American Journal of Epidemiology

Vol. 177, No. 9
DOI: 10.1093/aje/kws335
Advance Access publication:
April 11, 2013

Original Contribution

Host Risk Factors, Ultraviolet Index of Residence, and Incident Malignant Melanoma In Situ Among US Women and Men

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Initially submitted May 6, 2012; accepted for publication July 23, 2012.

The incidences of malignant melanoma in situ (MMIS) and invasive malignant melanoma are rising in the United States, but few studies have examined risk factors for MMIS. We evaluated the risk of MMIS according to the host phenotype and the ultraviolet index of the state of residence. Prospective data were collected via biennial questionnaires from 250,151 women and men aged ≥20 years in the Nurses' Health Study (1980–2008), the Nurses' Health Study 2 (1989–2009), and the Health Professionals Follow-up Study (1986–2008). During 7,144,820 person-years of follow-up, 888 incident MMIS lesions occurred, representing 33% of all incident malignant melanoma. Meta-analysis across the cohorts demonstrated that the presence of multiple nevi on the extremities conferred the highest relative risk for MMIS (relative risk = 3.18, 95% confidence interval: 2.59, 3.90). Family history of melanoma, number of severe sunburns, sunburn susceptibility, hair color, and Fitzpatrick skin types I, II, and III were significantly associated with an increased risk of MMIS. Conversely, the ultraviolet index of the state of residence at birth, at age 15 years, and at age 30 years was not associated with increased risk of MMIS. Continued study of MMIS and associated risk factors will help identify persons who are most at risk and elucidate the role of MMIS within the spectrum of cutaneous melanoma.

Hutchinson's melanotic freckle; melanoma; nevus; sunburn; ultraviolet rays

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; MMIS, malignant melanoma in situ; NHS, Nurses' Health Study; NHS2, Nurses' Health Study 2; RR, relative risk.

The incidence of invasive malignant melanoma is rapidly rising both in the United States (1–3) and worldwide (4–9). Although malignant melanoma in situ (MMIS) trails invasive malignant melanoma in absolute numbers, the incidence of MMIS has been increasing at a greater rate than that of invasive malignant melanoma (10–13). MMIS now represents about 40% of all melanoma diagnosed in the United States, up from an estimated 22% in 1988 (14). The reasons for this increase are multifactorial; they may include increased screening and diagnosis, as well as environmental, behavioral, and educational changes over time (2, 15–17). Recent studies on melanoma in the United States have demonstrated that despite the increased diagnosis of thinner melanoma lesions, overall melanoma mortality has remained constant, and investigators have called for better risk identification and screening modalities (2, 14).

MMIS is thought to represent the noninvasive precursor lesion to invasive and metastatic melanoma, in which malignant melanocytes grow in the epidermis during a noninvasive radial growth phase (18). It has been proposed that MMIS accumulates mutations, such as those in the neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*); the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*); the SRY (sex determining region Y)-box 2 gene (*SOX2*); and others in a stepwise fashion, gaining the capability to invade the underlying dermis and to metastasize (19, 20).

A recent study of MMIS showed that it is smaller than its invasive counterpart, with approximately 50% of tumors measuring less than 6 mm in diameter (21). MMIS is more likely to be detected by a dermatologist than by the patient or a family member, and patient concern upon presentation of MMIS lesions is usually low (21, 22). Although

melanoma, when diagnosed in situ, does not affect host mortality, invasive malignant melanoma, even in its earliest stages, confers increased mortality (10, 23). For these reasons, identification of persons at high risk and their enrollment in careful screening programs are important and have proven effective in decreasing invasive melanoma and subsequent mortality (22, 24).

To further characterize risk factors for MMIS, we conducted a prospective study on 3 large cohorts of US women and men with 888 incident MMIS lesions, which, to our knowledge, is the largest study of its kind to date. Strict criteria excluded any person with a history of cancer or skin cancer to minimize diagnostic bias. To further characterize risk, we conducted analyses by Fitzpatrick skin phototype (25) and the ultraviolet index of state of residence at birth, at age 15 years, and at age 30 years.

MATERIALS AND METHODS

Study population

Data were collected from 3 large prospective cohort studies: the Nurses' Health Study (NHS), the Nurses' Health Study 2 (NHS2), and the Health Professionals Follow-Up Study (HPFS). The NHS began in 1976 with 121,701 registered nurses aged 30–55 years, and the NHS2 began in 1989 with a cohort of 116,686 registered nurses aged 25–42 years. Data were initially limited to participants from 11 and 14 states, respectively, but now include participants in every US state. The HPFS began in 1986 and is an all-male cohort consisting of 51,529 US men aged 40–75 years working in various health-related professions. In all 3 cohorts, information on lifestyle habits and disease history is collected via biennial questionnaires.

For this study, follow-up began with collection of data on skin cancer risk and phenotype in the respective cohorts with 28, 20, and 22 years of follow-up, respectively (NHS, 1980–2008; NHS2, 1989–2009; and HPFS, 1986–2008). Data on state of residence at birth, at age 15 years, and at age 30 years were collected in 1992. Those who died during the follow-up period were excluded as were those with a diagnosis of invasive melanoma, squamous cell carcinoma, basal cell carcinoma, or any other cancer at study inception or during follow-up. Those with a history of MMIS prior to enrollment were also excluded. Because melanoma is rare in nonwhite populations (2) and the cohorts are each approximately 97% Caucasian (reflecting the ethnic background of registered nurses and male health professionals nationally at the time of cohort inception), nonwhite participants were also excluded from analysis. Appropriate research approval for institutional human studies was obtained at Brigham and Women's Hospital (Boston, Massachusetts).

Case ascertainment

Incident cases of MMIS were self-reported by participants via the biennial questionnaires during each 2-year cycle. All cases were then confirmed by study physicians through acquisition and review of patient medical records and primary pathology reports of the lesions. Cases were subsequently categorized as lentigo maligna and nonlentigo maligna (superficial spreading) type MMIS. Only pathologically confirmed cases were included for analysis. For mortality data, primary death certificates were obtained and reviewed by physicians for confirmation of melanoma-related death.

Exposure assessment

All data on risk factors, states of residence, and exposures were collected via the biennial questionnaires. Questionnaires are mailed to each participant, and for each cycle, average follow-up has been more than 90%. Across all 3 cohorts, the following data were collected: 1) family history of malignant melanoma in first-degree relatives; 2) the number of nevi measuring ≥3 mm on an extremity; 3) natural hair color at age 21 years; 4) skin burning reaction after ≥2 hours of bright sun exposure during childhood/adolescence; and 5) the number of lifetime severe or blistering sunburns. Family and personal disease history are updated with each questionnaire cycle. For the nevus count on an extremity, the left arm (shoulder to wrist) was used in the NHS, the bilateral lower legs (knee to ankle) were used in the NHS2, and the bilateral forearms (wrist to elbow) were used in the HPFS. In the NHS cohort only, tanning ability was assessed by asking what kind of tan developed after repeated sun exposures (e.g., a 2-week vacation outdoors) during childhood or adolescence. This information was combined with participants' responses regarding susceptibility to burn to determine the Fitzpatrick skin type of NHS participants.

Fifty US states and Washington, DC, were stratified according to the average ultraviolet index in the month of August as determined by the National Oceanic and Atmospheric Administration (26). By using residential data from the study participants at birth, at age 15 years, and at age 30 years, we categorized states into low, medium, and high indices of ≤5, 6, and ≥7, respectively (27).

Statistical analysis

Each participant contributed person-time from the date of the collection of phenotypic data to the date of incident MMIS or the end of the follow-up period, whichever came first. Categories representing the lowest perceived risk of MMIS (i.e., no burning reaction, no family history, lowest ultraviolet index) were used as referents except in the case of hair color, in which light brown was used because it is the most common hair color. For both age-adjusted (5-year categories) and multivariate regression models, variables were modeled as dichotomous or categorical. Family history of melanoma was a dichotomous variable (yes/no), and categorical variables were based on the questions and answers from the original questionnaires.

Age-adjusted relative risk, multivariate relative risk, and 95% confidence intervals were calculated by using Cox proportional hazards regression to adjust for age and other covariates including family history, number of nevi, number of sunburns, skin reaction to sunlight, and natural hair color at age 21 years for each cohort. Models were adjusted for calendar year because the time parameter and person-time for each participant were calculated from the date of return

of the questionnaires (1980 for the NHS, 1989 for the NHS2, and 1986 for the HPFS) to the first endpoint (incident MMIS, death, or the end of the follow-up period). All multivariate analyses were rerun by controlling for tanning response in the NHS cohort with no appreciable changes in relative risks (data not shown). A meta-analysis was then conducted by using a random effects model and *P* values for trend, and *Q* statistics for heterogeneity were calculated. We used SAS, version 9.2, software for all analyses (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 250,151 participants (97,309 from the NHS; 107,844 from the NHS2; and 44,998 from the HPFS) were followed over the aforementioned period with 2,682 primary incident cases of melanoma lesions diagnosed during 7,144,820 person-years of follow-up. MMIS represented 33% ($n = 888$) of the melanoma cases (32% in the NHS; 40% in the NHS2; and 27% in the HPFS). In all 3 cohorts, participants were older at the time of diagnosis of MMIS compared with the time of diagnosis of invasive malignant melanoma; by using Student's *t* test, we found that this age difference was statistically significant among women but not men (in the NHS, the mean age at MMIS diagnosis was 64.8 years vs. the mean age at invasive malignant melanoma diagnosis of 59.4 years, $P < 0.0001$; in the NHS2, the mean age at MMIS diagnosis was 47.0 years vs. the mean age at invasive malignant melanoma diagnosis of 44.9 years, $P < 0.0001$; and in the HPFS, the mean age at MMIS diagnosis was 67.4 years vs. the mean age at invasive malignant melanoma diagnosis of 65.9 years, $P = 0.10$). The melanoma-specific mortality rates for women and men with MMIS were similarly low in each cohort with no statistically significant difference among

Table 1. Characteristics of US Women and Men With Malignant Melanoma In Situ

Characteristic	NHS (1980–2008) ($n = 406$)[a]		NHS2 (1989–2009) ($n = 294$)[a]		HPFS (1986–2008) ($n = 188$)[a]	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age, years[b]		64.8 (9)		47.0 (6)		67.4 (10)
Mortality from melanoma	0.25		0.34		0.53	
Lentigo maligna melanoma in situ[c]	26		6		33	
Family history of malignant melanoma[d]	8		14		11	
≥6[e] Nevi on an extremity[f]	12		41		14	
Natural red or blond hair[g]	20		31		13	
History of ≥6[e] severe or blistering sunburns	10		18		40	
Painful or blistering skin reaction to the sun[h]	17		32		30	
UV index of residence at birth[i]						
Low	28		25		30	
Medium	62		48		41	
High	10		27		29	
UV index of residence at age 15 years[i]						
Low	29		28		29	
Medium	60		44		37	
High	11		28		34	
UV index of residence at age 30 years[i]						
Low	23		24		26	
Medium	64		41		39	
High	13		35		35	

Abbreviations: HPFS, Health Professionals Follow-Up Study; MMIS, malignant melanoma in situ; NHS, Nurses' Health Study; NHS2, Nurses' Health Study 2; SD, standard deviation; UV, ultraviolet.

[a] Number of participants forall incident MMIS age/mortality data ($n = 888$); for complete phenotypic data ($n = 852$); and for complete phenotypic and residential data ($n = 835$).

[b] Age at the time of diagnosis of MMIS.

[c] Proportion of incident MMIS lesions of the lentigo maligna melanoma subtype.

[d] Family history of malignant melanoma at the time of diagnosis of MMIS.

[e] For the NHS2, ≥5 nevi.

[f] Defined as nevi ≥3 mm on the left arm in the NHS, on bilateral forearms in the HPFS, and on bilateral lower legs in the NHS2.

[g] At age 21 years.

[h] The kind of reaction the subject's skin would have had during childhood or adolescence after 2 or more continuous hours in the sun on a bright sunny day after having had previous exposure to the sun several times.

[i] UV index of residence of low, medium, or high, corresponding to ≤5, 6, or ≥7, respectively, as previously described in Qureshi et al. (*Arch Intern Med.* 2008;165(5):501–507) (27).

Table 2. Multivariate[a] and Meta-Analysis of Incident Malignant Melanoma In Situ in US Women and Men

	NHS (1980–2008) (*n* = 382)			NHS2 (1989–2009) (*n* = 288)			HPFS (1986–2008) (*n* = 182)			Meta-Analysis (*n* = 852)			
	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	*P* for Heterogeneity
Family history of melanoma[b]	29	1.42	0.97, 2.08	41	2.00	1.43, 2.79	11	2.63	1.41, 4.93	81	1.85	1.36, 2.53	0.19
P value		0.07			<0.0001			0.002			0.0001		
No. of nevi on extremity[c]													
None	152	1.00	Referent	86	1.00	Referent	69	1.00	Referent	307	1.00	Referent	
Low	79	1.37	1.04, 1.80	49	1.45	1.02, 2.06	32	1.59	1.04, 2.42	160	1.44	1.19, 1.74	0.85
Medium	35	1.88	1.30, 2.71	28	1.58	1.03, 2.42	16	1.98	1.15, 3.42	79	1.79	1.39, 2.29	0.76
High	37	3.47	2.42, 4.98	112	2.96	2.23, 3.92	19	3.45	2.07, 5.75	168	3.18	2.59, 3.90	0.74
P_{trend}		<0.0001			<0.0001			<0.0001			<0.0001		
Hair color[d]													
Red	25	1.71	1.10, 2.66	22	2.02	1.26, 3.25	5	1.02	0.40, 2.60	52	1.75	1.29, 2.38	0.41
Blond	40	0.94	0.66, 1.33	59	1.30	0.94, 1.79	15	0.74	0.42, 1.31	114	1.02	0.75, 1.38	0.17
Light brown	145	1.00	Referent	102	1.00	Referent	57	1.00	Referent	304	1.00	Referent	
Dark brown or black	117	0.68	0.54, 0.87	79	0.84	0.63, 1.13	77	0.91	0.64, 1.29	273	0.78	0.66, 0.93	0.34
P_{trend}		0.0001			0.0004			0.91			0.01		
Susceptibility to burn[e]													
No burn or some redness	189	1.00	Referent	110	1.00	Referent	31	1.00	Referent	330	1.00	Referent	
Burn	80	1.07	0.81, 1.40	87	1.44	1.08, 1.92	85	1.82	1.19, 2.77	252	1.36	1.02, 1.81	0.09
Painful or blistering burn	56	1.05	0.76, 1.45	91	1.58	1.04, 2.39	49	1.91	1.18, 3.09	142	1.32	0.98, 1.77	0.13
P_{trend}		0.69			0.02			0.007			0.05		
No. of severe or blistering sunburns[f]													
None	158	1.00	Referent	68	1.00	Referent	20	1.00	Referent	246	1.00	Referent	
Low	70	1.27	0.96, 1.69	105	1.16	0.85, 1.58	41	1.27	0.74, 2.17	215	1.23	1.01, 1.49	0.91
Medium	34	1.56	1.07, 2.27	63	1.42	1.00, 2.03	39	1.15	0.67, 1.99	136	1.43	1.13, 1.81	0.67

Table continues

Table 2. Continued

	NHS (1980–2008) (n = 382)			NHS2 (1989–2009) (n = 288)			HPFS (1986–2008) (n = 182)			Meta-Analysis (n = 852)			
	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	P for Heterogeneity
High	29	1.43	0.95, 2.16	51	1.78	1.21, 2.64	66	1.26	0.75, 2.13	146	1.55	1.21, 1.99	0.45
P_{trend}			0.007			0.002			0.51			0.0006	

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHS2, Nurses' Health Study 2; RR, relative risk.

[a] Multivariate analysis controlled for age, family history of melanoma, number of nevi on an extremity, hair color, susceptibility to burn, and number of severe or blistering sunburns.

[b] Family history of malignant melanoma (first-degree relative), dichotomous variable with yes/no response.

[c] Number of nevi (size ≥3 mm) on the left arm from the shoulder to the wrist in the NHS, on bilateral forearms in the HPFS, and on bilateral lower legs (ankle to knee) in the NHS2. "Low" indicates 1–2 nevi in all studies; "Medium" indicates 3–5 nevi in the NHS and the HPFS or 3–4 nevi in the NHS2; "High" indicates ≥6 nevi in the NHS and the HPFS or ≥5 nevi in the NHS2.

[d] Natural hair color at age 21 years.

[e] The kind of reaction the subject's skin would have had during childhood or adolescence after 2 or more continuous hours in the sun on a bright sunny day after having had previous exposure to the sun several times.

[f] Number of severe or blistering sunburns. "Low" indicates 1–2 sunburns in all studies; "medium" indicates 3–5 sunburns in NHS and HPFS or 3–4 sunburns in NHS2; "high" indicates ≥6 sunburns in NHS and HPFS or ≥5 sunburns in NHS2.

cohorts by Fisher's exact test (0.25% in the NHS, 0.34% in the NHS2, and 0.53% in the HPFS; $P = 0.16$). Cohorts were well matched in regard to exposure to MMIS risk factors, with a consistent proportion of participants living in each ultraviolet index stratum (Table 1 and Web Table 1 available at http://aje.oxfordjournals.org/). As compared with the NHS and HPFS cohorts, the younger NHS2 cohort had a lower proportion of lentigo MMIS. Family history of melanoma at the time of diagnosis was similar across all 3 cohorts. Additionally, the younger population of women (in the NHS2) had an increased percent of participants with 6 or more nevi on an extremity, and the male cohort had a higher prevalence of 6 or more severe or blistering sunburns. Red hair was most prevalent among the younger women and least prevalent among men.

Table 2 shows multivariate analyses and meta-analyses of known skin cancer phenotypes and the relative risk of MMIS across the 3 cohorts. The presence of 6 or more nevi on the extremities was associated with the greatest multivariate-adjusted relative risk in both individual and meta-analysis across the 3 cohorts (relative risk (RR) in the meta-analysis = 3.18, 95% confidence interval (CI): 2.59, 3.90; RR in the NHS = 3.47, 95% CI: 2.42, 4.98; RR in the NHS2 = 2.96, 95% CI: 2.23, 3.92; RR in the HPFS = 3.45, 95% CI: 2.07, 5.75).

In the meta-analysis, family history of malignant melanoma in a first-degree relative conferred statistically significant increased relative risk (RR = 1.85, 95% CI: 1.36, 2.53). In individual cohort multivariate analyses, relative risk ranged from 1.42 to 2.63 with slight loss of significance in the NHS cohort (NHS multivariate RR = 1.42, 95% CI: 0.97, 2.08; NHS2 multivariate RR = 2.00, 95% CI: 1.43, 2.79; and HPFS multivariate RR = 2.63, 95% CI: 1.41, 4.93).

In women but not in men, red hair color was associated with a statistically significant elevated risk of MMIS (NHS multivariate RR = 1.71, 95% CI: 1.10, 2.66; NHS2 multivariate RR = 2.02, 95% CI: 1.26, 3.25; and HPFS multivariate RR = 1.02, 95% CI: 0.40, 2.60). Moreover, black or dark brown hair was found to be protective against MMIS in all cohorts. There was an increasing risk of MMIS with increasingly lighter hair color from black to red, which was significant in the meta-analysis but not in the individual male cohort (in the meta-analysis, $P_{trend} = 0.01$; in the NHS, $P_{trend} < 0.0001$; in the NHS2, $P_{trend} = 0.0004$; and in the HPFS, $P_{trend} = 0.9098$).

In the meta-analysis, a burning skin reaction to sun exposure was associated with significantly increased risk for MMIS (RR = 1.36, 95% CI: 1.02, 1.81), whereas the risk associated with a painful or blistering burn reaction was nearly identical but not significant (RR = 1.32, 95% CI: 0.98, 1.77). Increasing skin sensitivity to the sun was associated with increased risk of MMIS in the NHS2 and HPFS cohorts as well (in the NHS, $P_{trend} = 0.69$; in the NHS2, $P_{trend} = 0.02$; and in the HPFS, $P_{trend} = 0.007$). The number of severe lifetime sunburns was associated with statistically significant risk of MMIS beginning with 1–2 sunburns and increasing as participants reported 6 or more sunburns ($P_{trend} = 0.0006$).

Table 3 shows the relative risks of MMIS according to the Fitzpatrick skin type of women in the NHS. With type IV as the referent, type I skin was associated with a nearly 3-fold

Table 3. Age-Adjusted and Multivariate Analysis[a] by Fitzpatrick Skin Type in US Women, Nurses' Health Study, 1980–2008 ($n = 313$)

Fitzpatrick Skin Type[b]	No. of Cases	%	Age-Adjusted RR	95% CI	Multivariate RR	95% CI
I	35	11	2.84	1.81, 4.45	2.01	1.24, 3.25
II	132	42	2.24	1.58, 3.18	1.81	1.26, 2.59
III	105	34	1.63	1.14, 2.34	1.50	1.04, 2.16
IV	41	13	1.00	Referent	1.00	Referent
P_{trend}			<0.0001		0.0008	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Multivariate analysis adjusted for Fitzpatrick skin type, number of severe or blistering sunburns, number of nevi on the left arm, hair color at age 21 years, and family history of malignant melanoma.

[b] Type I is defined as no tan and blistering burn; no tan and painful burn; or no tan and burn. Type II is defined as light tan and painful burn; light tan and blistering burn; light tan and burn; light tan and some redness; average tan and painful burn; or average tan and burn. Type III is defined as average tan and some redness; average tan and no burn; or deep tan and burn. Type IV is defined as good tan and no burn; or deep tan and some redness.

increase in relative risk in the age-adjusted analysis and a 2-fold risk in the multivariate analysis (NHS age-adjusted RR = 2.84, 95% CI: 1.81, 4.45; NHS multivariate RR = 2.01, 95% CI: 1.24, 3.25). In both the age-adjusted and the multivariate analyses, statistically significant increased relative risk was seen even in type III skin and increased in a stepwise fashion from type IV to type I ($P_{trend} = 0.0008$).

Table 4 and Web Table 2 show the risk of MMIS according to the ultraviolet index of state of residence. Of the participants with incident MMIS, 72% lived in states of the same ultraviolet index at birth, at age 15 years, and at age 30 years. In individual multivariate analysis, residence in US states with a medium ultraviolet index was associated with increased risk of MMIS among older women but not among younger women or men (NHS multivariate RR = 1.45, 95% CI: 1.08, 1.95; NHS2 multivariate RR = 0.82, 95% CI: 0.57, 1.18; and HPFS multivariate RR = 0.67, 95% CI: 0.42, 1.06). Although in the meta-analysis there was a slight increase in risk in states with ultraviolet indices of 7 or higher, we found no significant differences among states of low, medium, or high ultraviolet indices.

DISCUSSION

To date, there have been few large studies on in situ melanoma, and there are scant data on risk factors for MMIS. Past studies examining phenotypic risk have either excluded MMIS entirely or have pooled the lesions with invasive malignant melanoma, although the proportion of invasive to in situ lesions varies widely (9, 28–33). Park et al. (34) conducted the only previous phenotypic prospective study of MMIS lesions in participants residing in 2 US states, and they did not assess the number of nevi, which is a significant risk factor in invasive malignant melanoma as well as in multiple primary melanoma (29, 32).

In this study, we examined data on cases of malignant melanoma in situ as confirmed by primary pathology report in a large population of US women and men, allowing for comparison of 3 separate cohorts that are well matched in regard to race, education, occupation, and risk factor exposure. Individual multivariate and meta-analyses demonstrated that the number of extremity nevi is associated with increased risk of MMIS, with risk increasing with higher nevus counts. Importantly, this risk was significant even for subjects with only 1 or 2 nevi on an extremity. Fitzpatrick skin type demonstrated increasing risk from type IV (least risk) to type I (a 2-fold risk). Family history, hair color, skin reaction to the sun, and the number of severe sunburns also made statistically significant contributions to the risk of melanoma in situ. Conversely, ultraviolet index of state of residence at birth, at age 15 years, and at age 30 years was not associated with significant differences in risk.

These findings are consistent with the limited data that exist for MMIS and nevi. In a prospective study of 40,000 Swedish women, Nielsen et al. (9) demonstrated that self-reported nevi counts of the left arm were significantly associated with increased risk of pooled invasive/in situ melanoma, although given the relatively small number of in situ lesions ($n = 60$) grouped with the invasive malignant melanoma lesions ($n = 155$), it is difficult to ascertain the exact relative contribution of MMIS. Interestingly, the younger women in the NHS2 cohort had a strikingly higher prevalence of 6 of more nevi. This could be attributed to a variety of reasons, including propensity for nevi on the legs due to clothing and sun exposure behavior, increased surface area of the legs as compared with the arms, or the fact that nevi counts tend to peak in the second decade of life and then regress or alter their pigment with aging (35). However, the data may also indicate that nevus-prone persons are susceptible to younger-onset MMIS and may therefore require closer screening. Moreover, the data may suggest that nevi contribute to the risk of superficial spreading melanoma in situ more than to lentigo maligna melanoma in situ. Lentigo maligna melanoma in situ, a subtype of melanoma in situ, is more commonly diagnosed in elderly patients and is thought to result from chronic sun exposure (12). The younger population of women had a much lower incidence of lentigo maligna melanoma in situ, and when phenotypic risk was analyzed excluding lentigo maligna melanoma in situ, the relative risk in subjects with

Table 4. Multivariate and Meta-Analysis[a] of Risk of Malignant Melanoma In Situ in US Women and Men Residing in a State With the Same UV Index at Birth, at Age 15 Years, and at Age 30 Years

UV Index of Residence[b]	NHS (1980–2008) ($n = 243$)			NHS2 (1989–2009) ($n = 180$)			HPFS (1986–2008) ($n = 114$)			Meta-Analysis ($n = 537$)			
	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	No. of Cases	Multivariate RR	95% CI	*P* for Heterogeneity
Low	59	1.00	Referent	48	1.00	Referent	30	1.00	Referent	137	1.00	Referent	
Medium	167	1.45	1.08, 1.95	78	0.82	0.57, 1.18	43	0.67	0.42, 1.06	288	0.95	0.59, 1.52	0.007
High	17	1.11	0.64, 1.90	54	1.20	0.81, 1.76	41	1.01	0.63, 1.62	112	1.12	0.86, 1.45	0.85
P_{trend}		0.14			0.38			0.70			0.10		

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHS2, Nurses' Health Study 2; RR, relative risk; UV, ultraviolet.

[a] Multivariate analysis controlled for age, family history of melanoma, number of nevi on an extremity, hair color, susceptibility to burn, and number of severe or blistering sunburns.

[b] UV index of residence of low, medium, or high, corresponding to ≤5, 6, or ≥7, respectively, as previously described in Qureshi et al. (*Arch Intern Med.* 2008;165(5):501–507) (27).

high nevus burdens increased further in the NHS and HPFS cohorts (Web Table 3), whereas susceptibility to burn and number of sunburns were associated with significantly decreased risk in all 3 cohorts. Divergence of risk for superficial spreading melanoma and lentigo maligna melanoma has been supported by past studies of small numbers of pooled in situ/invasive lesions, which found no association between nevi and lentigo maligna melanoma risk (28, 30), whereas no previous data exist for a population of purely in situ lesions.

Family history of malignant melanoma was associated with increased relative risk in all 3 cohorts. These results are consistent with what has been demonstrated in combined in situ/invasive analyses (29, 36) as well as the findings from Park et al. (34), who found a comparable increased relative risk in MMIS, although without statistical significance. Natural red hair, but not blond, was associated with a significantly elevated risk of MMIS among women, whereas dark brown or black hair was protective. Nonsignificance of hair color among men is most likely attributable to the small sample size, although it is not clear why few incident cases of MMIS occurred in red-haired male participants.

In regard to sun exposure, these data show that the number of sunburns as well as the host's skin reaction to bright sunlight plays a more significant role in MMIS risk than does the ultraviolet index of the state of residence at birth, at age 15 years, and at age 30 years. The ultraviolet index, developed by the National Weather Service (Silver Spring, Maryland) and the US Environmental Protection Agency (Washington, DC), is a measure of ultraviolet radiation levels weighted according to the McKinlay-Diffey erythema action spectrum and adjusts for altitude, cloud cover, stratospheric ozone concentrations, and latitude (26). Past analyses have shown an association between ultraviolet index and the development of single or multiple basal or squamous cell carcinomas, whereas the association between ultraviolet index and melanoma has rarely been studied, and no consensus exists for the role of ultraviolet index in melanoma risk (27, 37–39). No previous data exist for melanoma in situ, and this study did not demonstrate a significant association. It is important to note that the risk of MMIS increases with an increasing number of sunburns, and although more men reported high sunburn counts than did women, risk for each stratum was similar across the cohorts with no significant heterogeneity in the meta-analysis. Burn susceptibility was also associated with increased risk, and when incorporated into a Fitzpatrick skin score, it showed a strong trend of increasing risk for more sun-sensitive participants. It is known that intense, intermittent sun exposure and its interaction with differentially pigmented skin play a role in the development of both invasive melanoma and benign nevi (40–43), and although this has only begun to be investigated in MMIS (22, 34), the contribution appears to be similar. Importantly, these findings indicate that a history of the number of sunburns, as well as an estimate of sun sensitivity via Fitzpatrick skin type or other measure, should be included in all patient evaluations when screening for malignant melanoma.

The relative strengths of this study were the ability to analyze both phenotypic risk and ultraviolet index in a large

number of pathologically confirmed MMIS lesions and to assess similarities across 3 large cohorts of women and men living in every US state. The cohorts were similar with regard to occupational and cultural exposure, education, socioeconomic status, medical knowledge, and access to health care, thus minimizing many confounders of studies of this magnitude; the consistency of findings across all 3 cohorts increases the validity of the data. For these same reasons, however, conclusions should be limited to a population of US women and men with similar characteristics. This underscores the need for further examination of MMIS in persons of different national, racial, and economic backgrounds. The ultraviolet index analysis is limited in that it accounts for only 3 time points (birth, age 15 years, and age 30 years) and cannot account for residence between or after those time points. More complete lifetime residential data would provide a more accurate assessment of the role of ultraviolet index in the risk for MMIS. Because lifetime duration and intensity of sun exposure are difficult to quantify, the ultraviolet index of residence, number of sunburns sustained, and self-reported burning responses are imperfect measures of this exposure. In an attempt to minimize misclassification of the outcome, all primary pathology reports were reviewed by an experienced dermatologist (A.A.Q.). Further, to accommodate any potential recent trends in the diagnostic behavior of clinicians, all analyses were repeated on MMIS diagnosed only within the last 10 years; there were no appreciable changes in patterns of risk factors across the 3 cohorts that could not be attributed to decreased sample size (data not shown). Similarly, to investigate whether the association with phenotypic factors may have been a result of increased screening within a high-risk population, sensitivity analyses were conducted in multivariate models adjusting for marital status in the NHS cohort and physical examination and prostate-specific antigen testing in the HPFS cohort. Controlling for these variables did not alter the relative risks or the significance of the data (data not shown).

This study is the largest analysis of phenotypic risk of MMIS to date in 3 large cohorts with more than 20 years of follow-up, and it is the first to demonstrate the risk conferred by nevi. The presence of photodistributed nevi was the strongest predictor of MMIS, and family history, hair color, burning reaction, the number of lifetime sunburns, and Fitzpatrick skin type all contributed to additional increased risk. The lack of association with ultraviolet index suggests that host phenotypic characteristics and sun protection behaviors, particularly in regard to severe sunburns, play a more significant role in risk for MMIS than does ambient ultraviolet exposure and should serve as a basis for patient education and risk modification. These findings are largely congruent with what is known regarding invasive melanoma, but as our understanding of malignant melanoma becomes more sophisticated, investigation of in situ lesions and how they compare with deeper, aggressive forms is important to our overall understanding of malignant melanoma. Further study should aim to elucidate the role of in situ melanoma within the greater spectrum of cutaneous malignant melanoma and to allow practitioners a better understanding of persons at risk, providing the basis to further develop effective screening practices.

ACKNOWLEDGMENTS

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This work was supported by the National Institutes of Health (grants CA87969 and CA055075).

We are deeply indebted to the staff of the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study for their valuable contributions. We also thank the state cancer registries in the following states for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

Conflict of interest: none declared.

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