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Risk Factors for Malignant Melanoma in White and Non-White/ Non-African American Populations: The Multiethnic Cohort

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Abstract

It is unknown whether the established risk factors for malignant melanoma in whites influence malignant melanoma risk in non-whites. We examined the risk factors for melanoma among 39,325 whites and 101,229 non-whites/multiracials (Japanese American [47.5%], Latino American [34.8%], Native Hawaiian [2.1%] and multiracial [15.6%], excluding African Americans) in the Multiethnic Cohort study. With an average follow-up of 12.7 years, 581 invasive malignant melanoma (IMM) and 412 melanoma *in situ* (MIS) cases were identified, of which 107 (IMM) and 74 (MIS) were among non-whites/multiracials. The relative risks (RRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models using days from cohort entry as the underlying time variable. Among non-white/multiracial males, location of IMM tumors differed from those of white males ($p<0.001$); and non-white/multiracial females were more likely to be diagnosed with later stage of disease ($p<0.001$). After adjusting for potential confounders, age at cohort entry, male sex, higher education, and sunburn susceptibility phenotypes were associated with an increased risk of invasive malignant melanoma in non-whites/ multiracials ($p<0.05$). The risk estimates for age at cohort entry and lighter hair and eye color were greater in non-whites/multiracials than in whites (p-heterogeneity=0.062, 0.016, and 0.005, respectively). For MIS risk, RRs between whites and non-whites/multiracials also differed for study location and education (p-heterogeneity ≤ 0.015). In conclusion, similar to whites, age at cohort entry, male sex, and susceptibility to sunburn phenotypes may be predictive of malignant melanoma risk in non-white populations excluding African-Americans.

Keywords

melanoma risk factors; non-whites

Introduction

Melanoma is one of the few cancers with increasing incidence worldwide (1–2). Although the incidence and its increase are predominantly found among non-Hispanic whites (3),

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populations commonly known for having lower incidence of disease, such as Japanese in Japan (4–5), Puerto Ricans (6), Hispanics in California (7) and Florida (8), and the non-whites in New Zealand (9) have also shown an increase in rates. The exact reasons for this are unknown. This increase has been hypothesized to be a result of the growing accessibility to recreational sun exposure (10–11) and UV radiation (UVR) from tanning beds (12–13); as well as increasing cancer surveillance and/or reporting (1). Most epidemiologic studies of malignant melanoma have been conducted in whites and they have identified these risk factors: exposure to UVR from the sun or artificial sources, older age, sunburns, and phenotypes that increase the risk of sunburns (*e.g.* fair skin color) (14–15).

The incidence of malignant melanoma among non-whites is relatively low in the U.S. The respective age-adjusted incidence rates (per 100,000) for men and women are 4.0 and 3.9 in Hispanics and 1.6 and 1.3 in Asian/Pacific Islanders, compared to 30.9 and 19.7 in whites (16). Epidemiologic studies of malignant melanoma in non-European or African descendents are scarce, thus, risk factors in non-whites have not been well characterized. This population is often diagnosed at an advanced stage of disease compared to their white counterparts (8, 17–19). Therefore, knowing risk factors in non-whites is necessary for melanoma prevention and the reduction of melanoma-related deaths.

We are unaware of any published cohort studies investigating risk factors for malignant melanoma in non-white or multiethnic populations. Using the Multiethnic Cohort Study (MEC) data, we examined whether tumor characteristics and known risk factors for malignant melanoma vary between white and non-white/multiracial (Japanese American, Latino, Native Hawaiian and multiracial, excluding African American) populations.

MATERIALS AND METHODS

Study population

The MEC is a prospective cohort study established to investigate the association of lifestyle and dietary factors with chronic diseases in a multiethnic population. Details of the study design have been previously published (20). The cohort is comprised of 215,251 men and women between the ages of 45 to 75 at recruitment, primarily belonging to one of these racial/ethnic groups: African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites. Potential participants were identified in Hawaii and California (primarily Los Angeles County) through drivers' license files, voter registration lists, and Health Care Financing Administration files. Between 1993 and 1996, each participant completed a mailed, self-administered questionnaire regarding demographic, dietary, lifestyle, and other exposure factors. The institutional review boards of the University of Hawaii, the University of Southern California, and the University of California, Los Angeles approved this study.

Inclusion and exclusion criteria

In preliminary analyses among non-whites, we found that heterogeneity of risk estimates were greater for some risk factors, such as ever-sunburned status, when including African Americans compared to when excluding African Americans (p=0.05 vs. 0.15). Therefore, to reduce heterogeneity and possible residual confounding within the non-white/multiracial group, African Americans and part-African Americans (n=28,119, with just 7 melanoma cases) were excluded. We also excluded participants who: *i*) did not belong to one of the five main racial/ethnic groups (n=13,488), *ii*) had an implausible dietary history (n=8,263), *iii*) had a prior history of melanoma or were missing non-melanoma skin cancer (NMSC) history (n=2,318), *iv*) had a prior history of cancer (other than NMSC) before the date of the baseline questionnaire (n=14,632), or *vi*) had missing data on variables of interest:

education, natural hair and eye color, ever-sunburned status, tanning ability, and skin's reactivity to acute sunlight (n=7,877).

After all exclusions, the eligible population for invasive malignant melanoma (IMM) included 67,521 men and 73,033 women. Although some melanoma in situ (MIS), if left untreated, may evolve into IMM, the risk of developing into an invasive form is unknown. For instance, in lentigo maligna, a type of MIS, the risk of progression has been reported to be as low as 5% and as high as 50% (21). Therefore, to examine the outcome of MIS, an additional 21 males and 26 females who had a previous history of MIS were also excluded from the at-risk eligible population. We performed a sensitivity analysis where we used a common at-risk population including participants without a history of IMM or MIS and found the associations did not differ. Here, malignant melanoma (MM) refers to both IMM and MIS. Excluded participants were slightly older (3.4 years) than those who remained in the analysis. A sensitivity analysis was conducted including those with prior non-melanoma cancers; findings were similar.

Follow-up and case identification

Participants' follow-up began at the completion of the baseline questionnaire and continued until reaching one of these endpoints: 1) diagnosis of invasive malignant melanoma, 2) death, or 3) end of follow-up, December 31, 2007 and, in the instances where MIS was the outcome of interest, 4) diagnosis of MIS. All incident cases of malignant melanoma were identified by record linkage to the Hawaii Tumor Registry (HTR), the Cancer Surveillance Program (CSP) for Los Angeles County, and the California Cancer Registry (CCR). The Hawaii and California tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, estimated to have a >99% data completeness (22). Record linkages to the Hawaii and California registries are performed at least annually. The HTR and the CCR cover their respective state populations, while the CSP covers the Los Angeles County area. Linkage was performed by the tumor registries using personal identifiers of name, birthdate, sex, race and social security number. Partial matches were manually checked to identify further cases. Cases of malignant melanoma were defined by International Classification of Diseases for Oncology (ICD-O-3) histology codes 8720–8790 and site code C44.

We used annual linkages to state death certificate files in California and Hawaii, and periodical linkages to the National Death Index in order to identify deaths within the cohort. Cohort participants were followed for an average of 12.7 years, contributing to a total of 1,780,408 person-years. At the end of follow-up, 581 IMM cases and 412 MIS cases were identified among this eligible population of whites and non-whites/multiracials.

Data

Each participant self-reported one or multiple racial/ethnic categories for themselves and for each parent. This study was restricted to those who selected for themselves at least one of the following: non-Hispanic white, Latino, Japanese American, or Native Hawaiian. Here, race/ethnicity was defined by self-report of a single racial/ethnicity (e.g. single-race whites will be referred to as "whites"). Participants with more than one of the four above mentioned racial/ethnic groups were classified as multiracial, of which, the majority categorized themselves as having European-American (70.7%) and/or Native Hawaiian ancestry (65.3%). To account for white admixture in multiracials, which presumably would affect risk for melanoma, we also created a part-white status variable (yes and no). Due to the small number of malignant melanoma cases identified in Japanese American, Latino, Native Hawaiian, and multiracial populations, these groups were combined and labeled as "non-whites/multiracials" (non-whites or multiracials).

Baseline characteristics from the questionnaire were previously published (20). Participants answered questions regarding their natural hair color at the age of 20 (black, medium or dark brown, light brown, blonde, or red) and eye color (brown or black, blue, grey, and green). Over 99.5% of participants provided a single response. Among those with more than one response, traits were classified according to the greatest pigmented phenotype (i.e. "darkest"). Participants were asked about their skin's tanning ability after repeated sun exposure and unprotected skin's reactivity to one hour of acute sun exposure. Ever-sunburned status was defined as ever having a blistering sunburn. The age at which this first occurred and total lifetime number of sunburns were also reported.

Due to the high correlations among sunburn susceptibility phenotypes: hair color, eye color, tanning ability (deeply, moderately, lightly, not at all), and skin's reactivity to acute sunlight (no effect or tans, mild sunburn then tans, severe sunburn, severe sunburn with blistering), we created a sunburn susceptibility phenotype index that categorized the summation of the four above-mentioned propensity to sunburn phenotypes. The categories of hair color, tanning ability, and skin's reactivity to acute sunlight each had four levels (0 to 3), scaled from lowest to highest risk. We did not detect a gradient of risk within blue, grey, and green eye colors, therefore, the measure of eye color was given two levels: dark=0 and light=1. The sum of all four phenotypes assumes equal weight of each of the four phenotypic factors on an additive scale (0 to 10), where 0 is having dark hair, dark eyes, deeply tans, and has no reaction or tans in reaction to sunlight and 10 is having red hair, light eyes, does not tan at all, and has blistering sunburn reaction to sunlight. Subsequently, this summed value was categorized into a five-category sunburn susceptibility phenotype index (0–1: "lowest risk," 2–3: "low risk," 4–5: "medium risk," 6–7: "high risk", >7: "highest risk").

Statistical analyses

Tests for difference in the distribution of stage, histology and tumor location between whites and non-whites/multiracials were conducted using the chi-square test and Fisher's exact test when expected values for one of the cells was less than 5.

Due to differing etiological factors, acral lentiginous melanoma (ALM) cases were excluded from calculations of relative risks (RR). The other more common histologic subtypes remained in the analysis, since ~58% of cases had not otherwise specified (NOS) histologies. RRs and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models and stratified by race: whites and non-whites/multiracials (Japanese Americans, Latinos, Native Hawaiians, and multiracials). The underlying time variable was days of follow-up, date of cohort entry to date of exit at one of the previously mentioned endpoints. For the IMM analysis, incident MIS cases were followed until death or end of follow-up. For the MIS analysis, incident IMM cases were censored at diagnosis of IMM. All variables of interest met the proportional hazard assumption.

In the minimally-adjusted model, we adjusted for age at cohort entry, sex, race/ethnicity, part-white status, study site and education. For associations between sunburn susceptibility phenotypes and MM, the full regression model included the covariates from the minimally-adjusted model with further adjustment for ever-sunburned status, family history of melanoma and personal history of NMSC. For associations between all other risk factors of interest and MM, a sunburn susceptibility phenotype index (five-levels, explained above) was also included in the full regression model. The results were consistent whether adjusting for all four sunburn susceptible phenotypes (hair and eye color, ability to tan, or reactivity to acute sun exposure), one of the four phenotypes, or the sunburn susceptibility phenotype index. To maximize precision, the index score was used in place of all or one of these phenotypic measures.

Tests for heterogeneity by racial/ethnic groups were evaluated using the likelihood ratio test, which compared the full regression model including the interaction term, product of the race/ethnicity and variable of interest, and a main effects model. Interaction terms were created using the categories described above. The test of heterogeneity between MIS and IMM was performed using competing risk techniques, where each outcome was a different event. A Wald test was used to compare the parameters between outcomes. All statistical analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Whites were more likely than non-whites/multiracials to have: college attendance, phenotypes that increase susceptibility to sunburn (sunburn susceptibility phenotype index >7), blistering sunburns after acute sun exposure, ever-sunburn, a family history of melanoma and a personal history of NMSC (Table 1). Japanese Americans had the greatest homogeneity in hair and eye color (Supplementary Table 1).

The tumor characteristics for IMM and MIS among MEC participants stratified by sex and race/ethnicity are presented in Table 2. Approximately, 42% of cases had specific tumor histology information. Non-white/multiracial females were more likely to be diagnosed with later stage disease ($p<0.001$). This difference was not found in males. The anatomical location of IMM lesions differed between white and non-white/multiracial males; white males were more likely to have lesions located on the trunk (44.8% vs. 25.8%) and non-white/multiracial males were more likely to have such lesions on the lower limbs, including hips (19.7% vs. 6.3%). In women, the anatomical locations of IMM did not differ by race. However, non-white/multiracial women were more likely to present with MIS on the face (41.2% vs. 21.7%).

Table 3 presents both the minimally-and fully-adjusted RRs for IMM among whites and non-whites/multiracials. We found that the direction of associations were consistent between the minimally-and fully-adjusted models. In non-whites/multiracials, the association with ever-sunburned status was slightly attenuated where the association was no longer significant in the fully adjusted model ($p=0.305$). With the exception of age at cohort entry (p-heterogeneity=0.062) and hair and eye color (p-heterogeneity≤0.016), we found that the other IMM risk factors did not differ between whites and non-whites/multiracials (p-heterogeneity≥0.10). Age at cohort entry was suggestive of greater IMM risk among non-white/multiracials and lighter hair and eye colors were associated with greater IMM risk among non-white/multiracials.

Table 4 presents both the minimally-and fully-adjusted RRs for MIS among whites and non-whites/multiracials. We found that the RRs for MIS between whites and non-whites/multiracials also differed for geographical location and education (p-heterogeneity≤0.015), where both of these factors were not associated with MIS in non-whites/multiracials. The comparison of risk factors between IMM and MIS within whites and within non-whites/multiracials showed no difference in associations (p-heterogeneity>0.10) (data not shown), although the RRs for age at cohort entry and sunburn susceptible phenotypes appear stronger for IMM than MIS.

DISCUSSION

To our knowledge, this is the first prospective study to investigate tumor characteristics and risk factors for malignant melanoma in non-whites other than African-Americans and to compare these factors between this population and whites.

We found that non-white/multiracial males had a lower proportion of IMM on the anatomical trunk and non-white/multiracial females were more likely to present with later stage disease. Previous studies using cancer registry data have also reported that non-whites were more likely to present with tumors on the lower extremities, of ALM histological subtype and at later stage of disease (17–20, 23–28). Based on these observations, it has been suggested that UVR exposure may play less of an etiologic factor in melanoma development in non-whites.

To examine this, first, we confirmed the associations for established risk factors (14–15, 29–32): latitudinal location (Hawaii), higher education, male sex, age, lighter hair and eye color, propensity to sunburn phenotypes, ever-sunburned status, personal history of NMSC and family history of melanoma, with risk of IMM and MIS in our white population. Here, we showed that the association of these risk factors for IMM did not differ between whites and non-whites/multiracials. All factors, with the exception of latitudinal location and higher education, were associated with an increased risk of MIS in non-whites/multiracials. These findings suggest that, similar to whites phenotypes exhibiting greater susceptibility to sunburn are associated with an increased risk of MM in non-white/multiracial populations. Supporting this suggestion, experimental studies have shown that the amount of UVR-related DNA damage did not differ among those with darker skin phototype compared to whites (33). The difference in disease incidence may be partially explained from the observations that among non-whites, the UVR-related DNA damage may have a higher rate of repair (33) and/or may be restricted to the upper layers of skin (34).

Two sun exposure pathways to malignant melanoma have been postulated (35–37), acute and chronic sun exposure. The former is characterized by younger age at diagnosis, lesions often located on the trunk for men and lower limbs for females, and superficial spreading histological subtype (35, 38–45). Alternatively, tumors that may arise from chronic sun exposure have been associated with history of NMSC, older age, lesions found on the face and neck, and the lentigo maligna melanoma (LMM) histological subtype (35, 38–40, 42, 44). In non-whites/multiracials, the distribution of tumor characteristics, associations found with age and no clear association with ever-sunburned status suggests that in this population, chronic sun exposure may be more predictive of MM risk than acute exposure. However, due to the sizable number of unspecified tumor histologies, we were unable to confirm the proportion of LMM cases to support the chronic sun exposure hypothesis. In addition, test for heterogeneity between whites and non-whites/multiracials showed no difference in risk estimates for ever-sunburned status, suggesting that the role of acute sun exposure cannot be ruled out. The sample size may have been too small to detect a modest effect with ever-sunburned status, or heterogeneity of risk estimates between these two racial groups may have been insufficient. Studies with measures of chronic sun exposure, such as degree of solar keratoses (36) or tumor characteristics that have been associated with chronic exposure, such as TP53-positive status (46), would help to clarify the association of sun exposure patterns with malignant melanoma risk in non-whites/multiracials.

In contrast, chronic sun exposure may promote epithelial thickening and protect melanocytes from UVR damage (44, 47): in occupational studies, workers with chronic sun exposure have lower risk of melanoma (37, 48) than those with intermittent exposure (41, 49). Although occupational information exists for our participants, the sample size was too small to evaluate a potential difference in MM incidence among non-whites/multiracials with occupational variations of sun exposure (e.g. office vs. farm work). Further study to investigate the association with cumulated lifetime chronic sun exposure is needed.

The MM risk estimates for sunburn susceptible phenotypic score and hair and eye color differed between non-whites/multiracials and whites, where MM risk was greater among

non-whites/multiracials with lighter hair and eye color. This may be due to the differences within this group. For instance, in our study, the risk estimates for hair and eye color likely reflects a comparison of Latinos and multiracials, who have fairer hair and eye colors, to Japanese Americans, who have uniform dark hair and eyes. A study conducted by Wagner JK, et al. found that in Hispanics (n=45) and East Asians (n=15), melanin content, as measured by Adjusted Melanin Index (AMI), was similar between these two populations (p=0.371); however, tanning response, as measured by Melanogenic Dose-Response (MDR), was higher among East Asians than Hispanics (p<0.001) (50), suggesting that East Asians may be a lower risk of disease than Hispanics. In our study, we did not detect heterogeneity of sunburn susceptibility phenotypes within non-whites/multiracials. However, in future studies, quantitative measurements such as these, may improve accuracy and comparability within a multiethnic study population. In addition, adjustment for ancestral markers and/or investigating the association of polymorphisms in *MC1R*, which has been found to be associated with melanoma risk independently of these constitutional factors (51–53), may decrease residual confounding by race and improve risk predictability in populations that present with homogenous susceptibility to sunburn phenotypes. However, these markers were not available for this study.

Studies have found that non-whites are more likely to be diagnosed with later stage disease (17–18, 27) and thereby have decreased disease survival. Risk factors for MIS may represent risk for early stage disease, as well as associations with screening behaviors and accessibility to medical care. A case-only study using CCR data found that when accounting for socioeconomic status (SES), as derived from principle component analysis of census block-level data, survival for Asians (p=0.745) and Hispanics (p=0.296) did not differ from that for whites (54). In our study, no clear association was found between education and risk of MIS among non-whites/multiracials, suggesting that either higher education, as a proxy for SES, did not improve early detection of disease or delayed diagnosis may have occurred for other reasons, such as perceived lower susceptibility of disease. Further evaluation of SES, education and screening behaviors would helpful.

In addition, the risk profile of MIS and IMM may be very different; not all MIS progress to IMM (21, 55). MIS is a form of radial growth phase melanomas; therefore, *in situ* cases have not been identified in melanomas without a radial growth phase, such as nodular melanoma (55). The molecular pathology of these lesions have shown that MIS have lower frequencies of genetic mutations, such as NRAS and BRAF, and it has been suggested that MIS may acquire additional mutations to progress to invasive disease (56–57). Our study had the potential to elucidate lifestyle factors that are associated with melanoma screening and risk factors for radial growth phase melanomas among non-whites/multiracials. Although it appeared that the sun susceptibility variables were stronger for IMM than for MIS, when we used the competing risk model, no differences in risk estimates was detected for these two outcomes.

This study had some limitations. We were unable to adjust for length of sun exposure and freckling patterns or moles (58). Information regarding tumor Breslow index was unavailable, which is regrettable since studies have found that Hispanics in California and Pacific peoples in New Zealand may present with greater tumor thickness (7, 9). Residual confounding by constitutional factors may be present. However, the results were similar in models that included a single phenotypic factor, the sunburn susceptible phenotype index, or all phenotypic factors. This suggests that if such confounding was present, it was not captured in the baseline questionnaire data. Due to the limited number of cases in our California and non-white/multiracial populations we were unable to stratify by state of recruitment. With longer follow-up and additional cases, we will have improved power in analysis of non-whites. Hair and eye color, skin's tanning ability, and skin's reaction to

acute sun exposure may also have differential misclassification depending on perceived self-identity and self-image. The high proportion of melanoma histological subtypes coded as unspecified is a limitation, although rather consistent with what has been reported by other tumor registries (17, 59). Lastly, since we were unable to account for the cancer status of participants who moved out of both Hawaii and California, we censored out-of state migrants at the end of follow-up. This may have introduced bias to our analysis; however, this out-migration has been found to be extremely low (20).

Study strengths include the ability to investigate a range of potential risk factors for malignant melanoma within non-whites/multiracials, the prospective design, and a greater accuracy in measures of race/ethnicity compared to registry data.

In conclusion, this study presents the challenges in identifying risk factors for malignant melanoma in populations with a low incidence of disease. Here, age and susceptibility to sunburn phenotypes were associated with an increased risk of malignant melanoma in non-whites/multiracials. Awareness of these potential risk factors and screening among individuals who are older or have phenotypes that are susceptible to sunburns may help with disease prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IMM	invasive malignant melanoma
MIS	melanoma in situ
MM	malignant melanoma
RR	relative risks
CI	confidence intervals
IR	incidence rates
NOS	not otherwise specified
NM	Nodular Melanoma
LMM	Lentigo Maligna Melanoma
SSM	Superficial Spreading Melanoma
ALM	Acral Lentiginous Melanoma
NMSC	non-melanoma skin cancer

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Table 1

Percent distribution of baseline characteristics, constitutional factors, and sunburn history among eligible participants of the Multiethnic Cohort Study, 1993– 1996.

Characteristics	whites	non-whites/multiracials*	P_{value}
Totals	n=39,325	n=101,229	
Study Site	%	%	
California	29.0	47.3	
Hawaii	71.0	52.7	<0.001[a]
Sex			
Male	47.3	48.3	
Female	52.7	51.7	<0.001[a]
Race			
Japanese American		47.5	
Latino		34.8	
Native Hawaiian		2.1	
Whites	100.0		
Multiracials		15.6	
Multiracial part-white		70.7	
Multiracial not part-white		27.3	
Education			
≤ High school	25.9	51.7	
Some college	31.2	26.8	
≥ College	42.9	21.6	<0.001[a]
Age at baseline			
Mean (SD)	58 (9.0)	60 (8.6)	<0.001[b]
Hair color			
Black/Medium dark brown	57.0	93.2	
Light brown	26.2	6.1	
Blonde	13.6	0.5	
Red	3.1	0.2	<0.001[a]
Eye color			
Dark (black/dark brown)	40.7	95.6	
Light (blue, grey, and green)	59.3	4.4	<0.001[a]
Tanning ability			
Deeply	23.5	30.5	
Moderately	56.6	53.2	
Lightly	17.5	14.1	
Not at all	2.3	2.2	<0.001[a]
Skin's reactivity to sunlight			
No effect, or tans	20.0	45.0	
Mild sunburn, then tans	49.5	41.0	

Characteristics	whites	non-whites/multiracials*	P_{value}
Severe sunburn without blistering	19.8	10.1	
Severe sunburn with blistering	10.7	3.9	<0.001[a]
Sunburn susceptibility phenotype index			
0–1	15.8	45.5	
2–3	40.6	47.9	
4–5	29.0	5.9	
6–7	11.4	0.7	
>7	3.1	0.1	<0.001[a]
Ever-sunburned			
No	38.2	77.4	
Yes	61.8	22.6	<0.001[a]
Lifetime number of sunburns			
No sunburn	38.2	77.4	
≤ 3 sunburns	40.5	15.9	
>3 sunburns	20.7	6.2	
Missing	0.6	0.5	<0.001[a]
First age of sunburn			
Never sunburned	38.2	77.4	
<13 years	13.3	3.1	
13 to 17 years	16.8	5.0	
≥ 18 years	31.1	14.1	
Missing	0.7	0.4	<0.001[a]
Family history of melanoma			
No	98.8	99.8	
Yes	1.2	0.2	<0.001[a]
History of non-melanoma skin cancer			
No	88.5	99.0	
Yes	11.5	1.0	<0.001[a]

Abbreviations: SD, standard deviations; NMSC, non-melanoma skin cancer.

[a] *P*-values calculated using the chi, square test.

[b] *P*-values calculated using one, way ANOVA.

Table 2

Invasive malignant melanoma and melanoma *in situ* tumor characteristics among participants recruited to the Multiethnic Cohort Study, 1993–1996, stratified by sex.

	Males				Females			
	whites		non-whites/multiracials		whites		non-whites/multiracials	
Invasive Malignant Melanoma								
No. eligible	18,612		48,909		20,713		52,320	
Total person-years	231,927.6		606,194.1		266,832.2		675,453.8	
No. of cases	288		66		186		41	
Race	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Japanese American			12	18.2			16	39.0
Latino			30	45.5			10	24.4
Multiracials			20	30.3			15	36.6
Native Hawaiian			4	6.1			0	0.0
Whites	288	100	0	0.0	186	100	0	0.0
Histology								
Melanoma, NOS	179	62.2	33	50.0	96	51.6	17	41.5
NM	18	6.3	5	7.6	9	4.8	5	12.2
LMM	23	8.0	10	15.2	11	5.9	2	4.9
SSM	57	19.8	9	13.6	61	32.8	9	22.0
ALM	2	0.7	4	6.1	0	0.0	6	14.6
Other	9	3.1	5	7.6	9	4.8	2	4.9
P_{value}[a]			0.015				<0.001	
Stage								
Localized	259	89.9	57	86.4	166	89.3	26	63.4
Regional	15	5.2	3	4.6	10	5.4	9	22.0
Distant	9	3.1	5	7.6	7	3.8	4	9.8
Unknown	5	1.7	1	1.5	3	1.6	2	4.9
P_{value}[a]			0.266				<0.001	
Location								
Face	59	20.5	16	24.2	13	7.0	4	9.8

	Males				Females			
	whites		non-whites/multiracials		whites		non-whites/multiracials	
Trunk	129	44.8	17	25.8	55	29.6	10	24.4
Upper limbs, including shoulders	72	25.0	15	22.7	69	37.1	11	26.8
Lower limbs, including hips	18	6.3	13	19.7	45	24.2	11	26.8
Skin, NOS	10	3.5	5	7.6	4	2.2	5	12.2
P_{value}[a]			<0.001				0.680	
Melanoma *in situ*								
No. eligible men	18,594		48,906		20,695		52,312	
Total person-years	230,462.4		605,912.5		265,774.2		675,143.8	
No. of cases	218		40		120		34	
Histology								
Melanoma, NOS	127	58.3	21	52.5	68	56.7	17	50.0
NM	0	0.0	0	0.0	0	0.0	0	0.0
LMM	72	33.0	17	42.5	45	37.5	13	38.2
SSM	14	6.4	2	5.0	5	4.2	2	5.9
ALM	1	0.5	0	0.0	0	0	2	5.9
Other	4	1.8	0	0.0	2	1.7	0	0.0
P_{value}[a]			0.779				0.068	
Location								
Face	77	35.3	18	45.0	26	21.7	14	41.2
Trunk	84	38.5	14	35.0	40	33.3	5	14.7
Upper limbs, including shoulders	47	21.6	6	15.0	35	29.2	6	17.7
Lower limbs, including hips	10	4.6	2	5.0	19	15.8	9	26.5
Skin, NOS	0	0.0	0	0.0	0	0.0	0	0.0
P_{value}[a]			0.639				0.019	

Abbreviations: NOS, not otherwise specified; NM, Nodular melanoma; LMM, Lentigo Maligna Melanoma; SSM, Superficial Spreading Melanoma; ALM, Acral Lentiginous Melanoma.

[a] *P*-values exclude NOS and other.

Table 3

Relative Risks (RR) for invasive malignant melanoma (IMM) Among whites and non-whites/multiracials recruited to the Multiethnic Cohort Study, 1993–1996

	whites					non-whites/multiracials					
Characteristics	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
Study Site											
California	70	1.00		1.00		45	1.00		1.00		
Hawaii	402	2.42	(1.97, 2.98)	2.01	(1.55, 2.60)	52	1.75	(0.89, 3.43)	1.82	(0.93, 3.60)	
P-value			<0.001		<0.001			0.107		0.083	0.600
Sex											
Male	286	1.00		1.00		62	1.00		1.00		
Female	186	0.62	(0.53, 0.74)	0.59	(0.49, 0.71)	35	0.52	(0.34, 0.78)	0.47	(0.31, 0.72)	
P-value			<0.001		<0.001			0.002		0.001	0.582
Education											
≤ High school	61	1.00		1.00		42	1.00		1.00		
Some college	137	2.70	(2.10, 3.46)	1.63	(1.20, 2.21)	34	1.85	(1.16, 2.96)	1.79	(1.12, 2.87)	
≥ College	274	4.40	(3.49, 5.56)	2.08	(1.57, 2.77)	21	1.74	(1.00, 3.02)	1.60	(0.91, 2.80)	0.472
P-trend			<0.001		<0.001			0.019		0.046	
Age											
1 year increase		1.04	(1.03, 1.05)	1.03	(1.02, 1.05)		1.06	(1.03, 1.09)	1.06	(1.03, 1.08)	
P-value			<0.001		<0.001			<0.001		<0.001	0.062
Hair color											
Black/Medium dark brown	208	1.00		1.00		77	1.00		1.00		
Light brown	161	1.68	(1.37, 2.06)	1.57	(1.28–1.93)	16	2.56	(1.46, 4.50)	2.33	(1.32, 4.11)	
Blonde	79	1.58	(1.22, 2.05)	1.40	(1.08, 1.82)	2	3.17	(0.77, 13.1)	2.61	(0.63, 10.8)	
Red	24	2.23	(1.46, 3.40)	1.73	(1.13, 2.65)	2	6.39	(1.55, 26.4)	5.12	(1.23, 21.4)	
P-trend			<0.001		<0.001			<0.001		<0.001	0.016
Eye color											
Dark (black/dark brown)	138	1.00		1.00		76	1.00		1.00		
Light (blue, grey, and green)	334	1.51	(1.24, 1.85)	1.34	(1.09, 1.64)	21	3.39	(2.03, 5.66)	2.99	(1.76, 5.06)	
P-value			<0.001		0.005			<0.001		<0.001	0.005

	whites					non-whites/multiracials					
Characteristics	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
Tanning ability											
Deeply	79	1.00		1.00		20	1.00		1.00		
Moderately	271	1.44	(1.12, 1.84)	1.33	(1.03, 1.71)	56	1.59	(0.95, 2.66)	1.59	(0.95, 2.66)	
Lightly	106	2.05	(1.53, 2.75)	1.69	(1.26, 2.27)	21	2.36	(1.26, 4.40)	2.37	(1.27, 4.42)	
Not at all	16	2.68	(1.56, 4.60)	2.07	(1.20, 3.57)	0		--			0.803
P-trend			<0.001		<0.001			0.071		0.066	
Skin reaction to sunlight											
No effect, or tans	51	1.00		1.00		36	1.00		1.00		
Mild burn, then tans	233	1.79	(1.32, 2.43)	1.55	(1.14, 2.11)	47	1.52	(0.98, 2.36)	1.43	(0.92, 2.23)	
Severe burns without blistering	129	2.61	(1.89, 3.62)	2.03	(1.45, 2.83)	10	1.44	(0.71, 2.92)	1.21	(0.59, 2.49)	
Severe burning with blistering	59	2.42	(1.66, 3.53)	1.73	(1.17, 2.55)	4	1.38	(0.49, 3.90)	1.00	(0.34, 2.93)	
P-trend			<0.001		0.001			0.152		0.51	0.362
Sunburn susceptibility phenotype index											
0–1	40	1.00		1.00		26	1.00		1.00		
2–3	163	1.59	(1.12, 2.24)	1.44	(1.02, 2.04)	56	2.13	(1.33, 3.40)	2.06	(1.29, 3.30)	
4–5	161	2.20	(1.56, 3.12)	1.81	(1.27, 2.57)	10	2.68	(1.28, 5.64)	2.3	(1.07, 4.92)	
6–7	77	2.86	(1.95, 4.20)	2.13	(1.44, 3.16)	4	7.75	(2.66, 22.6)	5.82	(1.92, 17.6)	
>7	31	4.35	(2.71, 6.98)	2.97	(1.84, 4.82)	1	15.8	(2.10, 118)	10.3	(1.32, 80.4)	
P-trend			<0.001		<0.001			<0.001		<0.001	0.048
Ever-sunburned [d]											
No	113	1.00		1.00		63	1.00		1.00		
Yes	359	1.87	(1.51, 2.31)	1.52	(1.22, 1.89)	34	1.56	(1.02, 2.38)	1.26	(0.81, 1.98)	
P-value			<0.001		<0.001			0.04		0.305	0.655
Lifetime number of sunburns [d,e]											
No sunburn	119	1.00		1.00		63	1.00		1.00		
≤ 3 sunburns	216	1.70	(1.36, 2.13)	1.45	(1.15, 1.82)	21	1.42	(0.86, 2.34)	1.18	(0.71, 1.98)	
>3 sunburns	137	1.95	(1.52, 2.50)	1.45	(1.12, 1.88)	13	2.04	(1.11, 3.76)	1.6	(0.85, 3.01)	
P-trend			<0.001		0.004			0.014		0.148	0.711
First age of sunburn [d,e]											

	whites					non-whites/multiracials					
Characteristics	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
Never sunburned	120	1.00		1.00		63	1.00		1.00		
<13 years	110	2.31	(1.78, 3.00)	1.69	(1.28, 2.22)	5	1.67	(0.67, 4.21)	1.18	(0.45, 3.08)	
13 to 17 years	96	1.71	(1.31, 2.24)	1.39	(1.05, 1.83)	8	1.68	(0.79, 3.53)	1.35	(0.63, 2.87)	
≥ 18 years	146	1.54	(1.21, 1.97)	1.35	(1.06, 1.72)	21	1.56	(0.95, 2.57)	1.31	(0.79, 2.19)	
P-trend			0.003		0.068			0.046		0.25	0.720
Family history of melanoma [d]											
No	458	1.00		1.00		96	1.00		1.00		
Yes	14	2.47	(1.45, 4.21)	2.04	(1.19, 3.48)	1	3.27	(0.45, 23.64)	2.55	(0.35, 18.7)	
P-value			0.001		0.009			0.241		0.357	0.808
History of non-melanoma skin cancer [d]											
No	337	1.00		1.00		91	1.00		1.00		
Yes	135	2.51	(2.04, 3.08)	2.19	(1.78–2.70)	6	3.97	(1.71–9.21)	2.98	(1.25–7.10)	
P-value			<0.001		<0.001			0.001		0.014	0.336

Abbreviations: ca, cases; RR, relative risks; CI, confidence intervals.

[a] Model adjusted for age, study site, race/ethnic groups, part-white status, sex, and education.

[b] Additionally adjusted for ever-sunburned status, family history of melanoma, personal history of non-melanoma skin cancer.

[c] Tests heterogeneity between whites and non-whites/multiracials.

[d] Also adjusted for sunburn susceptibility phenotype index.

[e] One melanoma *in situ* case with missing information regarding lifetime number of sunburns and age of first sunburn.

Table 4

Relative Risks (RR) for melanoma *in situ* (MIS) Among whites and non-whites/multiracials recruited to the Multiethnic Cohort Study, 1993–1996

	whites					Non-whites/Multracials					
Characteristics	**Ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
Study Site											
California	37	1.00		1.00		33	1.00		1.00		
Hawaii	300	3.13	(2.20, 4.44)	2.88	(2.03, 4.09)	39	1.06	(0.54, 2.09)	1.07	(0.54, 2.12)	
P-value			<0.001		<0.001			0.867		0.839	<0.001
Sex											
Male	217	1.00		1.00		40	1.00		1.00		
Female	120	0.56	(0.45, 0.70)	0.53	(0.42, 0.66)	32	0.71	(0.44, 1.13)	0.68	(0.42, 1.08)	
P-value			<0.001		<0.001			0.143		0.103	0.309
Education											
≤ High school	42	1.00		1.00		37	1.00		1.00		
Some college	98	1.90	(1.32, 2.73)	1.68	(1.16, 2.42)	22	1.18	(0.68, 2.05)	1.14	(0.65, 1.98)	
≥ College	197	2.50	(1.78, 3.50)	2.11	(1.50, 2.97)	13	0.91	(0.46, 1.78)	0.84	(0.43, 1.65)	0.015
P-trend			<0.001		<0.001			0.906		0.724	
Age											
1 year increase		1.04	(1.03, 1.05)	1.03	(1.02, 1.05)		1.03	(1.01, 1.06)	1.03	(1.00, 1.06)	
P-value			<0.001		<0.001			0.028		0.046	0.184
Hair color											
Black/Medium dark brown	163	1.00		1.00		60	1.00		1.00		
Light brown	100	1.32	(1.03, 1.70)	1.25	(0.97, 1.60)	7	1.91	(0.83, 4.38)	1.77	(0.77, 4.07)	
Blonde	64	1.65	(1.23, 2.20)	1.48	(1.11, 1.98)	5	15.0	(5.76, 38.9)	12.4	(4.64, 33.0)	
Red	10	1.20	(0.64, 2.28)	0.96	(0.50, 1.82)	0		--		--	
P-trend			0.002		0.036			<0.001		0.001	0.002
Eye color											
Dark (black/dark brown)	103	1.00		1.00		59	1.00		1.00		
Light (blue, grey, and green)	234	1.40	(1.11, 1.76)	1.25	(0.99, 1.59)	13	4.44	(2.28, 8.66)	3.97	(2.00, 7.88)	
P-value			0.005		0.059			<0.001		<0.001	0.002
Tanning ability											

	whites					Non-whites/Multracials					
Characteristics	**Ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
Deeply	64	1.00		1.00		21	1.00		1.00		
Moderately	204	1.35	(1.02, 1.78)	1.25	(0.94, 1.66)	36	0.95	(0.55, 1.63)	0.95	(0.55, 1.64)	
Lightly	61	1.51	(1.06, 2.15)	1.26	(0.88, 1.80)	15	1.52	(0.77, 2.98)	1.53	(0.78, 3.00)	
Not at all	8	1.76	(0.84, 3.69)	1.39	(0.66, 2.92)	0		--			
P-trend			0.012		0.166			0.708		0.694	0.804
Skin reaction to sunlight											
No effect, or tans	45	1.00		1.00		33	1.00		1.00		
Mild burn, then tans	174	1.51	(1.09, 2.10)	1.32	(0.95, 1.84)	24	0.82	(0.48, 1.39)	0.79	(0.46, 1.35)	
Severe burns without blistering	83	1.92	(1.33, 2.76)	1.51	(1.04, 2.00)	12	1.76	(0.90, 3.44)	1.57	(0.79, 3.12)	
Severe burning with blistering	35	1.69	(1.08, 2.63)	1.23	(0.78, 1.94)	3	1.14	(0.35, 3.74)	0.93	(0.27, 3.23)	
P-trend			0.002		0.206			0.381		0.647	0.963
Sunburn susceptibility phenotype index											
0–1	35	1.00		1.00		30	1.00		1.00		
2–3	122	1.36	(0.93, 1.97)	1.23	(0.85, 1.80)	31	1.00	(0.60, 1.66)	0.98	(0.59, 1.63)	
4–5	119	1.86	(1.27, 2.71)	1.54	(1.05, 2.26)	8	2.13	(0.96, 4.76)	1.91	(0.84, 4.38)	
6–7	44	1.90	(1.22, 2.97)	1.44	(0.92, 2.28)	3	6.63	(1.96, 22.5)	5.22	(1.47, 18.6)	
>7	17	2.82	(1.58, 5.06)	1.98	(1.09, 3.58)	0		--			
P-trend			<0.001		0.01			0.306		0.091	0.256
Ever-sunburned [d]											
No	85	1.00		1.00		52	1.00		1.00		
Yes	252	1.74	(1.36, 2.23)	1.5	(1.16, 1.94)	20	1.24	(0.73, 2.09)	1.00	(0.58, 1.74)	
P-value			<0.001		0.002			0.422		0.992	0.311
Lifetime number of sunburns [d,e]											
No sunburns	85	1.00		1.00		52	1.00		1.00		
≤ 3 sunburns	138	1.53	(1.17, 2.01)	1.38	(1.05, 1.82)	14	1.26	(0.69, 2.28)	1.03	(0.56, 1.92)	
>3 sunburns	114	2.25	(1.70, 2.99)	1.85	(1.38, 2.48)	6	1.29	(0.55, 3.04)	1.00	(0.41, 2.41)	
P-trend			<0.001		<0.001			0.401		0.962	0.233
First age of sunburn [d,e]											
Never sunburned	86	1.00		1.00		52	1.00		1.00		

	whites					Non-whites/Multracials					
Characteristics	**Ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**ca**	**RR**	**95% CI[a]**	**RR**	**95% CI[b]**	**p-heterogeneity[c]**
<13 years	73	2.10	(1.53, 2.88)	1.69	(1.22, 2.35)	6	2.79	(1.18, 6.59)	2.10	(0.87, 5.11)	
13 to 17 years	82	2.04	(1.50, 2.77)	1.77	(1.30, 2.41)	5	1.37	(0.54, 3.46)	1.10	(0.43, 2.82)	
≥ 18 years	96	1.43	(1.07, 1.92)	1.31	(0.97, 1.75)	9	0.91	(0.44, 1.85)	0.76	(0.36, 1.57)	
P-trend			0.014		0.082			0.918		0.55	0.395
Family history of melanoma [d]											
No	330	1.00		1.00		71	1.00		1.00		
Yes	7	1.72	(0.81, 3.65)	1.48	(0.70, 3.14)	1	5.64	(0.78, 41.0)	5.56	(0.76, 40.6)	
P-value			0.155		0.304			0.087		0.091	0.379
History of non-melanoma skin cancer [d]											
No	246	1.00		1.00		67	1.00		1.00		
Yes	91	2.31	(1.80, 2.95)	2.12	(1.65, 2.72)	5	6.15	(2.44, 15.5)	5.10	(1.98, 13.2)	
P-value			<0.001		<0.001			<0.001		0.001	0.099

Abbreviations: ca, cases; RR, relative risks; CI, confidence intervals.

[a]Model adjusted for age, study site, race/ethnic groups, part-white status, sex, and education.

[b]Additionally adjusted for ever-sunburned status, family history of melanoma, personal history of non-melanoma skin cancer.

[c]Tests heterogeneity between whites and non-whites/multiracials.

[d]Also adjusted for sunburn susceptibility phenotype index.

[e]One melanoma *in situ* case with missing information regarding lifetime number of sunburns and age of first sunburn.