuals with incident NMSCs may consider paying special attention to those at highest risk for developing additional tumours, especially males and those with a history of ≥10 lifetime sunburns, by performing routine full skin examinations and counselling for aggressive photo-protection.

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Introduction

The most common types of epithelial skin cancers in the United States are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), collectively known as non-melanoma skin cancer (NMSC). Personal history of NMSC is associated with increased risk of developing subsequent skin cancers.[1] The risk of additional primary tumours after the first tumour is estimated at 35–65% (mean 47%).[2] Although single NMSC is easy to treat, multiple tumours can result in substantial morbidity to the affected individual and cost to the health-care system. There is a considerable burden borne by individuals who develop more than one tumour in a lifetime, requiring frequent dermatology visits and often locally destructive therapy or surgery. NMSC is the fifth most expensive cancer to treat in the US.[3] The number of procedures for NMSC has continued to increase, increasing by 16% in the Medicare population from 2002 to 2006.[3]

As NMSC has become an important public health concern, recent research efforts have focused on determining risk factors for the disease. Few studies have systematically assessed factors that contribute to the incremental risk of developing multiple tumours. An important reason for the lack of data on multiple NMSCs is that national cancer registries, such as SEER (Surveillance, Epidemiology and End Results), do not include data on BCC and SCC. We were fortunate to have data on NMSC in two large occupational cohorts in the US, collected since 1976 and 1986. In our study, we evaluated host factors that predispose to multiple BCCs and/or SCCs among 80 275 American men and women from Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

Methods

Study populations

Nurses' Health Study (NHS) The Nurses' Health Study (NHS) is an ongoing prospective cohort study, first established in 1976, and includes 121 700 female registered nurses (RN). At enrollment, study participants were 30 to 55 years of age and resided in 11 states: California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania and Texas. Since cohort inception, participants now reside in every US state. No restrictions were made on the basis of ethnicity or race. However, the participants were 97% Caucasian, reflecting the ethnic background of women trained as RNs in 1976.

The Health Professionals Follow-Up Study (HPFS) The Health Professionals Follow-Up Study (HPFS) is an ongoing prospective cohort study, established in 1986, to complement the all-female NHS. HPFS is comprised of 51 529 men in health professions. At the onset of the study, minimum participant age was set at 40, with maximum set at 75. Similarly, the participants were 97% Caucasian.

The two cohorts have similar socioeconomic background and educational attainment. Although the two cohorts differed in the distribution of age, we adjusted for age in all analyses. Combined data from HPFS and NHS have been widely used in numerous cancer-related studies.[4–8]

Skin cancer disease follow-up

Participants reported new diagnosis of SCC, BCC and melanoma each 2-year questionnaire cycle. All reported cases of SCC and melanoma were confirmed by pathology record review. Squamous cell carcinoma in situ, actinic keratoses and SCC of the oral mucosa or genitalia were excluded from this analysis. Validation studies to assess BCC self-reporting in our cohort demonstrated a >90% confirmation rate by histopathology.[9, 10]

Ascertainment of outcome

Information on the cumulative number of NMSCs was collected through the cohort questionnaire (2004 in the NHS and 2008 in the HPFS). The question posed was, 'How many basal cell and/or squamous cell carcinoma(s) have you ever had removed by surgery, cryotherapy or other means? (Include only new primary cancers. Exclude melanoma and benign lesions like nevi or actinic keratoses).' The possible choices were: 0, 1, 2–4, 5–10 and 11+. To minimize misclassification of outcomes, the eligible cases were Caucasians who reported at least one NMSC and had pathologically confirmed diagnosis of SCC or self-reported BCC in the cohort follow-up questionnaire from 1976 to 2004. In addition, to eliminate potential underlying predilection for malignancy, we excluded individuals with history of malignancy other than NMSC. Exclusion of melanoma further served to eliminate potential confounders, such as increase in surveillance and changes in sun behaviour after a personal diagnosis of melanoma.

To confirm the number of NMSCs in the higher tumour-count groups, a validation study was performed. A random sample of approximately 200 men and women who reported 5–10 and ≥11 NMSCs were contacted by mail and asked for the exact number of tumours removed by surgery, cryotherapy or other means. Results from the first wave of respondents showed a confirmation rate of 92%. In addition, participants were asked for the total number of each type of NMSC (SCC or BCC) removed.

Ascertainment of exposures (covariates)

Risk factor and exposure information was collected in the main questionnaires offered every other year. The following information was collected: (i) natural hair colour (1982 in NHS; 1988 in HPFS); (ii) ability to tan (1982 in NHS; 1992 in HPFS); (iii) family history of melanoma in mother, father, brother or sister (1982, 1992, 1996, 2000, and 2008 in NHS; 1990, 1992, and 2008 in HPFS); (iv) number of nevi (size ≥3 mm) on the left arm, from the shoulder to the wrist (1986 in NHS; 1987 in HPFS); and (v) number of sunburns (1982 in NHS; 1992 in HPFS).

Statistical analysis

For the age-adjusted (5 year categories) and multivariate logistic models, variables were modelled as dichotomous (family history of melanoma and gender) or in categories. We chose the categories based on the original questions asked in 1982 and 1986. Given the large size of our population, we were able to use the category with single life-time NMSC as the reference group to assess the incremental relative risk beyond the initial tumour. We used multinomial logistic regression to evaluate the association between host risk factors and the number of NMSCs, and calculate the relative risk (RR) for each of the three outcome groups

(2–4, 5–10, 11+) compared with the outcome group of one. Ordinal logistic regression models were used to provide the P value for cumulative relative risk (RR) of each risk factor in relation with the risk of multiple NMSCs. To test for trend, we modelled the exposures as ordinal variables. For a given risk factor, a statistically significant cumulative RR indicates a trend of increase in RRs across the tumour strata (2–4 to 11+). All statistical analyses were two-sided and carried out using SAS V9.1 (SAS Institute, Cary, NC, USA).

Results

The characteristics of the NHS and HPFS cohorts are shown in Table 1. Of 61 194 women who satisfied inclusion criteria from the NHS, 11 889 (19.4%) had at least one NMSC; 9% developed a single lifetime NMSC and 10% developed multiple tumours. Among those who reported a history NMSC, 5689 (47.9%) had one, 4674 (39.3%) had two to four, 1143 (9.61%) had five to ten and 383 (3.2%) had eleven or more tumours. Of 19 081 men who satisfied inclusion criteria from the HPFS, 5370 (28.14%) had at least one NMSC; 11% had a single lifetime NMSC, whereas 17% had multiple tumours. Among individuals who reported a history of NMSC, 2061 (38.4%) had one, 2331 (43.4%) had two to four, 741 (13.8%) had five to ten and 237 (4.4%) had eleven or more tumours.

Risks of developing 2–4, 5–10 and ≥11 NMSCs are increased with age, at RRs of 1.12 (95% CI: 1.10–1.15), 1.17 (95% CI: 1.13–1.21) and 1.27 (95% CI: 1.20–1.35) respectively. The age-adjusted and multivariate RRs are presented in Table 2. After mutually adjusting for age, gender, inability-to-tan, number of painful sunburns, number of nevi, natural hair colour and history of melanoma, we found individuals who experience painful burns without the ability-to-tan have a greater risk for developing multiple NMSCs than individuals with the ability-to-tan after sunburn (i.e. ≥11 NMSCs, RR = 1.91, 95% CI: 1.50–2.43 vs. RR = 1.26, 95% CI: 1.00–1.58). Having more than one painful sunburn was associated with development of multiple NMSCs, with the highest association seen with 10 or more sunburns (2–4 NMSCs, RR = 1.24, 95% CI: 1.08–1.42, 5–10 NMSCs, RR = 1.76, 95% CI: 1.40–2.21 and ≥11 NMSCs, RR = 2.33. 95% CI: 1.57–3.46). We found that family history of melanoma was associated with risk of developing multiple NMSCs (2–4 NMSCs, RR = 1.17, 95% CI: 1.03–1.33 and 5–10 NMSCs, RR = 1.24, 95% CI: 1.02–1.50). This association is no longer statistically significant at the highest tumour stratum. Red hair colour was associated with an increased relative risks of developing 2–4, 5–10 and ≥11 NMSCs (RR = 1.29, 95% CI: 1.09–1.53, RR = 1.52, 95% CI: 1.20–1.94, RR = 1.46, 95% CI: 0.99–2.14). Blonde hair colour was also marginally associated with increased risks of developing multiple NMSCs (2–4 NMSCs, RR = 1.15, 95% CI: 1.03–1.28, 5–10 NMSCs, RR = 1.10, 95% CI: 0.92–1.31 and ≥11 NMSCs, RR = 1.38, 95% CI: 1.06–1.81). Number of nevi on the left arm was associated with a significantly higher risk of developing 2–4, 5–10 and ≥11 NMSCs skin cancers (≥6 nevi, RR = 1.26, 95% CI: 1.08–1.48, RR = 1.42, 95% CI: 1.12–1.79 and RR = 1.49, 95% CI: 1.03–2.14).

The age-adjusted and multivariate cumulative relative risks for each risk factor are presented in Table 3. Inability-to-tan showed a positive monotonic trend across increased tumour counts (burn then tan, cumulative RR = 1.19, 95% CI: 1.11–1.28, painful burn, cumulative RR = 1.29, 95% CI 1.18–1.40). Having had 10+ sunburns was associated with a cumulative

RR of 1.21 (95% CI: 1.07–1.36). Similarly, the cumulative relative risk for male gender revealed a positive trend across tumour counts (cumulative RR = 1.53, 95% CI: 1.40–1.66). Family history of melanoma also showed a significant cumulative relative risk across tumour strata (cumulative RR = 1.15, 95% CI: 1.03–1.28). Although having black or light brown hair did not show a significant positive association uniformly across the tumour strata, blonde and red hair phenotypes demonstrated significant monotonic positive association (blonde hair, cumulative RR = 1.12, 95% CI: 1.02–1.24, red hair, cumulative RR = 1.23, 95% CI: 1.07–1.42). Similarly, having 1–2, 3–5 and 6+ nevi on the left arm are cumulatively significant across increasing number of NMSCs (1–2 nevi, cumulative RR = 1.11, 95% CI: 1.03–1.20, 3–5 nevi, cumulative RR = 1.14, 95% CI: 1.02–1.27, ≥6 nevi, cumulative RR = 1.22, 95% CI: 1.07–1.40).

Discussion

This research has described the incremental risk factors for the development of NMSCs. The results confirmed and elaborated upon the risk factors found in a Dutch cohort of 10 994 individuals with multiple BCCs.11 Specifically, this study differed from the Dutch cohort in its exclusion of any individual with history malignancies, inclusion of SCC, and a larger study population size. In addition to risk factors uncovered in the Dutch study, we found that male gender, inability-to-tan, number of painful sunburns, number of nevi, red/blonde hair colour and positive family history of melanoma are independent risk factors for the development of multiple NMSCs. Of these risk factors, male gender and having ≥10 painful sunburns were most likely to be seen in those with higher tumour count. One advantage of the occupational cohort model is the elimination of potential variations in occupational sun exposure. However, unlike the Dutch cohort, in this study, we were unable to use education level as an exposure variable, given that cohort members were health-care workers with similar educational background.

Skin pigmentation is understood as the product of two intrinsic mechanisms. The first is the basic skin colour of an individual, which derives from constitutive melanin expression. The second is the ability to tan, which is the product of inducible melanogenesis. Skin cancer rate is lowest amongst individuals with high levels of constitutive and inducible black/brown (eumelanin) pigmentation. Melanin pigmentation protects against photo-damage directly by absorbing ultraviolet (UV) photons and UV-generated free radicals,[12–14] contributing to epidermal photo-protection.[15] In addition, individuals who tan easily have more efficient DNA repair responses than individuals who do not.[16, 17] The amount of melanogenesis can serve as a litmus indicator for epidermal DNA repair. Individuals with low constitutive and facultative pigmentation have decreased photo-protection against photo-damage of cells in the epidermis, including keratinocytes and basal cells. The number of sunburns an individual experiences in a lifetime can serve as a surrogate for the amount of genetic insults that exceeds the immediate repair abilities of the skin. Not surprisingly, in this study, both ‘inability-to-tan’ and ‘number of sunburns’ are found to have a strong monotonic positive association with increasing number of NMSCs.

Our results showed a significant trend of increased risk of multiple NMSCs with family history of melanoma, independent of pigmentation traits. These results would suggest that

there are other factors contributing to this association beyond our current understanding. These results suggest that there are non-pigmentary genes that predisposes to both melanoma and NMSC development. However, there is likely to be a behavioural component as well. For instance, parents who believed in the health benefits of sun exposure may be less likely to apply sunblock on their children, resulting in increased sun exposure during critical periods in these individuals. In addition, children of parents who do not practice sun-protection may behave similarly as adults. Interestingly, after controlling for pigmentary characteristics, family history of melanoma was found to be a risk factor for the developing of 2–4 and 5–10 NMSCs, but not for the 11+ group. The cumulative RR, the trend test across the tumour-count groups was marginally significant at RR of 1.15 (95% CI: 1.03–1.28), which suggests that the RRs increase significantly from lowest tumour count group to the highest. The loss of significance in the highest tumour count group may be due to the limited number of individuals in the 11+ group. Albeit unlikely, it is also possible that those who develop 11+ NMSC are phenotypically and genotypically different to those who are at risk for melanoma. As the two types of skin cancer arise from different cell lineages, those at extreme risk of NMSC (11+ tumours) may not have a familial risk for melanoma.

There are several limitations to our study. One major limitation is that the outcomes are based on self-report. However, these two cohorts of health-care professionals are more likely to have a basic understanding of skin cancer types (melanoma, SCC and BCC), and the distinction between precancerous (i.e. atypical nevi, actinic keratosis) and cancerous lesions than the general population. Furthermore, all cases of SCC and melanoma have been confirmed through reviews of primary pathology reports. Another limitation to our study is that participants were not a random sample of US men and women, although it is unlikely that the intrinsic biological mechanisms of cancer development among participants in the NHS and HPFS differ from those of the general population. Finally, a major limitation of this study is that we did not have sufficient information to differentiate multiple BCCs from SCCs. It is important to note that as the BCC incidence is higher compared with SCC incidence in the general population with the exact ratio varying with latitude of inhabitance.18 BCC also has a much higher incidence rate and tendency for relapsing than SCC.2 A random sample of individuals in our population who had five or more lifetime NMSCs reported a BCC to SCC ratio of 2.3–1. However, host and host risk factors are generally shared for both SCC and BCC, which suggests common underlying predisposition for developing NMSC.

One advantage of this study is its ability to evaluate the incremental increase in risk above the first primary NMSC. BCC and SCC can be locally destructive and have a predilection for the face. Minimizing tissue destruction in these areas has important implications in patient self-perception and quality of life. Although BCC and SCC are relatively easy to treat and are highly curable, the importance of primary and secondary prevention is nevertheless important in those with the highest tumour burden. Improved understanding of the host risk factors for NMSC development will allow physicians to identify the individuals who are at the greatest risk of multiple tumours. Early detection will reduce morbidity with some albeit minimal impact on mortality. Identification of individuals at high risk for development of multiple lesions allows for dedicated effort for disease prevention and screening.

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Table 1

Characteristics of NHS and HPFS participants by outcome stratum

	1 NMSC	2–4 NMSCs	5–10 NMSCs	‡11 NMSCs
Total participants – no.(%)				
NHS (n = 61 194*)	5689 (9†)	4674 (8)	1143 (2)	383 (1)
HPFS (n = 19 081*)	2061 (11)	2331 (12)	741 (4)	237 (1)
6+ Nevi on left arm – no. (%)				
NHS	9179 (15)	10 403 (17)	11 015 (18)	11 627 (19)
HPFS	1546 (13)	1783 (15)	1783 (15)	1546 (13)
Painful Burn/blistering sunburns‡ – no. (%)				
NHS	9791 (16)	12 851 (21)	15 910 (26)	18 358 (30)
HPFS	3210 (27)	3686 (31)	4399 (37)	5350 (45)
Red or blonde natural hair colour§ – no. (%)				
NHS	11 015 (18)	14 075 (23)	15 299 (25)	15 910 (26)
HPFS	1664 (14)	1902 (16)	2140 (18)	2616 (22)
History of 10+ severe sunburn – no. (%)				
NHS	26 925 (44)	31 821 (52)	36 104 (59)	39 776 (65)
HPFS	2853 (24)	3091 (26)	3567 (30)	4518 (38)
Prevalence of melanoma cases – no. (%)				
NHS	612 (1)	1224 (2)	2448 (4)	1836 (3)
HPFS	119 (1)	238 (2)	476 (4)	357 (3)
Family history of melanoma – no. (%)				
NHS	4896 (8)	6119 (10)	6119 (10)	6731 (11)
HPFS	594 (5)	594 (5)	713 (6)	476 (4)

*Total number of individuals in NHS or HPFS who satisfied the inclusion criteria of no prior malignancies.

†Percentage of total population who satisfied the inclusion criteria.

‡Sun reaction after 2 h of sun exposure during childhood.

§Natural adult hair colour at age 20.

Table 2

Age-adjusted and multivariate* RR of constitutional risk factors for multiple non-melanoma skin cancers

		1 NMSC	2–4 NMSCs	5–10 NMSCs	11+ NMSCs
Age	Age only	1.00	1.11 (1.08–1.13)	1.14 (1.10–1.18)	1.22 (1.15–1.29)
	MV adjusted	1.00	1.12 (1.10–1.15)	1.17 (1.13–1.21)	1.27 (1.20–1.35)
Male	Age adjusted	1.00	1.61 (1.47–1.75)	2.14 (1.88–2.44)	2.36 (1.92–2.89)
	MV adjusted	1.00	1.65 (1.49–1.82)	2.28 (1.96–2.64)	2.75 (2.18–3.47)
Skin reaction to the sun (ref. tan)					
Burn then tan	Age adjusted	1.00	1.29 (1.18–1.40)	1.40 (1.23–1.60)	1.55 (1.24–1.93)
	MV adjusted	1.00	1.20 (1.10–1.30)	1.24 (1.08–1.42)	1.26 (1.00–1.58)
Painful burn	Age adjusted	1.00	1.53 (1.39–1.68)	2.08 (1.81–2.39)	2.79 (2.24–3.48)
	MV adjusted	1.00	1.34 (1.21–1.48)	1.63 (1.40–1.90)	1.91 (1.50–2.43)
Number of severe sunburns (ref. none)					
1–2	Age adjusted	1.00	0.95 (0.81–1.11)	1.06 (0.81–1.37)	0.89 (0.55–1.45)
	MV adjusted	1.00	0.92 (0.79–1.08)	1.02 (0.78–1.33)	0.84 (0.52–1.36)
3–5	Age adjusted	1.00	1.08 (0.94–1.24)	1.34 (1.06–1.70)	1.44 (0.95–2.19)
	MV adjusted	1.00	1.02 (0.89–1.18)	1.24 (0.97–1.57)	1.29 (0.85–1.96)
6–9	Age adjusted	1.00	1.22 (1.05–1.41)	1.50 (1.18–1.92)	1.71 (1.12–2.62)
	MV adjusted	1.00	1.12 (0.97–1.30)	1.33 (1.04–1.70)	1.45 (0.94–2.22)
10+	Age adjusted	1.00	1.44 (1.27–1.64)	2.24 (1.80–2.79)	3.18 (2.17–4.66)
	MV adjusted	1.00	1.24 (1.08–1.42)	1.76 (1.40–2.21)	2.33 (1.57–3.46)
Family history of melanoma (ref. no)					
Yes	Age adjusted	1.00	1.19 (1.05–1.35)	1.27 (1.05–1.54)	1.27 (0.93–1.73)
	MV adjusted	1.00	1.17 (1.03–1.33)	1.24 (1.02–1.50)	1.23 (0.90–1.69)
Natural hair colour (ref. dark brown hair)					
Black	Age adjusted	1.00	0.94 (0.78–1.14)	0.96 (0.72–1.28)	0.80 (0.48–1.35)
	MV adjusted	1.00	0.94 (0.78–1.14)	0.96 (0.72–1.29)	0.82 (0.49–1.38)
Light brown	Age adjusted	1.00	1.10 (1.02–1.19)	1.10 (0.97–1.24)	1.30 (1.06–1.61)
	MV adjusted	1.00	1.06 (0.97–1.14)	1.02 (0.90–1.15)	1.17 (0.95–1.44)

		1 NMSC	2–4 NMSCs	5–10 NMSCs	11+ NMSCs
Blonde	Age adjusted	1.00	1.25 (1.12–1.40)	1.26 (1.07–1.50)	1.69 (1.30–2.21)
	MV adjusted	1.00	1.15 (1.03–1.28)	1.10 (0.92–1.31)	1.38 (1.06–1.81)
Red	Age adjusted	1.00	1.53 (1.29–1.80)	2.06 (1.64–2.59)	2.26 (1.56–3.27)
	MV adjusted	1.00	1.29 (1.09–1.53)	1.52 (1.20–1.94)	1.46 (0.99–2.14)
Nevi on left arm (ref. none)					
1–2	Age adjusted	1.00	1.13 (1.04–1.24)	1.04 (0.91–1.19)	1.15 (0.92–1.43)
	MV adjusted	1.00	1.13 (1.04–1.23)	1.04 (0.91–1.20)	1.15 (0.92–1.44)
3–5	Age adjusted	1.00	1.16 (1.02–1.31)	1.12 (0.92–1.36)	1.10 (0.79–1.53)
	MV adjusted	1.00	1.15 (1.01–1.30)	1.11 (0.91–1.36)	1.08 (0.78–1.51)
6+	Age adjusted	1.00	1.30 (1.11–1.52)	1.48 (1.18–1.87)	1.59 (1.11–2.29)
	MV adjusted	1.00	1.26 (1.08–1.48)	1.42 (1.12–1.79)	1.49 (1.03–2.14)

* Multivariate regression for a given exposure of interest uses all other exposures as covariates

Table 3

Multivariate* cumulative relative risk of multiple skin cancers

	Age-adjusted	P-value	MV Adjusted	P-value
Skin reaction to the sun				
Burn then tan	1.27 (1.18–1.36)	<0.0001	1.19 (1.11–1.28)	<0.0001
Painful burn	1.45 (1.34–1.56)	<0.0001	1.29 (1.18–1.40)	<0.0001
Number of severe sunburns				
1–2 burns	0.96 (0.83–1.10)	0.56	0.94 (0.82–1.08)	0.38
3–5 burns	1.07 (0.95–1.22)	0.26	1.03 (0.91–1.16)	0.69
6–9 burns	1.19 (1.05–1.36)	0.0062	1.11 (0.98–1.26)	0.11
10+ burns	1.38 (1.23–1.55)	<0.0001	1.21 (1.07–1.36)	0.002
Family history of melanoma				
Yes	1.17 (1.05–1.30)	0.006	1.15 (1.03–1.28)	0.013
Male gender				
Yes	1.22 (1.18–1.27)	<0.0001	1.53 (1.40–1.66)	<0.0001
Natural hair colour				
Black	0.95 (0.81–1.12)	0.56	0.95 (0.81–1.13)	0.57
Light brown	1.09 (1.02–1.17)	0.016	1.05 (0.98–1.12)	0.21
Blonde	1.21 (1.10–1.33)	<0.0001	1.12 (1.02–1.24)	0.02
Red	1.42 (1.23–1.63)	<0.0001	1.23 (1.07–1.42)	0.005
Nevi on left arm				
1–2 nevi	1.11 (1.03–1.20)	0.005	1.11 (1.03–1.20)	0.005
3–5 nevi	1.14 (1.02–1.27)	0.02	1.14 (1.02–1.27)	0.025
6+ nevi	1.25 (1.09–1.43)	0.001	1.22 (1.07–1.40)	0.004

*Multivariate regression for a given exposure of interest uses all other exposures as covariates.