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CIGARETTE SMOKING AND MALIGNANT MELANOMA: A CASE-CONTROL STUDY

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Abstract

Background—Several previous studies have reported inverse associations between cigarette smoking and melanoma. Often these studies have not adjusted for ultraviolet (UV) exposure history, skin type, or number of blistering sunburns, which could confound the observed associations between cigarette smoking and melanoma.

Objective—To assess whether this reported inverse association persists after adjusting for UV exposure, skin type, and number of blistering sunburns.

Methods—We conducted a population-based case-control study (82 melanoma cases, 164 controls). Two controls were matched to each case by age, sex, race, and skin type. Conditional logistic regression models were fit to assess the association between cigarette smoking history and melanoma, with additional adjustments for UV exposure and sunburns.

Results—Compared to never smokers, both former (OR 0.43, 95% CI 0.18–1.04) and current (OR 0.65, 95% CI 0.19–2.24) smoking were inversely associated with melanoma, but the associations were not statistically significant.

Limitations—The number of cutaneous nevi was not assessed in this study. Additionally, the relatively small number of cases limits the statistical precision of the observed associations.

Conclusions—After matching for age, sex, race, and skin type, and further adjusting for UV exposure and number of sunburns, cigarette smoking was not statistically significantly associated with melanoma risk, but the results were consistent with previous observations of an inverse association.

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INTRODUCTION

Cigarette smoking is causally associated with cancers of the lung, bladder, pancreas kidney, oral cavity, esophagus, larynx and uterine cervix.¹ Studies of cigarette smoking in relation to the risk of cutaneous malignant melanoma (CMM) have been reported, but the evidence to date has not been clear-cut. Surprisingly, the results have often suggested the possibility that smoking may be inversely associated with melanoma risk (Table 1).^{2–12} These previous findings raise the question as to whether these observed inverse associations are real or, rather, due to methodologic weaknesses of the studies.

Before a definitive conclusion can be reached, inconsistencies in the evidence concerning the association between cigarette smoking and CMM need to be resolved. For instance, most of these previous studies have reported only weak inverse associations, raising the possibility that the observed inverse association may actually be indirect and due to potential confounding factors such as ultraviolet (UV) exposure history, number of blistering sunburns, or skin type,^{10–12} which are well-established risk factors for melanoma. Even in previous studies that have attempted to control for UV exposure and skin type, the potential for residual confounding is a lingering issue because the measurement of UV exposure and skin type have not always been optimal. For example, when UV exposure has been accounted for at all, it has often been measured by proxy information such as job task classification² or area of residence.^{3,12} Only one of the previous studies accounted for history of blistering sunburns (Table 1). However, in the five studies that did adjust for sun exposure and/or skin type^{2–4,7,10}, all showed at least some evidence of an inverse association. We therefore designed the present case-control study to attempt to more completely account for potential confounding by skin type, sun exposure, and sunburn history.

MATERIALS AND METHODS

Study Design

This matched case-control study was designed within a larger parent study, the “Give Us a Clue to Cancer and Heart Disease” (CLUE II) cohort that is approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health. The CLUE II cohort is a community-based prospective study that enrolled 32,898 volunteers in Washington County, Maryland from May 1st, 1989 to November 30th, 1989. At baseline, the demographic information collected from questionnaires included history of cigarette smoking, height, weight, and years of school completed.

Subsequent questionnaires have been sent to cohort members, with the 2007 questionnaire relevant to the present investigation because of its skin cancer focus. The 2007 survey was mailed to cohort members who had responded to at least one of the four previous follow-up surveys (n = 14,779), and who were at least 13 years of age at study baseline. This survey collected an updated medical history, with a focus on history of skin cancer, skin type, UV exposure history, sun protection habits, and smoking history. Because the data on the history of UV exposure, sunburns, and skin type were so critical to this investigation, the cases and controls for the present study were limited to those who completed the 2007 survey (n = 8,186).

Pathologically confirmed incident cases of cutaneous melanoma, ICD 9 code 172 or ICD 10 codes D03 or C43, were ascertained via the Comstock Center Cancer Registry. Eligible cases were those who responded to the 2007 survey and had complete data on age, sex, race, and skin type. Cases were excluded if they had a prior history of any cancer except non-melanoma skin cancer. Based on these criteria, a total of 82 confirmed cases of malignant

melanoma were identified and included in the present study. Cases were comprised of both melanoma in situ and invasive melanomas, and were diagnosed between 1990 and 2007.

As with the cases, controls were drawn from those who responded to the 2007 survey and who resided in or near Washington County, Maryland. From this pool of potential controls, those with a confirmed or self-reported history of any cancer, including nonmelanoma skin cancer, were excluded. Potential controls with missing information on age, sex, race, or skin type were also excluded. For each case, two controls, one younger and one older, were matched on sex, race, skin type, and age (± 5 years). All cases and controls were Caucasian.

Skin type was determined from the following responses to the question “If you spent an hour in the mid-day sun for the first time without sunscreen, which of these reactions best describes what would happen to your skin?”: blistering sunburn (skin type I), sunburn without blisters (skin type II), mild sunburn that becomes a tan (skin type III), tan or darken with no sunburn (skin type IV), or no change in skin color (skin types V/VI).

The primary independent variable was smoking history measured at baseline in 1989. Participants were classified as never, former, or current smokers. Those with a positive history of smoking were further classified according to the number of cigarettes (<20 or 20+) smoked per day.

Additional variables used in the analysis were the lifetime number of blistering sunburns, and the frequency and duration of sun exposure and sun protection behaviors. A series of questions from the 2007 survey asked the number of hours spent in the midday (10am–4pm) sun in the summer on both weekdays and weekends for different decades of the respondent’s lifetime (i.e. teens, twenties, thirties, and the past decade). Sun exposure was classified as low (0–1 hour per day), medium (2–3 hours per day), and high (4–6 hours per day). Regular use of sunscreen and sun protective clothing was defined by “often” or “always” engaging in that form of sun protection. Non-regular use of sunscreen and sun protective clothing was defined as “never,” “rarely,” or “sometimes” engaging in that form of sun protection.

Statistical analysis

The chi-square test was used to estimate p-values for case-control comparisons for gender, age, education, skin type, smoking status, UV exposure and number of blistering sunburns. To account for the matched design, conditional logistic regression was used to estimate odds ratios and 95% confidence limits for the association between cigarette smoking status in 1989 and melanoma. We performed ancillary analyses that accounted for the change in smoking status that could have occurred between 1989 and 2007. A two-sided p-value of 0.05 or less was considered to be statistically significant. All data analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Cases and controls were matched exactly by gender and skin type, and had similar age distributions (Table 2). No significant case-control differences were observed for UV exposure history ($p=0.56$ for weekend exposure; $p=0.92$ for weekday exposure) or sunscreen use ($p=0.13$). Cases were significantly more likely than controls ($p < 0.01$) to report five or more blistering sunburns, but not 1–4 blistering sunburns ($p=0.67$).

Cigarette smoking was inversely associated with melanoma risk, but none of these associations was statistically significant. In the analyses adjusted for the matching factors of age, race, sex, and skin type, compared to never smokers, there was a nonsignificant decrease in odds of melanoma among former smokers (OR 0.73, 95% CI 0.38–1.42), and

among current smokers (OR 0.81, 95% CI 0.28–2.36) (Table 3). With further adjustments for UV exposure, sunburn history, sun-protective clothing and sunscreen use, compared to never smoking, the fully adjusted odds ratios were 0.43 for former smoking (95% CI 0.18–1.04), and 0.65 for current smoking (95% CI 0.19–2.24). In the adjusted models, compared to those with no previous blistering sunburns, history of 1–4 blistering sunburns was not significantly associated with melanoma risk (OR 1.98, 95% CI 0.69–5.69), but five or more blistering sunburns was significantly associated with increased melanoma risk (OR 5.42, 95% CI 1.66–17.64). The associations between regular sunscreen use, regular sun-protective clothing use, and lifetime sun exposures and melanoma were not statistically significant ($p > 0.05$ for each).

In analyses that accounted for the possible changes in smoking status that could occur between 1989 and 2007, compared to never smokers the odds ratio among current smokers in 1989 who had quit smoking by 2007 was 1.14 (95% CI 0.21–6.34) and in persistent smokers was 0.36 (95% CI 0.05–2.37).

DISCUSSION

By carefully matching on age, sex, race, and skin type, and by further adjusting for sun exposure history and history of blistering sunburns in the data analyses, our goal was to overcome limitations from previously published research on the association between cigarette smoking and melanoma. Using this design, we observed that the associations between cigarette smoking and melanoma persisted in the inverse direction, but were not statistically significant. In our study, the point estimates of the fully adjusted estimates of the odds ratio were consistently in the direction of decreased risk, 0.65 (95% CI 0.19–2.24) for current smoking and 0.43 (95% CI 0.18–1.04) for former smoking. Interestingly, the associations in the fully adjusted model were further from the null than the minimally adjusted analyses; that is, more complete control for potential confounding factors actually strengthened the inverse association rather than diminished it. The fact that the inverse association between cigarette smoking and malignant melanoma persisted after carefully controlling for skin type, UV exposure history and number of blistering sunburns suggests that previous observations of an inverse association may have not been due to confounding by these important melanoma risk factors. In fact, this raises the possibility that even more careful and complete control for potential confounding variables could potentially have resulted in stronger and statistically significant associations.

Some previous studies have observed an inverse association between cigarette smoking and melanoma.^{2–9} Often, the results of the individual studies were not statistically significant.^{3–7,9} Nonetheless, the primary drawback of these collective studies is the sub-optimal control for variables that would affect melanoma outcome, specifically UV exposure history, skin type, and history of blistering sunburns. For example, in the lone cohort study to report a statistically significant inverse association between cigarette smoking and melanoma, skin type was not controlled for and job task classification was used as a proxy measure for UV exposure.²

The matching on skin type and adjustment for UV exposure history and history of blistering sunburns in the present study provided inferential advantages lacking in previous studies. Further, our measurement of UV exposure history that included multiple decades of life is a more direct measure of sun exposure history than proxy measurements such as geographic region or county of residence.^{6,12} We adjusted for history of blistering sunburns, sunscreen and sun-protective clothing use, and lifetime sun exposures. Having five or more blistering sunburns was significantly associated with melanoma in our adjusted models. The association between the 1–4 blistering sunburn category and melanoma was in the direction

of increased risk but was not statistically significant. Regular use of sun-protective clothing or sunscreen, and chronic sun exposure were not significantly associated with melanoma risk in these models, either. Despite the careful control for potential confounding in the present study, we acknowledge several limitations. Foremost among these is the relatively small number of melanoma cases. Even though we attempted to compensate for this by selecting two matched controls per case, the size of the study limited the degree of statistical precision, as evidenced by the relatively wide confidence intervals around the odds ratios. Another limitation in the design of our study was the fact that the melanoma cases may have had a personal history of nonmelanoma skin cancer, whereas a history of nonmelanoma skin cancer was an exclusion criteria for the control group. A history of nonmelanoma skin cancer is an established risk factor for melanoma¹³, and to the extent the association between NMSC and melanoma is independent of solar UV exposure, this may have introduced a bias. This would be of even more concern if cigarette smoking was associated with nonmelanoma skin cancer, but the evidence to date does not support a consistent association¹⁴. Furthermore, we do not have knowledge of full body skin examinations or adherence to health maintenance examinations among the study participants. This, along with absence of information on nevi, introduces the possibility that there may have been some cohort members with melanoma that was not yet clinically diagnosed when this study was carried out. This would introduce potential biases, but we expect the number of such cases to be small and therefore not a major concern. We also did not measure the number or classification of cutaneous nevi. The presence of atypical or dysplastic nevi is associated with substantially increased melanoma risk, with more nevi conferring a greater risk.^{15–22} Moreover, even an increased number of banal-appearing nevi confers a two- to four-fold elevated risk for melanoma.²¹ Thus, future studies that incorporate a larger number of subjects and control for the number of total body nevi will help to better elucidate the relationship between cigarette smoking and melanoma.

CONCLUSION

After carefully controlling for age, sex, race, skin type, UV exposure history, and history of blistering sunburns, we observed that, compared to never smokers, former smokers had a roughly 60% decreased risk of melanoma and current smokers had a 35% decreased risk. Even though the findings were not statistically significant, that we observed evidence of an inverse association between cigarette smoking and the development of malignant melanoma even after carefully controlling for skin type, UV exposure history and number of blistering sunburns suggests that previous reports of a potential inverse association may not have been due to confounding by these important melanoma risk factors. The possibility that cigarette smoking is inversely associated with melanoma therefore cannot be ruled out.

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Abbreviations

UV	Ultraviolet
CMM	Cutaneous malignant melanoma
NMSC	Nonmelanoma skin cancer

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Table 1
Summary of studies that reported on the association between cigarette smoking and melanoma

Author (Year)	Location	Number melanoma cases	Number of controls/subjects	OR or RR ¹ (95% CI)	Adjustments
Cohort Studies					
Veierod (1997)	Norway (registry-based)	108	50,757 total cohort (Norwegian National Health Screening)	Former: 0.9 (0.5–1.4) Curr <10/d: 0.6 (0.4–1.1) Curr >10/d: 0.7 (0.4–1.4)	Age, sex, county of residence
Freedman (2003)	USA	140	68,588 total cohort Radiologic Technologists Study	Former: 0.9 (0.7–1.3) Current: 0.8 (0.5–1.1)	Age, sex, skin color, hair color, history of NMSC, residential history, sunlight exposure (proxy), alcohol, education
Odenbro (2007)	Sweden	1639	339,802 total cohort of male construction workers	Former: 0.8 (0.7–0.9) Current: 0.6 (0.5–0.7)	Age, birth cohort, BMI, UV exposure (based on job task)
Case-Control Studies					
Williams (1977)	USA	Not stated	7,518 controls with other cancers	Males: 1.1, 0.4, 0.5 ² Females: 1.1, 0.4, 0.9 ²	Age, race, education, income, geographic location
Paffenbarger (1978)	USA (Harvard alumni)	45 deaths	180 controls	Ever: 1.4 (p=0.4) >10 per day: 0.8 (p=0.7)	Age
Green (1986)	Australia (Queensland)	183	236 controls matched by age, sex residence	Low: 0.7 (0.2–2.1) Med: 0.8 (0.3–2.4) High: 1.3 (0.3–5.0)	Age, sex, residence location; skin type, lifetime sun exposure
Osterlind (1988)	Denmark	474 (registry)	926 controls (population-based)	Former: 1.0 (0.7–1.3) Current: 0.8 (0.6–1.1)	Uncertain
Stemiatycki (1995)	Canada (Montreal)	103 (all men)	533 controls (population-based)	Ever: 0.5 (0.3–0.9)	Age, race, socioeconomic status, selected dietary factors
Westerdahl (1996)	Sweden	327 (registry)	519 controls matched by sex, age, residence (population-based)	Former: 1.0 (0.3–3.5) Current: 0.7 (0.5–1.1)	Age, sex, residence location, hair color, nevi, sunburn history
De Hertog (2001)	Netherlands	125	396 controls (hospital-based)	Smokers: 0.8 (0.5–1.2)	Age, sex, cumulative sun exposure
Shors (2001)	USA (Washington)	386 (registry)	727 controls (population-based)	Former: 0.8 (0.6–1.1) Current: 0.6 (0.4–0.8)	Age, sex

¹ Compared to referent category of never smokers = 1.0.

² Odds ratios for three categories of increasing levels of cigarette use.

Table 2

Demographic characteristics, sun exposure history and skin cancer prevention behaviors among melanoma cases and matched controls*

Factor	CASES (n=82) %	CONTROLS (n=164) %	P value
Gender			1.00
Male	51.2	51.2	
Female	48.8	48.8	
Age(years)[†]			0.99
40–49	8.3	7.7	
50–59	16.7	17.3	
60–69	25.0	25.0	
70–84	42.9	43.5	
85+	7.1	6.6	
Education			0.59
Less than high school	13.1	16.1	
High school	39.3	42.9	
More than high school	47.6	41.1	
Skin reaction to sunlight			1.00
Blistering burn	13.4	13.4	
Burn without blisters	42.7	42.7	
Burn that tans	35.4	35.4	
Tan without burn	8.5	8.5	
Midday sun exposure: weekend[‡]			0.63
Low	52.8	47.4	
Medium	31.9	32.5	
High	15.3	20.1	
Midday sun exposure: weekday[‡]			0.69
Low	55.6	59.1	
Medium	33.3	27.9	
High	11.1	13.0	
Lifetime blistering sunburns[‡]			<0.01
0	23.5	32.7	
1–4	44.4	52.7	
5+	32.1	14.6	
Sunscreen Use[‡]			
Regular	26.8	23.2	0.53
Non-regular	73.2	76.8	
Sun-protective clothing use[‡]			0.11
Regular	35.4	25.6	

Factor	CASES (n=82) %	CONTROLS (n=164) %	P value
Non-regular	64.6	74.4	

* Percentages calculated out of total cases and controls for whom there was sufficient information on UV exposure history and sun protective behaviors

[†] Taken at midpoint of when the 2007 survey was in the field (09/01/2007)

[‡] Based on n=72 cases and n=154 controls Midday sun exposure during last decade

Table 3

Odds ratios (and 95% confidence intervals) for the association between cigarette smoking and melanoma.

Smoking status	Cases (n = 82)	Controls (n=164)	Odds Ratio [†] (95% CI)	Odds Ratio ^{†‡} (95% CI)
	%	%		
Never	59.2	55.8	1.00 (referent)	1.00 (referent)
Former	27.2	33.5	0.73 (0.38–1.42)	0.43 (0.18–1.04)
Current	13.6	10.7	0.81 (0.28–2.36)	0.65 (0.19–2.24)

[†] Adjusted for matching factors of age, race, sex, and skin type

[‡] Adjusted for matching factors plus history of sunburns, sun-protective clothing use, sunscreen use, and sun exposure history