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Simultaneous Assessment of Risk Factors for Malignant Melanoma and Non-Melanoma Skin Lesions, with Emphasis on Sun Exposure and Related Variables

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The purpose of this case-control study was to identify differences in risk factors between melanoma and non-melanoma skin lesions. The study group, interviewed from 1979 to 1982, consisted of 289 subjects with melanoma, 75 subjects with non-melanoma sun-related skin lesions and 527 controls. Simultaneous comparison of the three subgroups was accomplished by polychotomous logistic regression. The highest exposure category of lifetime sun exposure was associated with a nearly threefold risk of both melanoma and non-melanoma. Poor tanning was associated with an approximately twofold risk of both disease types. Similarly, northern European ethnicity was associated with an approximately twofold risk of disease. Number of moles on the body exhibited a relationship with melanoma only: having more than 25 moles, compared to their absence, was associated with a thirteenfold risk of melanoma. History of freckling was associated with a twofold risk of melanoma, but no increase in the risk of non-melanoma. Alternatively, mixed indoor-outdoor recreational exposure was associated with a 50% increased risk of non-melanoma, but a 25% decreased risk of melanoma. History of severe sunburn was associated with a twofold risk of non-melanoma only. For history of prior sun-related lesions the nearly sevenfold risk of melanoma was exceeded by the 14-fold risk of non-melanoma.

An aetiological role for sun exposure in the development of malignant melanoma has been suggested by epidemiological studies, although the evidence for this relationship has often been ambiguous. This ambiguity can be seen in studies attempting to associate melanoma with latitude gradients,[1-3] as well as case-control studies attempting to relate melanoma to lifetime cumulative and intermittent sun exposure and to lesions known to be associated with high-dose solar ultraviolet irradiation.[4-14]

Previously we investigated, using a case-control design, the relationship of host susceptibility to sun exposure with the development of malignant melanoma.[15] It was found that, in general, the risk associated with sun exposure was greater for individuals expected to be susceptible on the basis of poor ability to tan, but not other pigmentary-related traits, such as freckling, mole count, prior non-melanoma skin lesions, prior severe sunburn, parents' ethnicity and eye colour. The types of sun exposure for which poorly tanning subjects had higher relative risks of melanoma than easily tanning subjects included qualitative measures of occupational, recreational and overall lifetime sun exposure, as well as a history of severe sunburn with blistering.

Here we use a different approach to elucidate the relationship between melanoma and sun exposure. The design of our original case-control study of melanoma[12] was unusual in that, in addition to patients with malignant melanoma and non-cancer controls, there was a separate group of subjects with a current diagnosis of basal-cell carcinoma, squamous cell carcinoma or solar keratosis, all of which are non-melanoma skin lesions known to be associated with sun exposure.[16] These patients had been interviewed as potential controls and then excluded from the final control group, subsequent to ascertaining their diagnosis with a sun-

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TABLE 1 *Histological characteristics of cases*

	No. of patients	Per cent
Melanoma cases (n = 289)		
Superficial spreading	223	77.2
Unclassified radial growth phase	21	7.3
Nodular	12	4.1
Acral lentiginous	12	4.1
Lentigo maligna	12	4.1
Other	3	1.1
Unknown	6	2.1
Non-melanoma cases (n = 75)		
Solar keratosis	37	49.3
Basal-cell carcinoma	20	26.7
Squamous-cell carcinoma	3	4 0
More than one of above	15	20.0

related lesion. The availability of this latter group provided an opportunity to assess, within the context of a single study, the comparative strength of the association of sun exposure with the two disease subgroups. Finding comparable odds ratios relating sun exposure both to melanoma and non-melanoma cases would be supportive of a similar aetiology of disease, whereas finding statistically significant differences in odds ratios would suggest differences in aetiology. These differences might be such that only one of the disease subgroups were related to sun exposure, or that different types or amounts of exposure were necessary, or that different subgroups of individuals were susceptible to the different types of disease.

The conventional analytical method used for three-group risk factor analysis would be pairwise comparison of melanoma cases to controls and non-melanoma cases to controls, coupled with an ad hoc assessment of the differences in observed risk factor patterns.[17] However, our strategy was to carry out both a conventional Mantel-Haenszel analysis of each case group versus controls, as well as a simultaneous comparison of the three groups using polychotomous logistic regression analysis.[18,19] The polychotomous method is advantageous in that it not only allows estimation of disease-specific odds ratios, with adjustment for multiple confounding factors, but also permits direct tests of hypothesis for differences in risk factor patterns between the disease categories.

MATERIALS AND METHODS

Melanoma cases (histopathologically confirmed) consisted of 289 patients diagnosed at the New York University Skin and Cancer Unit from 1979 to 1982. Among 602 subjects randomly selected from among patients attending the New York University Skin and Cancer Unit during that same time period, 75 were diagnosed with non-melanoma skin lesions known to be associated with sun exposure. The remaining 527 subjects chosen from the Skin and Cancer Unit comprised our non-cancer controls. Potential study subjects were excluded if they were less than 20 years of age, were of non-white race, or reported previous melanoma. Details of subject selection, interview procedure and demographic characteristics have been published elsewhere.[12,15] Histological characteristics of melanoma and non-melanoma cases are given in Table 1. Current dermatological diagnoses for non-cancer controls are given in Table 2.

Measures of sun exposure included occupational and recreational exposure (mostly indoor, mostly outdoor, or both indoor and outdoor), overall sun exposure (none, little, moderate or much, compared to other people), whether the subject had ever experienced severe sunburn with blistering, and whether the subject previously (but not currently) had non-melanoma skin cancer or solar keratosis.

Potential confounders included age, sex, ability to tan, history of freckling, number of moles, hair colour, eye colour, father's ethnicity, and history of previous skin diseases. Details of the assessment of moles and freckles have been given previously,[12] as has the justification for using father's rather than mother's ethnicity.[15] Previous skin diseases were grouped according to whether sun exposure was likely to have been recommended or contraindicated in patients with such conditions (see Maddin and Brown[20] and A W Kopf, personal communication).

TABLE 2 *Current dermatological diagnosis of non-cancer controls (n = 527)*

	No of controls*	Per cent
Diagnosis		
Skin infections	53	10 1
Other infectious and parasitic diseases	81	15.4
Allergic diseases (internal agents)	18	3.4
Seborrhoeic dermatitis	41	7.8
Eczema	41	7.8
Contact and radiation dermatitis	40	7.6
Psoriasis and other scaling dermatoses	53	10.1
Pruritis and related conditions	41	7.8
Diseases of the nail, hair, hair follicles, and sweat and sebaceous glands	141	26.8
Non-malignant neoplasms unrelated to sun exposure	94	17.8
Other miscellaneous conditions†	112	21.3
Unknown	9	1.7

* Numbers do not total 527 and per cents do not total 100.0 because of multiple diagnoses of controls.

† Includes hypertrophic and atrophic conditions, lichen planus, erythematous conditions, pilonidal cyst, insect bite, diseases of the circulatory system, dermatitis NOS, and other conditions diagnosed among fewer than ten patients.

Data on most of the variables of interest were collected for all subjects, with very small percentages unknown. However, the question on history of severe sunburn with blistering was introduced after the study had already started and was available only for 132 melanoma cases, 71 non-melanoma cases, and 443 controls.

Statistical evaluation of epidemiological risk factors separately for melanoma cases (versus controls) and for non-melanoma cases (versus controls) employed the odds ratio (OR).[21] Age and sex adjustments were always included, the former by ten-year intervals. Statistical significance was determined by the two-tailed Mantel-Haenszel chi-square and pertinent two-tailed tests for linear trend.[21,22] The baseline exposure group for each study factor was either the unexposed category or the category most frequently reported by controls. Confidence intervals (CIs) based on the adjusted risk were determined by the asymptotic maximum likelihood method.[23]

Polychotomous logistic regression was used to compare simultaneously the three study groups (melanoma cases, non-melanoma cases and controls).[18,19] This technique allows one directly to test whether the magnitude of risk associated with a particular factor is different for melanoma cases and non-melanoma cases, after adjusting for the effects of multiple confounding variables. Two different polychotomous tests are reported in the text and tables, both based on specific likelihood-ratio comparisons. The first, called the joint test, evaluates the combined statistical significance of all possible disease-factor associations for a given risk factor. If this test is significant, it is then appropriate to test whether the magnitudes of association differ for melanoma and non-melanoma disease; otherwise it is not appropriate.[18,24] Further details of this procedure are given by Dubin and Pasternack.[18]

Polychotomous ORs for each study factor was obtained from the logistic regression model saturated with respect to that factor and including all terms from the multiple confounder model described below. These ORs are included in the tables, in addition to the Mantel-Haenszel ORs, but are not given in the text unless there were noteworthy differences. Statistical significance of the tabulated polychotomous ORs was obtained from Wald's test for the standardized regression coefficient.[17] Confidence intervals for the polychotomous ORs was obtained by exponentiating the CI for the relevant regression coefficient.[17]

All statistical tests were considered significant at the $p<0.05$ level. In the text, unless otherwise specified, ORs, CIs and trend tests refer to the Mantel-Haenszel procedure.[21,22]

In general, subjects with unknown values for any of the study factors were excluded from the polychotomous analysis, leaving 202 melanoma cases, 62 non-melanoma cases and 378 controls. The only risk factor for which an exception to this was made was a history of severe sunburn with blistering, for which there was a substantial per cent missing. For this variable we included a missing value indicator in the polychotomous analysis, in order to retain an appreciably greater number of subjects.[17] Subjects who were excluded from the polychotomous analysis were nonetheless retained in the Mantel-Haenszel analysis.

Development of the multiple confounder model proceeded according to modified stepwise backward elimination. Instead of entering all possible confounding associations at once (which was attempted and resulted in a lack of convergence), we entered potential confounders into the regression model in three consecutive groups. The model was first saturated with respect to all possible confounding associations for that group and followed by backward elimination of unnecessary terms ($p>0.05$ by Wald's test). The resulting model was then saturated with respect to all possible associations in the next consecutive group of confounders, until associations from all three groups were included in the final confounder model. The first group of potential confounders consisted of age, sex and history of prior skin conditions. The second group consisted of dermato-pigmentary variables: mole count, ability to tan and history of freckling. The third group consisted of other pigment-related variables: hair colour, eye colour and father's ethnicity. The final confounder model included associations of both disease types with age, ability to tan, hair colour, eye colour and father's ethnicity, and associations of melanoma with history of prior skin conditions, mole count and history of freckling.

Note that no sun exposure variables were included in the multiple confounder model, because the expected correlations between these variables would be likely to obscure the relationships which form the principal focus of this study. Note also that some of the polychotomous ORs, those for ability to tan, mole count and father's ethnicity, are categorized more parsimoniously than the Mantel-Haenszel ORs. This was done because of lack of convergence of the polychotomous model.

RESULTS

The risk of melanoma was elevated among subjects with no ability to tan (OR = 1.7) or little ability to tan (OR = 2.0, $p<0.01$), compared to subjects with average ability to tan, whereas a decreased risk was

TABLE 3a *Melanoma odds ratios (OR) by pigmentary characteristics*

Risk factor	No. of melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Ability to tan						
None	34	42	1.68	0.9–3 2	1.66**	1.1–2.6
Light	90	105	2.01*	1.4–3.2		
Average§	101	222	1.00	—	1 00	—
Dark	48	154	0.69	0.4–1.1	0.84	0.5–1.4
History of freckling						
No§	155	402	1.00	—	1.00	—
Yes	129	114	3.36*	2.4–4.9	1.89*	1 2–2.9
Mole count						
None	9	87	0.18*	0.1–0.3	0 16*	0.1–0.4
1–25§	214	357	1.00	—	1.00	—
26–100	45	62	1.60	1.0–2.6	2.13*	1 2–3.7
>100	10	11	2.26	0.8–7.1		

TABLE 3b *Non-melanoma odds ratios (OR) by pigmentary characteristics*

Risk factor	No. of non-melanoma patients	No of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Ability to tan						
None	11	42	1.80	0.7–4 9	2.10**	1.1–4 2
Light	28	105	2 41*	1.3–5.4		
Average§	22	222	1.00	—	1.00	—
Dark	14	154	0.89	0 4–2.1	1.17	0.5–2.7
History of freckling						
No§	57	402	1 00	—	1.00	—
Yes	18	114	1 27	0.6–2.5	1.08	0 5–2.1
Mole count						
None	12	87	0 66	0.3–1.5	0.54	0.2–1.3
1–25§	57	357	1.00	—	1.00	—
26–100	6	62	1.25	0 4–3.7	1.26	0.4–4.2
>100	0	11	0.00	0.0–20.1		

* $p<0.01$.
** $p<0.05$.
† Adjusted for age and sex. Linear trend for melanoma: Ability to tan, $p<0.001$; mole count, $p<0.001$. Linear trend for non-melanoma: Ability to tan, $p<0.05$; mole count, not significant.
‡ Adjusted for multiple confounding factors by polychotomous logistic regression (see text) Joint significance tests: Ability to tan, $p<0.05$. history of freckling, $p<0.05$; mole count, $p<0.005$. Tests for melanoma versus non-melanoma differences: Ability to tan, not significant; history of freckling, not significant; mole count, $p<0.05$.
§ Baseline.

observed among those reporting dark-tanning ability (OR = 0.7) (Table 3a). Similarly, the risk of non-melanoma was elevated among subjects with no ability to tan (OR = 1.8) or little ability to tan (OR = 2.4, $p<0.01$) (Table 3b). For both melanoma and non-melanoma, there were significant linear trends towards increasing risk of disease with decreasing ability to tan ($p<0.001$ and $p<0.05$, respectively). Analogously, in the polychotomous analysis the joint test of association between ability to tan and both types of disease was significant ($p<0.05$). This test is a global test of association and does not identify which of the disease types (either or both) is associated with ability to tan or whether the magnitude of the association differs between melanoma and non-melanoma disease. However, the specific test for a difference in the magnitude of risk with respect to ability to tan was not significant, which confirmed that the relationship was similar for the two disease groups.

History of freckling at first seemed to provide evidence of a substantial difference between the melanoma and non-melanoma disease groups (Table 3). For

TABLE 4a *Melanoma odds ratios (OR) by hair colour and eye colour*

Risk factor	No. of melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Hair colour						
Red	23	14	2.59**	1.2–6.9	1.15	0.4–3.0
Blond	34	61	1.06	0.6–1.9	0.51	0.2–1.0
Light brown	92	139	1 20	0.8–1.8	0.93	0 6–1.5
Dark brown§	125	233	1.00	—	1.00	—
Black	10	71	0.18*	0.1–0.4	0.28*	0.1–0.7
Eye colour						
Blue	94	77	2.57*	1 8–4.1	2.03**	1.2–3 5
Green-grey-hazel	70	170	0.92	0.6–1.4	0.86	0.5–1.4
Brown§	120	269	1.00	—	1.00	—

TABLE 4b *Non-melanoma odds ratios (OR) by hair colour and eye colour*

Risk factor	No. of non-melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Hair colour						
Red	3	14	1.36	0.2–7.0	0.71	0 2–3.1
Blond	15	61	1.56	0.7–3.8	0.84	0.3–2.1
Light brown	27	139	1 81	0.9–3.8	1.15	0.5–2.4
Dark brown§	23	233	1.00	—	1.00	—
Black	7	71	0.73	0.2–2.2	0.60	0.2–1.7
Eye colour						
Blue	15	77	1.87	0.8–4.5	1.63	0.7–3.7
Green-grey-hazel	37	170	2.18**	1.2–4.3	2.00**	1.0–3.9
Brown§	23	269	1.00	—	1.00	—

* $p<0.01$.
** $p<0.05$.
† Adjusted for age and sex
‡ Adjusted for multiple confounding factors by polychotomous logistic regression (see text). Joint significance tests: Hair colour, not significant; eye colour, $p<0.005$. Tests for melanoma versus non-melanoma differences: Hair colour, not performed; eye colour, $p<0$ 05.
§ Baseline.

melanoma, subjects reporting a history of freckling had a more than threefold risk (OR = 3.4, $p<0.01$), whereas, for non-melanoma, subjects reporting a history of freckling had a risk that was not significantly different from unity (OR = 1.3). This observed difference in magnitude was not found to be significant in the polychotomous analysis; removal of confounding by other variables considerably reduced the magnitude of association between history of freckling and melanoma (OR = 1.9, $p<0.01$), while leaving the magnitude of association between freckling and non-melanoma virtually unchanged (OR = 1.1).

For mole count, the observed differences in ORs for melanoma and non-melanoma were not only striking in the Mantel-Haenszel analysis, but in the polychotomous analysis as well (Table 3). For melanoma, considering subjects with 1–25 moles on the body as the baseline group, those without moles were at decreased risk (OR = 0.2, $p<0.01$), whereas those with 26–100 moles (OR = 1.6) or more than 100 moles (OR = 2.3) were at increased risk. The associated test for linear trend confirmed this relationship ($p<0.001$). For non-melanoma the findings for mole count were ambiguous, at best providing evidence for a non-significant linear trend. The polychotomous analysis resulted in only minor adjustments in the magnitudes of ORs; furthermore, the test for melanoma-non-melanoma differences was significant ($p<0.05$).

Subjects with red hair were at increased risk of melanoma (OR = 2.6, $p<0.05$), compared to subjects with dark brown hair, whereas subjects with black hair were at decreased risk (OR = 0.2, $p<0.01$) (Table 4a). After adjustment for multiple confounders in the polychotomous model, red hair was no longer significantly asso-

TABLE 5a *Melanoma odds ratios (OR) by father's ethnicity*

Risk factor	No. of melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Father's ethnicity						
English, Irish, Scottish or Welsh	54	81	2.17*	1.3–3 9	1.61**	1.0–2.5
Scandinavian or Germanic	34	50	1.68	0.9–3.3		
North Slavic	106	157	1.80*	1 2–2 9		
Other European§	55	157	1.00	—	1.00	—
Half or more non-European	6	34	0.76	0 2–2.2		

TABLE 5b *Non-melanoma odds ratios (OR) by father's ethnicity*

Risk factor	No of non-melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Father's ethnicity						
English, Irish, Scottish or Welsh	17	81	3 24**	1.3–11.4	2.37**	1.1–5 2
Scandinavian or Germanic	11	50	2 65	0.8–9.1		
North Slavic	30	157	2 50**	1.1–6.5		
Other European§	10	157	1.00	—	1.00	—
Half or more non-European	1	34	1.95	0 1–60.1		

* $p<0.01$.
** $p<0.05$.
† Adjusted for age and sex.
‡ Adjusted for multiple confounding factors by polychotomous logistic regression (see text). Joint significance test: $p<0.05$. Test for melanoma versus non-melanoma differences. Not significant
§ Baseline.

ciated with an increased risk of melanoma (OR = 1.2). For non-melanoma, there were no significant risks associated with hair colour, although there were ORs greater than one for subjects with red (OR = 1.4), blond (OR = 1.6) or light brown hair (OR = 1.8) (Table 4b). The joint test of association of hair colour with disease was not significant; hence a test for melanoma versus non-melanoma differences was inappropriate and not performed.

Compared to having brown eyes, having blue eyes was associated with an increased risk of melanoma (OR = 2.6, $p<0.01$), as well as non-melanoma (OR = 1.9) (Table 4). Having green, grey or hazel eyes was not associated with an increased risk of melanoma (OR = 0.9), but was associated with an increased risk of non-melanoma (OR = 2.2, $p<0.05$). This pattern remained after adjustment for multiple confounding, and the test for melanoma versus non-melanoma differences was significant.

Father's ethnicity was significantly associated with the risk of both disease types (Table 5). For melanoma, increased risks were observed for all three northern European ethnic categories, English, Irish, Scottish or Welsh (OR = 2.2, $p<0.01$), Scandinavian or Germanic (OR = 1.7), and North Slavic (OR = 1.8, $p<0.01$). These categories were combined in the polychotomous model, yielding an OR = 1.6 ($p<0.05$). Similarly for non-melanoma, increased risks were observed for subjects who were English, Irish, Scottish or Welsh (OR = 3.2, $p<0.05$), Scandinavian or Germanic (OR = 2.6), and North Slavic (OR = 2.5, $P<0.05$). The polychotomous non-melanoma OR for these categories combined was 2.4 ($P<0.05$). Although the observed OR was greater for non-melanoma compared to melanoma, the test for differences in magnitude between the two disease types was not significant.

Mostly outdoor occupation, compared to mostly indoor occupation, was associated with an almost two-fold risk of melanoma (OR = 1.8) (Table 6a). Partly outdoor occupation, however, appeared to be somewhat protective. After adjustment for multiple confounders these relationships were strengthened, especially for mostly outdoor occupation, for which the melanoma OR increased to 2.5 ($p<0.05$). Among

TABLE 6a *Melanoma odd ratios (OR) by subjective sun exposure history*

Risk factor	No. of melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Occupation type						
Mostly indoors§	242	458	1.00	—	1.00	—
Indoors/outdoors	20	50	0.79	0.4–1.4	0.77	0.4–1.6
Mostly outdoors	21	19	1.77	0.9–4.0	2.51**	1 1–6.0
Recreation type						
Mostly indoors§	103	174	1.00	—	1.00	—
Indoors/outdoors	91	259	0.68**	0.5–1.0	0.75	0.5–1 2
Mostly outdoors	86	93	1 53	1.0–2.4	1.82**	1.1–3.1
Overall sun exposure						
Little or none§	66	136	1 00	—	1.00	—
Moderate	111	254	0 99	0.6–1.5	1 22	0.7–2.0
Much	100	130	1.73**	1.1–2.8	2.79*	1.5–5.1

TABLE 6b *Non-melanoma odd ratios (OR) by subjective sun exposure history*

Risk factor	No. of non-melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Occupation type						
Mostly indoors§	72	458	1 00	—	1 00	—
Indoors/outdoors	2	50	0.35	0.0–1.6	0.32	0.1–1.5
Mostly outdoors	1	19	0 17	0.0–1 8	0.39	0 0–3.3
Recreation type						
Mostly indoors§	21	174	1 00	—	1.00	—
Indoors/outdoors	37	259	1.51	0.8–3.0	1.49	0.7–3.0
Mostly outdoors	17	93	1 81	0.8–4.3	1.49	0.6–3.5
Overall sun exposure						
Little or none§	19	136	1.00	—	1.00	—
Moderate	31	254	1.17	0.6–2 4	1.50	0.7–3.2
Much	22	130	2.01	0.9–5.3	2 90**	1.3–6.8

* $p<0.01$.

** $p<0.05$.

† Adjusted for age and sex Linear trend for melanoma: Occupation type, not significant; recreation type, not significant; overall sun exposure, $p<0$ 01 Linear trend for non-melanoma: Occupation type, $p<0.05$; recreation type, not significant; overall sun exposure, not significant.

‡ Adjusted for multiple confounding factors by polychotomous logistic regression (see text). Joint significance tests: Occupation type, $p<0$ 05; recreation type, $p<0$ 01; overall sun exposure, $p<0.005$ Tests for melanoma versus non-melanoma differences: Occupation type, not significant, recreation type, $p<0.05$; overall sun exposure, not significant

§ Baseline.

non-melanoma cases, only two subjects reported partly outdoor occupation and only one subject reported mostly outdoor occupation. Accepted statistical procedure would therefore dictate that one place little emphasis on the observed protective effects associated with outdoor occupational exposure in Table 6b.

Recreational exposure was also examined (Table 6). For melanoma, a mix of indoor and outdoor recreation was observed to be protective (OR = 0.7, $p<0.05$), whereas subjects who reported mostly outdoor recreation were at increased risk (OR = 1.5). This pattern remained after adjustment for multiple confounders. For non-melanoma, a different pattern was observed: engaging in both indoor and outdoor recreational activities carried a 50% increase in risk (OR = 1.5) and engaging in mostly outdoor recreational activities carried an 80% increase in risk (OR = 1.8). Adjustment for multiple confounders altered the magnitudes of these ORs only modestly. The polychotomous test indicated that this overall difference in risk pattern between melanoma and non-melanoma was significant, but does not specify for which exposure categories the ORs differ. Separate consideration of pertinent regression parameters demonstrated that the

TABLE 7a *Melanoma odd ratios (OR) by history of sunburn and sun-related lesions*

Risk factor	No. of melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Severe sunburn with blistering						
Never*	45	214	1.00	—	1.00	—
Ever	87	229	1.61**	1 0–2.6	0.92	0.5–1.6
Prior non-melanoma skin cancer or solar keratosis						
No§	236	515	1.00	—	1.00	—
Yes	53	12	7.28*	3.4–14.8	6.59*	2 9–15.2

TABLE 7b *Non-melanoma odd ratios (OR) by history of sunburn and sun-related lesions*

Risk factor	No. of non-melanoma patients	No. of controls	Mantel-Haenszel OR†	Mantel-Haenszel 95% CI	Polychotomous logistic OR‡	Polychotomous logistic 95% CI
Severe sunburn with blistering						
Never*	20	214	1.00	—	1.00	—
Ever	51	229	1.85	1.0–3 6	2.16**	1.1–4.2
Prior non-melanoma skin cancer or solar keratosis						
No§	42	515	1.00	—	1.00	—
Yes	33	12	20 16*	8.7–55.2	14.01*	5.9–33.4

* $p<0.01$.
** $p<0.05$.
† Adjusted for age and sex.
‡ Adjusted for multiple confounding factors by polychotomous logistic regression (see text). Joint significance tests: Severe sunburn with blistering, $p<0.05$; Prior non-melanoma skin cancer or solar keratosis, $p<0.005$. Tests for melanoma versus non-melanoma differences: Severe sunburn with blistering, $p<0.05$; prior non-melanoma skin cancer or solar keratosis, $p<0.05$.
§ Baseline.

significant difference here between melanoma and non-melanoma could be attributed to mixed ($p<0.05$), rather than mostly outdoor, recreational exposure.

As regards the subjects' overall assessment of their prior sun exposure, there did not appear to be an increased risk of melanoma associated with 'moderate' exposure (OR = 1.0) (Table 6). Nonetheless, there was an increased risk of melanoma for 'much' exposure (OR = 1.7, $p<0.05$). For non-melanoma a similar pattern was seen: no substantial excess risk associated with 'moderate' exposure (OR = 1.2) and a twofold risk associated with 'much' exposure (OR = 2.0). After adjustment for multiple confounders, the ORs increased for all exposure categories (except the baseline) and both disease types; 'much' exposure became associated with a nearly threefold risk (melanoma OR = 2.8, $p<0.01$, and non-melanoma OR = 2.9, $p<0.05$). The polychotomous test for melanoma versus non-melanoma differences in the magnitude of ORs for overall sun exposure was not significant.

A history of severe sunburn with blistering was associated with a 60% increased risk of melanoma (OR = 1.6, $p<0.05$) and an 80% increased risk of non-melanoma (OR = 1.8) (Table 7). Adjustment for multiple confounders entirely removed this excess risk of melanoma (OR = 0.9), but strengthened the association for non-melanoma (OR = 2.2, $p<0.05$). The joint test of overall association of sunburn history with disease risk was significant, as was the test for melanoma versus non-melanoma differences, from which one can conclude that only non-melanoma was associated with sunburn history.

A history of prior non-melanoma skin cancer or solar keratosis was associated with a more than sevenfold risk of subsequent melanoma (OR = 7.3, $p<0.01$) and a more than 20-fold risk of subsequent non-melanoma (OR = 20.2, $p<0.01$) (Table 7). Adjustment for multiple confounders reduced the magnitudes of these associations only modestly (melanoma OR = 6.6, $p<0.01$, and non-melanoma OR = 14.0, $p<0.01$). The joint test of overall association was significant ($p<0.005$), as was the test for melanoma versus non-melanoma differences ($p<0.05$). In this instance, given the two significant polychotomous ORs, one may

conclude from the latter test that the magnitude of association with prior non-melanoma is significantly greater for non-melanoma than for melanoma.

DISCUSSION

The use of polychotomous logistic regression allows comparison of the risk of melanoma with the risk of non-melanoma sun-related skin cancer and pre-cancer for a series of risk factors, after adjustment for multiple confounders. The principal finding is that some factors (high overall sun exposure, poor tanning ability and northern European ethnicity) were associated with similar increases in risk for melanoma and non-melanoma, one factor (high number of moles) with a greater increase in risk for melanoma, and some factors (mixed indoor/outdoor recreational exposure, history of severe sunburn and prior sun-related lesions) with a greater increase in risk for non-melanoma. The increased risk for melanoma associated with prior sun-related lesions was nevertheless substantial. Because of the relatively small number of non-melanoma cases available for analysis, ORs for this case subgroup will tend to be less precise than for melanoma. This suggests that there may be additional differences between melanoma and non-melanoma that could be identified with a larger sample size.

In another epidemiological study simultaneously investigating melanoma and non-melanoma skin cancer, Beral and Robinson[25] found outdoor occupation to be associated with increased incidence of non-melanoma, and indoor office work to be associated with increased incidence of melanoma of usually unexposed sites. Paradoxically, other indoor workers had a lower incidence of all types of skin cancer. Although these occupational categories do not directly measure sun exposure, these findings suggest (as do ours) a more direct relationship between non-melanoma and sun exposure.

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