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Risk factors for skin cancers: a nested case–control study within the Nurses' Health Study

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Background Constitutional factors and sun exposure are associated with skin cancer risk. However, these relations are complex and differ according to skin cancer type.

Methods We examined the associations of constitutional risk factors and sun exposure with the risks of three types of skin cancer simultaneously and evaluated the interaction between constitutional susceptibility and sun exposure in a nested case–control study within the Nurses' Health Study [200 melanoma, 275 squamous cell carcinoma (SCC), and 283 basal cell carcinoma (BCC) cases, and 804 controls]. Information regarding skin cancer risk factors was obtained from the retrospective supplementary questionnaire.

Results Constitutional susceptibility was an independent risk factor for all three types of skin cancer. Sunlamp usage or tanning salon attendance was a risk factor for melanoma after adjusting for potential confounding variables (OR for ever vs never usage, 2.06, 95% CI 1.30–3.26). Higher sun exposure while wearing a bathing suit was an independent risk factor for all three types of skin cancer. We observed a significant interaction between constitutional susceptibility and sun exposure while wearing a bathing suit on melanoma risk (*P*, interaction, 0.03); women with the highest susceptibility and highest exposure had an OR of 8.37 (95% CI 3.07–22.84). This interaction was weaker and non-significant for SCC and BCC.

Conclusions These data largely confirm past studies on risk factors for skin cancer but provide evidence of difference on the strength of these risk factors for melanoma compared with SCC and BCC.

Keywords constitutional susceptibility, sun exposure, skin cancer

Skin cancer is the most common form of cancer in the US and accounts for ~1 million new cases per year, including ~55 000 cases of cutaneous malignant melanoma (hereafter called melanoma).[1,2] There are three major types of skin cancer. Melanoma is the most fatal form. The most common type of non-melanoma skin cancer is basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC). The carcinogenic effects of sunlight exposure have been demonstrated in the aetiology of both melanoma and non-melanoma skin cancers.[3–7] Although certain host factors and sun exposure are thought to be associated with the development of skin cancer, the relations are complex and may differ according to the type of skin cancer. Risk factors for melanoma have been evaluated previously.[8–11] Few studies have directly compared risk factors for melanoma and non-melanoma skin cancers.[12,13] Previous epidemiological studies have suggested that melanoma and BCC arise from intermittent sun exposure and childhood sun exposure,[14] whereas SCC has been associated with cumulative sun exposure.[3,15] In addition, it remains unclear how constitutional susceptibility and sun exposure interact to determine

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skin cancer risk. The purpose of the study was to examine the associations of constitutional risk factors and sun exposure and their interactions with the risks of the three types of skin cancer simultaneously in a nested case–control study within the Nurses' Health Study (NHS) cohort.

Methods

Study population

The NHS was established in 1976, when 121 700 female registered nurses between the ages of 30 and 55 completed a self-administered questionnaire on their medical histories and baseline health-related exposures. Updated information has been obtained by questionnaires every 2 years. Between 1989 and 1990, blood samples were collected from 32 826 of the cohort members. Because the aims of our research included the evaluation of DNA-based markers of susceptibility, the baseline of the study was the blood collection in 1989–90. Eligible cases in this study consisted of Caucasian women with incident skin cancer from the subcohort who gave a blood specimen, including SCC and BCC cases with a diagnosis anytime after blood collection up to 1 June 1998 and melanoma cases up to 1 June 2000. All the cases had no previously diagnosed skin cancer. All available pathologically confirmed melanoma and SCC cases and 300 self-reported BCC cases randomly selected from about 2600 available self-reported BCC cases were included. The validity of self-report of BCC is high in this medically sophisticated population (90%).[16] A common control series (case : control = 1:1) was randomly selected from participants who gave a blood sample and were free of diagnosed skin cancer up to and including the questionnaire cycle in which the case was diagnosed. One control was matched to each case by year of birth (±1 year). At the time we selected cases and controls, 47 cases (19 melanoma, 11 SCC, and 17 BCC) and 69 controls were deceased. As we wished to obtain additional information by supplementary questionnaire, we randomly selected a second matched living control when the first control was deceased. The nested case–control study consisted of 200 melanoma cases, 275 SCC cases, 283 BCC cases, and 804 matched controls. We mailed to 758 living cases and 804 living controls a supplementary questionnaire on lifetime sun exposure and other skin cancer risk factors. In total, 695 cases responded, 15 cases refused to participate, and 48 cases did not respond after three mailings (participation rate = 92%). Among controls, 713 responded, 9 refused, and 82 did not respond (participation rate = 89%). The study protocol was approved by the Committee on Use of Human Subjects of the Brigham and Women's Hospital, Boston, MA.

Exposure data

Information regarding skin cancer risk factors was obtained from the retrospective supplementary questionnaire. The retrospective supplementary questionnaire was collected in 2002 and consisted of questions in three major areas: (i) pigmentation, constitutional, and susceptibility factors, such as skin colour, hair colour, childhood tendency to burn or tan, and the number of palpably raised moles on arms; (ii) history of residence (states and towns), sun exposure habits, and severe sunburns at different ages (during childhood and adolescence and then by decade of adult life up to date of questionnaire return); and (iv) family history of skin cancer (father, mother, and siblings). In addition, the 11 states of residence of cohort members at baseline were grouped into three regions: Northeast (Connecticut, Massachusetts, Maryland, New Jersey, New York, and Pennsylvania), Northcentral (Michigan and Ohio), and West and South (California, Texas, and Florida).

In order to estimate sunlight exposure for each subject, an ultraviolet (UV) database for 50 US states was developed. The database used reports from the Climatic Atlas of the US, which reported mean daily solar radiation (in Langleys) at the earth's surface for weather stations around the country.[17] The records of average annual solar radiation for January and July were extracted to represent winter and summer radiation, respectively. The mean solar radiation for each individual's past (at different age categories) and current residences was derived from the UV values measured at the nearest weather station. Both summer (Us) and winter (Uw) radiation indices were developed for the residence of each age category. A cumulative lifetime sun exposure was developed by combining the residence-linked UV value and hours spent outdoors at difference age categories obtained from the supplementary questionnaire. For example, we defined a cumulative lifetime intermittent (recreational) sun exposure variable for this behaviour as follows: in each age category (Y represents the number of years in each age category), we asked questions about average frequency and duration of sun exposure while wearing a bathing suit per year in summer (Fs and Ds represent average frequency and duration in summer, respectively) and in winter (Fw and Dw represent average frequency and duration in winter, respectively). For each age category, an individual's sun exposure for such behaviour was equal to ($Us*Fs*Ds*Y + Uw*Fw*Dw*Y$). We summed up this variable for each age category as a cumulative lifetime sun exposure while wearing a bathing suit.

Statistical methods

Unconditional logistic regression was employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the risk of each type of skin cancer compared with the common control series. Tests for trend were calculated when appropriate to assess the effects of multiple levels of exposure. To summarize multiple variables, we constructed a multivariate confounder score to create a constitutional susceptibility score for each type of skin cancer.[18] Briefly, we applied the logistic regression coefficients from a multivariate model including age, natural skin colour, natural hair colour, child or adolescent tendency to burn, and the number of palpably raised moles on arms, to each individual's values for the latter four of these variables and summed the values to compute a susceptibility risk score in the logit scale. We used this score to define women with low, intermediate, and high constitutional susceptibility based on tertiles among controls. We performed a statistical comparison of risk factors for the three types of skin cancer using polychotomous logistic regression models.[19] This programme provides formal tests of the differences in magnitude of the beta estimate of each risk factor for the outcome categories.

In the interaction analyses, the constitutional susceptibility score and cumulative sun exposure while wearing a bathing suit were categorized into tertiles with cutpoints based on the distribution of controls. We modelled these two variables as categorical variables and used the likelihood ratio test to compare nested models that included terms for all combinations of these two risk factors with the models with indicator variables for the main effects only. All *P*-values were two-sided.

We examined potential recall bias by comparing the individual responses to three questions with the same wording asked in both the 1982 prospective questionnaire and the 2002 retrospective supplementary questionnaire (natural hair colour, childhood or adolescent tendency to tan after repeated sun exposure, and childhood or adolescence tendency to burn after two or more hours of sunlight exposure).[20] The reliability between two responses was measured by the Kappa statistics. The shift of the absolute level of the responses to these three questions after the diagnosis was measured by mean change. The age-adjusted ORs were shown to illustrate the impact of recall bias for these variables.

Results

Constitutional risk factors of skin cancer

At the beginning of the follow-up of this nested case–control study, the nurses were between 43 and 68 years of age with the mean age of 58.7 years. The mean age at incident diagnosis of melanoma cases was 63.4 years and that of SCC cases and BCC cases was 64.7 and 64.0 years, respectively. The constitutional risk factors for skin cancer are shown in Table 1. Women with fair skin colour or red hair colour were more likely to be diagnosed with skin cancer, particularly melanoma, compared with those with darker pigmentation. Cases of each type of skin cancer had greater childhood or adolescence tendency to burn and less tendency to tan. Cases of each type of skin cancer, especially melanoma, were more likely to have more moles on arms than controls.

We created a constitutional susceptibility score to summarize these constitutional risk factors (Table 2). The association of tendency to tan with skin cancer risk was abolished after the above constitutional risk factors were mutually adjusted for, and, therefore, it was not integrated into the constitutional susceptibility score. Higher score predicted higher risk of skin cancer according to the combined effect of lighter natural skin colour, lighter natural hair colour, greater childhood or adolescent tendency to burn, and more moles. Each component contributed to the score to a different extent. For example, women with six or more moles on arms had an age-adjusted OR of 3.53 (95% CI 2.01–6.19) for melanoma risk. Red hair colour was strongly associated with melanoma risk in our study (age-adjusted OR, 4.74; 95% CI 2.47–9.09). The other two components of the score, i.e. natural skin colour and childhood or adolescent tendency to burn had risk estimates of ~2 for melanoma. The risk for the highest tertile of the susceptibility score was ~3.5-fold for melanoma, and 3-fold for SCC and BCC, compared with the lowest tertile. The ORs for constitutional susceptibility score slightly changed but remained significant in multivariate models (Table 2); and this variable significantly increased the goodness-of-fit of the model for three cancer types.

Table 1 Constitutional risk factors for skin cancer in this case–control study nested within the Nurses' Health Study

	Melanoma (n = 200) n (%)	SCC (n = 275) n (%)	BCC (n = 283) n (%)	Common controls (n = 804) n (%)
Natural skin colour				
Fair	125 (68.3)	156 (61.7)	159 (61.9)	348 (49.0)
Medium	56 (30.6)	92 (36.4)	94 (36.6)	320 (45.1)
Olive	2 (1.1)	5 (2.0)	4 (1.6)	42 (5.9)
Natural hair colour				
Black or dark brown	58 (31.9)	102 (40.3)	82 (31.8)	302 (42.5)
Light Brown	73 (40.1)	93 (36.8)	114 (44.2)	300 (42.2)
Blonde	29 (15.9)	44 (17.4)	49 (19.0)	85 (12.0)
Red	22 (12.1)	14 (5.5)	13 (5.1)	24 (3.4)
Skin reaction to 2 or more hours of sunlight in childhood or adolescence (tendency to burn)				
Practically none	12 (6.6)	12 (4.8)	17 (6.7)	92 (13.0)
Some redness only	62 (33.9)	94 (37.3)	82 (32.2)	327 (46.3)
Burn	72 (39.3)	81 (32.1)	91 (35.7)	201 (28.4)
Painful burn	37 (20.2)	65 (25.8)	65 (25.5)	87 (12.3)
Skin tan after repeated sun exposure in childhood or adolescence (tendency to tan)				
Practically none	42 (23.3)	47 (18.7)	42 (16.4)	101 (14.2)
Light tan	53 (29.4)	83 (32.9)	79 (30.9)	189 (26.7)
Average tan	65 (36.1)	98 (38.9)	107 (41.8)	323 (45.6)
Deep tan	20 (11.1)	24 (9.5)	28 (10.9)	96 (13.5)
Palpably raised moles on arms				
None	73 (47.4)	132 (59.5)	124 (53.9)	388 (61.3)
1–2	35 (22.7)	51 (23.0)	59 (25.7)	148 (23.4)
3–5	20 (13.0)	21 (9.5)	28 (12.2)	59 (9.3)
⩾6	26 (16.9)	18 (8.1)	19 (8.3)	38 (6.0)

The percentages may not add up to 100 due to rounding. The numbers do not add up to total due to missing values.

Sunlight exposure and other risk factors of skin cancer

Sunlight exposure and other risk factors of skin cancer are presented in Table 2. In age-adjusted models, family history of skin cancer, the number of lifetime severe sunburns, and cumulative sun exposure while wearing a bathing suit were significantly associated with all three types of skin cancer. A family history of skin cancer remained significant for the three types of skin cancer in multivariate models. Furthermore, melanoma risk was associated with both family history of melanoma (OR, 1.81; 95% CI 0.99–3.29) and that of non-melanoma skin cancer (OR, 1.49; 95% CI 0.99–2.25). For the risks of SCC and BCC, neither of them was associated with family history of melanoma (OR for SCC, 1.17; 95% CI 0.67–2.02; OR for BCC, 1.04; 95% CI 0.60–1.81). Family history of non-melanoma skin cancer was associated with the risks of SCC (OR, 1.86; 95% CI 1.29–2.68) and BCC (OR, 2.65; 95% CI 1.86–3.76).

For the number of lifetime severe sunburns that blistered, compared with the age-adjusted ORs, the multivariate ORs

Table 2 Risk factors for skin cancer in this case–control study nested within the Nurses' Health Study

	Melanoma n = 200			SCC n = 275			BCC n = 283			Common controls n = 804	
	n (%)	Age-adjusted OR[a]	Multivariate OR[b]	n (%)	Age-adjusted OR[a]	Multivariate OR[b]	n (%)	Age-adjusted OR[a]	Multivariate OR[b]	n (%)	P, for heterogeneity[c]
Constitutional susceptibility score (tertile)[d]											
Low	32/270[e]	1.00	1.00	55/278	1.00	1.00	52/267	1.00	1.00		
Intermediate	62/299	1.74 (1.10–2.75)	1.65 (0.99–2.76)	76/265	1.47 (1.00–2.16)	1.67 (1.05–2.65)	75/270	1.43 (0.96–2.11)	1.40 (0.90–2.19)		
High	106/235	3.67 (2.37–5.66)	3.26 (2.05–5.21)	144/261	2.89 (2.02–4.13)	3.15 (2.01–4.94)	156/267	2.99 (2.09–4.28)	2.72 (1.85–4.00)		
Trend		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		
LRT[f]			<0.001				<0.001		<0.001		
Family history of skin cancer											0.20
No	92 (54.4)	1.00	1.00	132 (56.4)	1.00	1.00	114 (47.7)	1.00	1.00	468 (68.5)	
Yes	77 (45.6)	1.72 (1.22–2.44)	1.53 (1.05–2.23)	102 (43.6)	1.72 (1.27–2.35)	1.50 (1.08–2.08)	125 (52.3)	2.43 (1.79–3.29)	2.05 (1.49–2.81)	215 (31.5)	
LRT			0.01			0.009			<0.001		
Sunlamp use or tanning salon attendance											0.15
No	140 (76.9)	1.00	1.00	212 (83.8)	1.00	1.00	215 (83.0)	1.00	1.00	625 (87.8)	
Yes	42 (23.1)	1.98 (1.30–3.02)	2.06 (1.30–3.26)	41 (16.2)	1.47 (0.98–2.22)	1.44 (0.93–2.24)	44 (17.0)	1.45 (0.97–2.16)	1.32 (0.87–2.03)	87 (12.2)	
LRT			0.01			0.24			0.35		
Lifetime severe sunburns which blistered											0.43
None	29 (17.1)	1.00	1.00	46 (20.0)	1.00	1.00	49 (20.1)	1.00	1.00	231 (34.5)	
1–4	48 (28.2)	1.63 (0.99–2.68)	1.43 (0.85–2.42)	80 (34.8)	1.85 (1.23–2.79)	1.65 (1.08–2.53)	82 (33.6)	1.70 (1.14–2.54)	1.38 (0.90–2.11)	226 (33.7)	
5–9	33 (19.4)	2.57 (1.48–4.48)	1.75 (0.97–3.16)	46 (20.0)	2.47 (1.53–3.98)	1.88 (1.14–3.11)	49 (20.1)	2.33 (1.47–3.71)	1.55 (0.95–2.55)	98 (14.6)	
⩾10	60 (35.3)	3.90 (2.36–6.47)	2.24 (1.30–3.84)	58 (25.2)	2.72 (1.73–4.29)	1.67 (1.02–2.72)	64 (26.2)	2.62 (1.69–4.06)	1.37 (0.84–2.21)	115 (17.2)	
Trend		<0.001	0.003		<0.001	0.04		<0.001	0.15		
LRT			0.04			0.01			0.37		
Cumulative sun exposure while wearing a bathing suit (tertile)											0.15
Low	37 (20.6)	1.00	1.00	58 (23.7)	1.00	1.00	55 (21.5)	1.00	1.00	227 (33.2)	
Intermediate	47 (26.1)	1.25 (0.78–2.00)	1.20 (0.73–1.97)	74 (30.2)	1.28 (0.87–1.90)	1.28 (0.85–1.93)	92 (35.9)	1.66 (1.13–2.43)	1.71 (1.14–2.56)	228 (33.4)	
High	96 (53.3)	2.58 (1.69–3.94)	2.37 (1.51–3.73)	113 (46.1)	1.97 (1.37–2.85)	2.15 (1.45–3.19)	109 (42.6)	1.95 (1.34–2.83)	2.05 (1.38–3.06)	228 (33.4)	
Trend		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		
LRT			<0.001			<0.001			<0.001		
Geographic region at baseline											0.18
Northeast	119 (59.5)	1.00	1.00	141 (51.3)	1.00	1.00	141 (49.8)	1.00	1.00	448 (55.7)	
Northcentral	35 (17.5)	0.74 (0.49–1.12)	0.75 (0.48–1.17)	48 (17.5)	0.83 (0.57–1.20)	0.82 (0.56–1.21)	58 (20.5)	1.00 (0.70–1.43)	1.04 (0.71–1.51)	182 (22.6)	
West and South	46 (23.0)	1.08 (0.74–1.60)	1.08 (0.72–1.64)	86 (31.3)	1.54 (1.12–2.14)	1.50 (1.07–2.12)	84 (29.7)	1.56 (1.13–2.17)	1.65 (1.17–2.34)	174 (21.6)	
LRT			0.32			0.01			0.01		

The percentages may not add up to 100 due to rounding. The numbers do not add up to total due to missing values.

[a] Unconditional logistic regression adjusted for age.

[b] Unconditional logistic regression adjusted for age and risk factors listed in Table 2.

[c] P-value was generated using polychotomous logistic tests in multivariate models.

[d] We constructed a multivariate confounder score to create a constitutional susceptibility score for each type of skin cancer. We summed natural skin colour, natural hair colour, child or adolescent tendency to burn, and the number of palpably raised moles on arms to compute a susceptibility risk score in the logit scale.

[e] The number of cases and controls

[f] Likelihood ratio test of the goodness fit of the model for each variable.

were substantially attenuated, mainly due to inclusion of the constitutional susceptibility score, but remained significant in each category for SCC and in the highest category for melanoma. Sunlamp usage or tanning salon attendance (ever vs never) was a risk factor for melanoma, and the association remained significant in the multivariate models. There was no apparent dose–response relation between the frequency of usage and melanoma risk with multivariate ORs of 2.06 (95% CI 1.15–3.68) for less than 10 times and 2.05 (95% CI 1.08–3.90) for 10 or more times. There were non-significant associations of sunlamp usage or tanning salon attendance with increased risks of SCC and BCC. Cumulative sun exposure while wearing a bathing suit remained a significant risk factor for the three types of skin cancers in the multivariate models, and the multivariate ORs were similar to those in age-adjusted models. This variable significantly increased the goodness-of-fit of the model for three cancer types. Among controls, women who had higher cumulative sun exposure while wearing a bathing suit were more likely to use a sunlamp or attend a tanning salon (*P*, Chi-square, 0.03). Women in the West and South regions were significantly more likely to be diagnosed with SCC or BCC compared with those in Northeast, but residence in the West and South was not associated with melanoma risk in both age-adjusted and multivariate models. Overall, there was no statistically significant difference in risks associated with these variables for each type of skin cancer in multivariate models, according to the heterogeneity test.

Table 3 Interaction between constitutional susceptibility score and sun exposure with a bathing suit on melanoma risk

Susceptibility score (tertile)	Sun exposure with a bathing suit (tertile) Low	Intermediate	High
Low			
Cases (%)	5 (20.0)	12 (48.0)	8 (32.0)
Controls (%)	62 (27.9)	70 (31.5)	90 (40.5)
OR (95% CI)	1.00	1.92 (0.63–5.90)	0.97 (0.30–3.16)
Intermediate			
Cases (%)	11 (21.2)	12 (23.1)	29 (55.8)
Controls (%)	78 (33.3)	86 (36.8)	70 (29.9)
OR (95% CI)	1.73 (0.56–5.32)	1.39 (0.46–4.23)	4.13 (1.47–11.61)
High			
Cases (%)	21 (20.4)	23 (22.3)	59 (57.3)
Controls (%)	87 (38.3)	72 (31.7)	68 (30.0)
OR (95% CI)	2.65 (0.93–7.60)	3.02 (1.06–8.62)	8.37 (3.07–22.84)

P, interaction, 0.03.

Unconditional logistic regression adjusted for age, family history of skin cancer, the number of lifetime severe sunburns which blistered (none, 1–5, 6–11, >11), sunlamp use or tanning salon attendance (yes/no), and geographic region. The percentages may not sum to 100 due to rounding.

Interaction between constitutional susceptibility score and sun exposure while wearing a bathing suit

We evaluated interactions between the constitutional susceptibility score and sun exposure while wearing a bathing suit on skin cancer risk. We observed a significant interaction for melanoma risk (*P*, interaction, 0.03) (Table 3). Compared with women with the lowest constitutional susceptibility score and the lowest level of sun exposure while wearing a bathing suit, those with the highest constitutional susceptibility score and the highest level of sun exposure while wearing a bathing suit had a significantly increased risk of melanoma (OR, 8.37; 95% CI 3.07–22.84). Controls with high constitutional susceptibility were less likely to have prolonged sun exposure while wearing a bathing suit compared with those with low constitutional susceptibility (*P*, Chi-square, 0.04). No statistically significant interactions were found for the risks of SCC (*P*, interaction, 0.52) and BCC (*P*, interaction, 0.20).

Assessment of recall bias

We had the opportunity to examine recall bias as we had prospectively and retrospectively obtained questionnaire data for a subset of variables (Table 4). Overall, the reliability of the responses on natural hair colour and childhood or adolescence tendency to tan was high, whereas the reliability of childhood or adolescence tendency to burn assessment was lower. We found no notable difference in the reproducibility correlations for the three variables between cases and controls. As shown in Table 4, the magnitude of absolute shift was similar among cases and controls, except for tendency to burn among SCC and BCC cases, for which cases retrospectively reported increased tendency to burn to a greater extent compared with controls. As a result, the ORs for tendency to burn based on retrospective data were relatively larger than those on prospective data for SCC and BCC.

Discussion

We examined the associations of constitutional risk factors and sun exposure and their interactions with the risks of the three types of skin cancer simultaneously in a nested case–control study within the Nurses' Health Study (NHS) cohort. The risks associated with the constitutional susceptibility score slightly changed but remained significant in multivariate models controlling for other exposure variables. This suggests that the constitutional susceptibility is an independent risk factor for all three types of skin cancer.

Sunburn at any age has been shown to be associated with an increased risk of melanoma.[14,21,22] The lifetime sunburn variable combines exposure intensity and biological response to sun exposure. We observed significant associations of the number of severe sunburns with three types of skin cancer in the age-adjusted models. The attenuation of the associations in the multivariate models indicated that the skin cancer risk attributed to severe sunburns was partially explained by other variables, particularly the constitutional susceptibility score. However, even though attenuated, this association remained significant in the multivariate models for melanoma and SCC, suggesting the number of lifetime severe sunburns may be an independent risk factor.

The usage of indoor tanning devices was previously associated with an increased risk of melanoma in several studies.[23,24] Even though most of the studies, including ours, performed retrospective assessment, it was reported recently

Table 4 Assessment of recall bias[a]

	Natural hair colour	Skin tan after repeated sun exposure in childhood or adolescence (tendency to tan)	Skin reaction to 2 or more hours of sunlight in childhood or adolescence (tendency to burn)
	Kappa statistics (*n*)[b]	**Kappa statistics (*n*)**	**Kappa statistics (*n*)**
Melanoma cases	0.84 (178)	0.61 (171)	0.45 (179)
SCC cases	0.82 (244)	0.65 (238)	0.44 (243)
BCC cases	0.83 (245)	0.66 (242)	0.40 (242)
Controls	0.81 (682)	0.61 (668)	0.42 (679)
	Mean change (SE)[c]	**Mean change (SE)**	**Mean change (SE)**
Melanoma cases	0.10 (0.03)	−0.24 (0.05)	0.11 (0.07)
SCC cases	0.03 (0.03)	−0.18 (0.04)	0.21 (0.06)
BCC cases	0.09 (0.03)	−0.19 (0.04)	0.26 (0.06)
Controls	0.04 (0.02)	−0.23 (0.02)	0.09 (0.03)
	Age-adjusted OR (95%CI)[d]	**Age-adjusted OR (95%CI)**	**Age-adjusted OR (95%CI)**
Melanoma cases			
P	2.08 (1.37–3.15)	0.55 (0.39–0.77)	1.94 (1.38–2.71)
R	2.27 (1.53–3.35)	0.58 (0.41–0.81)	2.17 (1.54–3.04)
SCC cases			
P	1.79 (1.23–2.60)	0.61 (0.45–0.83)	1.64 (1.22–2.21)
R	1.70 (1.18–2.44)	0.62 (0.46–0.84)	2.04 (1.51–2.74)
BCC cases			
P	1.73 (1.19–2.53)	0.68 (0.50–0.93)	1.55 (1.15–2.09)
R	1.86 (1.30–2.66)	0.75 (0.55–1.00)	2.26 (1.68–3.06)

[a] Hair colour was scored on a 5-point scale, where 1 was black and 5 was red. Tendency to tan was scored on a 4-point scale, where 1 was practically none and 4 was deep tan. Tendency to burn was scored on a 5-point scale, where 1 was practically none and 5 was painful burn with blisters.

[b] Kappa statistics of the responses to the three questions asked before and after skin cancer diagnosis in cases and in matched controls.

[c] Mean change was calculated as the retrospective questionnaire score minus the 1982 questionnaire score. Numbers in parentheses, standard error of the mean.

[d] Age-adjusted OR was calculated as follows: hair colour: blonde or red vs black, dark brown, or light brown; tendency to tan: average or deep tan vs practically none or light tan; skin reaction: burn, painful burn, or painful burn with blisters vs practically none or some redness only. *P* stands for ORs based on the 1982 prospective data; *R* stands for ORs based on the 2000 retrospective data.

that there was substantial reliability in reporting the use of sunlamps after melanoma diagnosis.[25] A prospective study showed that tanning device use was a significant risk factor for melanoma with an OR for use more than once/month during age 10–39 of 1.55 (95% CI 1.04–2.32).[21] Only a few studies have evaluated the relationship between tanning device use and non-melanoma skin cancer. One population-based case–control study reported a significantly positive association; the relative risks were 2.5 (95% CI 1.7–3.8) for SCC and 1.5 (95% CI 1.1–2.1) for BCC.[26] We simultaneously evaluated the sunlamp use or tanning salon attendance in relation to the three types of skin cancer. The association was strongest and significant for melanoma compared with SCC and BCC. Most of the previous studies only adjusted for pigmentation and phenotype factors. In this study, after additionally controlling for cumulative sun exposure while wearing a bathing suit, lifetime severe sunburns, family history of skin cancer, and geographic region at baseline, the associations did not change substantially and remained significant for melanoma risk. These data suggest that the risks associated with sunlamp use were not likely to be substantially confounded by sun exposure of other kinds.

The ratio of UVB to UVA emitted by indoor tanning devices was greatly reduced around 1980.[24,27,28] We did not differentiate age category or calendar year of the usage of indoor tanning devices on the questionnaire. Because the age of our study population at baseline (1976) ranged from 30 to 55, it is possible that the majority in this study was of older UVB-emitting devices. However, UVA has a carcinogenic effect by causing oxidative DNA damage via reactive oxygen species generated after the absorption of light energy by cellular chromophores.[5,29] Additional studies are warranted to evaluate the effect of the more contemporary UVA-emitting devices.

We used cumulative sun exposure while wearing a bathing suit as a measurement of recreational and intermittent sun exposure; it was associated with all three types of skin cancer in our study with the strongest risk for melanoma. The multivariate ORs for cumulative sun exposure while wearing a bathing suit were not substantially confounded by other variables.

Residence in geographic regions can be viewed as a rough estimation of chronic sun exposure. We observed that residence in West and South regions was associated with increased risks of SCC and BCC, but not that of melanoma, consistent with the descriptive epidemiological evidence of a stronger North–South gradient in the US for the risks of SCC and BCC than that of melanoma.[30]

We observed a significant interaction on a multiplicative scale between the constitutional susceptibility score and sun exposure while wearing a bathing suit on melanoma risk. Women with the highest constitutional susceptibility score and the highest level of sun exposure while wearing a bathing suit had the highest risk for melanoma. Among controls, there was evidence of a 'phenotype-behavior' feedback, i.e. the controls who were more constitutionally susceptible to sun exposure had less sun exposure while wearing a bathing suit compared with those who were less susceptible. In this study, constitutional susceptibility was the combination of hair colour, skin colour, childhood tendency to burn, and mole counts. These identifiable phenotypic phenomena may make people aware of their susceptibility, resulting in reduced recreational sun exposure.

Few studies examined melanoma risk factors prospectively.[31,32] For retrospective studies, information on sunlight exposure and skin cancer risk factors is potentially subject to recall bias as it was gathered after the onset of disease. We assessed potential recall bias by examining the correlations and the difference in mean changes between the responses on the prospective and retrospective questionnaires for the three questions on constitutional factors and comparing odds ratios calculated for these variables.[20] The reliability of each measure was approximately the same magnitude among the cases and the controls and the odds ratios based on the prospective and retrospective questions were similar, except for childhood and adolescence tendency to burn, which was slightly over-reported among SCC and BCC cases retrospectively. These data indicated that the retrospective assessment was not likely to substantially bias the estimate of risk in this study, at least for these variables. Weinstock *et al*.[20] examined recall bias in 143 melanoma cases with the diagnosis between June 1976 and June 1984 in a nested case–control study conducted in 1984 and 1986 within the NHS, and the authors observed recall bias in retrospective assessment of ability to tan, but not that of hair colour. In this study, we collected the retrospective questionnaires in 2002 among 200 melanoma cases who provided blood samples in 1989 and 1990 and had the diagnosis between June 1990 and June 2000. We did not observe substantial recall bias for the three variables among melanoma cases. The different design of the two studies may help explain the discrepancy of the results.

In summary, the nested case–control design, high follow-up rate, and high response rate for the retrospective supplementary questionnaire strengthen the validity of this study. The limitations of the study include self-reported assessment on pigmentation phenotypes and exposures, which may lead to misclassification. There is potential limitation in generalizability of the results in our cohort of nurses, e.g. outdoor occupations are underrepresented. We observed sunlamp use or tanning salon attendance remained a significant risk factor for melanoma in multivariate models. The cumulative sun exposure while wearing a bathing suit was an independent risk factor from constitutional susceptibility and other exposure variables. We observed a significant interaction between constitutional susceptibility and sun exposure while wearing a bathing suit on melanoma risk, suggesting that the interactions between host factors and sun exposure provide useful information for skin cancer prevention.

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References

1 American Cancer Society. *Cancer Facts and Figures.* Atlanta: American cancer society, 2004.

2 Howe HL, Wingo PA, Thun MJ *et al*. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. *J Natl Cancer Inst* 2001;**93**:824–42.

3 Armstrong BK, Kricker A, English DR. Sun exposure and skin cancer. *Aust J Dermatol* 1997;**38**:S1–6.

4 English DR, Armstrong BK, Kricker A, Fleming C. Sunlight and cancer. *Cancer Causes Control* 1997;**8**:271–83.

5 Brash DE. Sunlight and the onset of skin cancer. *Trends Genet* 1997;**13**:410–14.

6 Naldi L, Altieri A, Imberti GL, Gallus S, Bosetti C, La Vecchia C. Sun exposure, phenotypic characteristics, and cutaneous malignant melanoma. An analysis according to different clinico-pathological variants and anatomic locations (Italy). *Cancer Causes Control* 2005;**16**:893–99.

7 Naldi L, Altieri A, Imberti GL, Giordano L, Gallus S, La Vecchia C. Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005;**15**:545–50.

8 MacKie RM. Incidence, risk factors and prevention of melanoma. *Eur J Cancer* 1998;**34**:S3–6.

9 Osterlind A. Fair complexion and risk of malignant melanoma of the skin based on experience from the Danish Cancer Registry. *Recent Results Cancer Res* 1993;**128**:91–100.

10 Masback A, Westerdahl J, Ingvar C, Olsson H, Jonsson N. Clinical and histopathological characteristics in relation to aetiological risk factors in cutaneous melanoma: a population-based study. *Melanoma Res* 1999;**9**:189–97.

11 Autier P, Dore JF, Gefeller O *et al*. Melanoma risk and residence in sunny areas. EORTC Melanoma Co-operative Group. European Organization for Research and Treatment of Cancer. *Br J Cancer* 1997;**76**:1521–24.

12 Dwyer T, Blizzard L, Ashbolt R, Plumb J, Berwick M, Stankovich JM. Cutaneous melanin density of Caucasians measured by spectrophotometry and risk of malignant melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin. *Am J Epidemiol* 2002;**155**:614–21.

13 Rosso S, Zanetti R, Pippione M, Sancho-Garnier H. Parallel risk assessment of melanoma and basal cell carcinoma: skin characteristics and sun exposure. *Melanoma Res* 1998;**8**:573–83.

14 Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 1997;**73**:198–203.

15 Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001;**63**:8–18.

16 Colditz GA, Martin P, Stampfer MJ *et al*. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986;**123**:894–900.

17 National Oceanic and Atmospheric Administration. Climatic Atlas of the United States, 1983.

[18] Miettinen OS. Stratification by a multivariate confounder score. *Am J Epidemiol* 1976;**104**:609–20.

[19] Marshall RJ, Chisholm EM. Hypothesis testing in the polychotomous logistic model with an application to detecting gastrointestinal cancer. *Stat Med* 1985;**4**:337–44.

[20] Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE. Recall (report) bias and reliability in the retrospective assessment of melanoma risk. *Am J Epidemiol* 1991;**133**:240–45.

[21] Veierod MB, Weiderpass E, Thorn M *et al*. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2003;**95**:1530–38.

[22] Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Am J Epidemiol* 1995;**141**:923–33.

[23] Young AR. Tanning devices–fast track to skin cancer? *Pigment Cell Res* 2004;**17**:2–9.

[24] Gallagher RP, Spinelli JJ, Lee TK. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:562–66.

[25] Beane Freeman LE, Dennis LK, Lynch CF, Lowe JB, Clarke WR. Test-retest of self-reported exposure to artificial tanning devices, self-tanning creams, and sun sensitivity showed consistency. *J Clin Epidemiol* 2005;**58**:430–32.

[26] Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstock MA. Use of tanning devices and risk of basal cell and squamous cell skin cancers. *J Natl Cancer Inst* 2002;**94**:224–26.

[27] Spencer JM, Amonette R. Tanning beds and skin cancer: artificial sun + old sol = real risk. *Clin Dermatol* 1998;**16**:487–501.

[28] Lazovich D, Sweeney C, Weinstock MA, Berwick M. Re: a prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2004;**96**:335; author reply 7–8.

[29] Kielbassa C, Roza L, Epe B. Wavelength dependence of oxidative DNA damage induced by UV and visible light. *Carcinogenesis* 1997;**18**:811–16.

[30] Scotto J, Fears TR, F FJ. Incidence of non-melanoma skin cancer in the United States. NIH Pub. No. 83-2433, 1983.

[31] Schneider JS, Moore DH 2nd, Sagebiel RW. Risk factors for melanoma incidence in prospective follow-up. The importance of atypical (dysplastic) nevi. *Arch Dermatol* 1994;**130**:1002–07.

[32] Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. *J Clin Oncol* 2005;**23**:2669–75.