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BRIEF REPORT

Cigarette smoking and the risk of incident and fatal melanoma in a large prospective cohort study

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Abstract
Objective Previous studies suggest that smoking may be inversely associated with risk of melanoma. We attempted to replicate this finding using data from the Cancer Prevention Study II (CPS-II) and CPS-II Nutrition cohort, two large prospective cohort studies of cancer mortality and incidence, respectively, with long-term follow-up.
Methods Cox proportional hazards regression analysis was used to examine the association between smoking status and risk of melanoma mortality and incidence among Caucasians in these cohorts. Analyses were adjusted by age, occupation, latitude and educational status.
Results The incidence rate of melanoma was lower in current than never smokers in both men [hazard ratio (HR): 0.70, 95% confidence interval (CI): (0.48–1.02)] and women [0.50 (0.30–0.83)]; incidence was not lower in former than in never smokers for either sex. The death rate from melanoma was lower in male current than never smokers [0.77 (0.62–0.94)], and in male and female former smokers [0.86 (0.73–1.01)] and [0.83 (0.65–1.06)], respectively. No trends in incidence or mortality were observed in male or female current smokers with years of smoking or cigarettes per day.
Conclusions This study provides limited support for the hypothesis that smoking reduces melanoma risk. The inconsistent results by smoking status and lack of clear dose–response relationships weaken the evidence for causality.

Keywords Smoking · Melanoma · Cohort study

Introduction

Tobacco smoking is causally related to at least 18 types of cancer and harms nearly every organ in the body [1]. With respect to the skin, smoking is associated with several dermatologic conditions including premature skin aging and wrinkling, psoriasis, poor wound healing, and by some accounts, squamous cell carcinoma [2, 3].

Melanoma is projected to be the fifth most common cancer diagnosed in men and the seventh most common in women in the United States in 2010 [4]. Sun exposure, especially sunburns is the major risk factor for melanoma; other established risk factors include age, race, and inherited susceptibility. Fourteen studies have examined the association between smoking and risk of melanoma; all but one of these studies reported at least a small inverse relationship with current smoking [3, 5–17]. However, none of these studies examined the risk of melanoma- mortality, only one cohort study included more than 300 cases, and none presented results separately for men and women in the general population [6].

We examined the relationship between cigarette smoking and the incidence and death rates for melanoma in two large American Cancer Society cohorts based on 13 and 24 years of follow-up, respectively.

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Materials and methods

The mortality analyses were based on the Cancer Prevention Study II (CPS-II) cohort, a nationwide prospective mortality study initiated by the American Cancer Society (ACS) in 1982 and described in detail elsewhere [18]. Briefly, 521,555 men and 685,748 women 30 years of age or older were enrolled by ACS volunteers in all 50 states, the District of Columbia, and Puerto Rico. Upon entry into the study, each participant completed a confidential mailed questionnaire on demographic information, tobacco use, diet, and other factors potentially affecting mortality. Exposure data used in the mortality analyses were based on information collected at enrollment in 1982. No exposure variables were updated on this cohort during the 24-year follow-up.

The vital status of participants in the mortality cohort was determined through personal inquiries by volunteers in September 1984, 1986, 1988, with vital status validated and cause of death ascertained by subsequent examination of medical records. After 1988, both vital status and cause of death were ascertained through automatic linkage with the National Death Index (NDI). Mortality follow-up ended on December 31, 2006, at which point 41.5% of participants were deceased, 58.3% were alive, and 0.2% were lost to follow-up in 1988 due to insufficient data for linkage with the NDI. Underlying cause of death was coded according to ICD-9 and ICD-10 specifications, with melanoma (ICD 9, codes 172.0–172.9; ICD-10, codes C43-C43.9) being the outcome of interest.

Cigarette smoking status was specified at the time of enrollment using the question, "Do you now or have you ever smoked cigarettes, at least one a day for 1 year's time?" Ever smokers were then asked questions on the average number of cigarettes smoked per day, the age when they started smoking, and the total number of years they smoked. Former smokers were also asked the age at which they quit smoking. Information on covariates considered in the analyses was also obtained from responses to the questionnaire in 1982.

All analyses were restricted to Caucasians, the population at highest risk, who comprised 93 and 97% of the mortality and incidence cohorts, respectively. The mortality analysis also excluded people who provided incomplete or inconsistent information on smoking history, smoked pipes or cigars, reported initiating smoking before age 5 years old, reported asbestos exposure, or had a prevalent cancer. After exclusions, 309,236 men and 507,452 women were included in the mortality analysis.

The incidence analyses are based on the CPS-II Nutrition Cohort, a subset of the larger mortality cohort, described in detail elsewhere [19]. Men and women were eligible if they were participants in CPS-II, resided in any of 21 states with population-based state cancer registries, and were 50–74 years of age in 1992. In the two-year interval 1992–1993, 184,190 participants completed a mailed questionnaire on demographic, medical, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, and 2003 to update exposure information and to ascertain newly diagnosed health problems, including cancer. The follow-up period in the analyses of cancer incidence ended on June 30, 2005. Participants contributed person-time to the analysis until they were diagnosed with melanoma, died, were lost to follow-up, or reached the end of the follow-up period.

Incident cancers were identified by self-report, through linkage to state cancer registries, and/or linkage to the National Death Index. Self-reported cancers were verified by subsequent medical record abstraction or linkage to the state cancer registry. Twenty-five cases of melanoma were identified only from death certificates and lacked information on date of diagnosis. For these, the date of death was treated as the date of diagnosis.

For the incidence analyses, smoking status was assessed on the 1992 baseline questionnaire as stated above, and updated with additional questionnaires in 1997, 1999, 2001, and 2003. Additional information on smoking and several potential confounders (educational status, occupation, and place of residence/latitude when enrolled in the study) was determined by responses to the 1982 baseline questionnaire.

Participants were excluded from the incidence analysis if they were lost to follow-up, had a prevalent cancer (other than non-melanoma skin cancer) or had conflicting information on the date of diagnosis, reported cigar or pipe smoking, or provided missing or inconsistent smoking information in 1992–1993. Individuals were considered lost to follow-up if they did not return any of the questionnaires after baseline and were not identified as deceased prior to December 31, 1997. We also excluded individuals who were known to be alive (and completed questionnaires) after 1997 but did not return the 1997 questionnaire, as well as those who reported an unverified melanoma diagnosis in 1997. After exclusions, 49,801 men and 71,305 women were eligible for inclusion in the incidence analysis.

Statistical analysis

Cox proportional hazards regression analysis was used to calculate gender-specific hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the association between smoking and melanoma incidence and mortality, with time since enrollment as the underlying time metric.

All models were stratified by single year of age at enrollment and adjusted for level of education (less than high school graduate, high school graduate or vocational school, some college, college graduate, graduate school, or missing), occupation (white collar, blue collar, housewife, or missing), and latitude of primary residence (<37°, ≥37°), as determined by zip code. The Cox proportional hazards assumption was evaluated by an examination of Kaplan–Meier curves, as well as by testing for an interaction by time in the model.

Results

A total of 1,196 deaths from melanoma were identified during the 24-year mortality follow-up of CPS-II, and 1,239 incident cases of melanoma were diagnosed during the 13-year follow-up of the CPS-II Nutrition Cohort. Demographic information for the two analytic cohorts in relation to smoking status is presented in Table 1. Twenty-seven percent of men and 21% of women in CPS-II were current smokers at enrollment in 1982. Only 10% of men and 8% of women in the incidence cohort were current smokers at enrollment in 1992, reflecting their older age. Among men in both cohorts, current smokers were more likely to have less education and to be employed in a blue collar occupation than former or never smokers. Among women, former smokers were more educated than current or never smokers.

Results from the mortality analysis are presented in Table 2. The HRs (95% CI) for mortality from melanoma for male and female current smokers at baseline in 1982 compared to never smokers were 0.77 (0.62–0.94) and 1.04 (0.82–1.32), respectively. Among former smokers, the death rate from melanoma was approximately 15% lower in men and women relative to never smokers, although the association was not statistically significant. When categorized by duration of current smoking, the mortality analyses found consistent but statistically insignificant inverse associations with melanoma among men in most categories, without evidence of a trend. The findings were similar when categorized by cigarettes smoked per day. Analyses of duration of smoking and cigarettes per day among former smokers (results not shown) yielded results generally closer to the null value than current smokers for men and were null for women.

Results from the incidence analysis are presented in Table 3. Current smokers had a lower incidence of melanoma compared to lifelong nonsmokers during the 13-year follow-up in both men [HR: 0.70, 95% CI: (0.48–1.02)] and women [0.50 (0.30–0.83)]. No association was observed between former smoking and melanoma incidence in men or women. When categorized by duration of current smoking, we observed a decreased risk among smokers of 40–49 years, but not among smokers of less than 40 years or 50 or more years. We observed no association between duration of smoking and melanoma incidence among former smokers (results not shown).

Discussion

In this study, lower incidence and death rates from melanoma among current smokers relative to lifelong nonsmokers were observed. However, the inconsistent results by smoking status and lack of evidence of dose–response relationships complicate the interpretation of these results and weaken the evidence for causality. These results are similar to findings from other studies that reported a moderately reduced risk of melanoma incidence associated with current smoking. Our results are also consistent with two cohort studies that stratified by smoking status and reported gender-specific results [3, 6]. To date, only one case–control study has reported increased risk of incident melanoma associated with smoking [16].

Because smoking increases, rather than decreases the risk of most cancers and has other detrimental effects on the skin, one would not expect the inverse association between smoking and melanoma to be causal. However, neither latitude, occupation, or education appeared to explain the relationship in our study. Odenbro et al. [6] hypothesized that the immunosuppressive effect of tobacco smoke may protect against deleterious immune responses in reaction to sun exposure, which may explain the inverse association. Another hypothesis is that smoking accelerates skin aging and elastosis in a similar fashion as chronic ultraviolet radiation, which decreases the risk of melanoma [20]. Sun exposure is the major risk factor for melanoma, but there is evidence that risk is higher for recreational or intermittent exposure that results in sunburns, and risk is lower for continuous sun exposure as would be seen in occupational settings [21, 22]. Smoking prevalence is greater in outdoor workers who have more consistent sun exposure, so it is possible that an observed inverse association could reflect incomplete control for confounding by occupation [10]. Residual confounding from other factors such as screening or ascertainment, inadequate adjustment for sun exposure and socioeconomic status could also contribute to a spurious association between smoking and reduced risk, especially in the incidence analysis [3].

Strengths of our study include its size and number of cases, its prospective design, long follow-up, the ability to control for several important confounders including latitude, and to examine both incidence and mortality endpoints.

Table 1 Demographic characteristics of participants in the CPS-II incidence and mortality studies

Categories	Men (n = 49,801)			Women (n = 71,305)		
	Never smoker	Current smoker	Former smoker	Never smoker	Current smoker	Former smoker
Incidence						
n (%)	17,774 (35.7)	5,081 (10.2)	26,946 (54.1)	40,051 (56.2)	5,832 (8.2)	25,422 (35.7)
Cases	263	32	371	314	16	242
Age in 1992 (median, IQR)	63 (59–68)	62 (58–66)	64 (60–68)	63 (58–67)	61 (56–65)	62 (57–67)
Education (%)						
<HS grad	5.6	11.8	9.7	5.1	7.0	3.8
HS grad/voc	22.8	31.8	27.8	41.3	39.9	32.5
Some college	16.0	24.0	21.5	23.7	26.9	28.1
College grad	22.4	18.1	21.1	17.6	15.9	21.4
Grad school	32.5	13.6	19.2	11.7	9.6	13.5
Missing	0.6	0.7	0.6	0.6	0.7	0.7
Occupation (%)						
White collar	60.0	51.5	56.3	48.9	50.8	53.8
Blue collar	21.9	28.3	23.8	7.4	7.8	5.9
Housewife	0.0	0.1	0.0	33.8	30.5	28.8
Missing	18.0	20.1	19.9	9.9	10.9	11.5
Latitude (%)						
<37°	15.0	15.4	16.9	15.7	15.8	17.2
≥37°	76.5	75.1	74.0	76.0	74.8	73.4
Missing	8.5	9.5	9.1	8.3	9.4	9.4
	Men (n = 309,140)			Women (n = 507,381)		
Mortality						
n (%)	107,907 (34.9)	83,159 (26.9)	118,074 (38.2)	298,285 (58.8)	106,106 (20.9)	102,990 (20.3)
Deaths	306	136	275	307	91	81
Age in 1982 (median, IQR)	56 (49–64)	54 (49–61)	58 (52–64)	57 (49–65)	53 (47–60)	55 (48–62)
Education (%)						
<HS grad	11.3	17.5	14.6	13.7	11.6	7.2
HS grad/voc	24.0	29.9	26.9	38.4	39.4	31.9
Some college	17.6	23.0	21.9	22.6	26.7	28.3
College grad	19.9	16.1	19.1	14.1	13.5	19.0
Grad school	26.0	12.2	16.5	9.9	7.7	12.8
Missing	1.2	1.3	1.0	1.3	1.2	0.9
Occupation (%)						
White collar	54	48.2	53.4	47.2	49.7	52.5
Blue collar	25	28.3	24.6	8.7	8.7	6.5
Housewife	0.1	0	0	30.6	27.5	27.6
Missing	20.9	23.4	22.0	13.5	14.1	13.4
Latitude (%)						
<37°	25.4	28.3	28.2	27.5	26.5	26.9
≥37°	64.0	60.0	60.6	61.9	61.3	61.7
Missing	10.5	11.7	11.1	10.6	12.1	11.4

IQR Interquartile range (25th–75th percentile)

A limitation in our study is the lack of updated smoking exposure during follow-up for mortality. All participants were at least 30 years of age when enrolled and were therefore considered unlikely to initiate smoking during follow-up [23]. However, approximately half of the men (57.1%) and women (54.0%) who reported current

Table 2 Melanoma mortality by smoking status at baseline

Category	Men				Women			
	Deaths	Age-adjusted HR	Multivariate HR[a]	95% CI	Deaths	Age-adjusted HR	Multivariate HR[a]	95% CI
Smoking status								
Never smokers	306	1.00	1.00	Ref	307	1.00	1.00	Ref
Current smokers	136	0.76	0.77	(0.62–0.94)	91	1.04	1.04	(0.82–1.32)
Former smokers	275	0.85	0.86	(0.73–1.01)	81	0.82	0.83	(0.65–1.06)
Duration (current only)								
Never Smokers	306	1.00	1.00	Ref	307	1.00	1.00	Ref
<20 years	7	0.87	0.88	(0.40–1.95)	9	0.97	0.97	(0.49–1.93)
20–29 years	16	0.53	0.54	(0.32–0.91)	23	1.08	1.07	(0.69–1.67)
30–39 years	66	0.91	0.93	(0.70–1.23)	31	0.88	0.87	(0.60–1.28)
40+ years	47	0.68	0.69	(0.50–0.95)	28	1.25	1.26	(0.85–1.87)
	p-trend = 0.84				p-trend = 0.54			
Cigarettes per day (current only)								
Never smokers	306	1.00	1.00	Ref	307	1.00	1.00	Ref
1–9	9	0.54	0.54	(0.28–1.05)	9	0.66	0.65	(0.34–1.27)
10–19	17	0.64	0.65	(0.40–1.06)	22	1.03	1.04	(0.67–1.60)
20–29	45	0.70	0.72	(0.52–0.98)	37	1.10	1.09	(0.77–1.55)
30–39	30	0.93	0.95	(0.65–1.38)	12	1.20	1.20	(0.67–2.14)
40+	35	0.86	0.87	(0.61–1.25)	11	1.24	1.23	(0.67–2.25)
	p-trend = 0.72				p-trend = 0.34			

[a] Adjusted for BMI, education, occupation and latitude

Table 3 Melanoma incidence by smoking status, updated with follow-up questionnaires

Category	Men				Women			
	Cases	Age-adjusted HR	Multivariate HR[a]	95% CI	Cases	Age-adjusted HR	Multivariate HR[a]	95% CI
Smoking status								
Never smokers	263	1.00	1.00	Ref	314	1.00	1.00	Ref
Current smokers	32	0.65	0.70	(0.48–1.02)	16	0.49	0.50	(0.30–0.83)
Former smokers	371	0.93	0.97	(0.82–1.14)	242	1.16	1.13	(0.95–1.33)
Duration (current only)								
Never smokers	263	1.00	1.00	Ref	314	1.00	1.00	Ref
<40 years	8	0.90	0.94	(0.46–1.94)	7	0.69	0.71	(0.33–1.52)
40–49 years	11	0.45	0.49	(0.26–0.90)	6	0.42	0.42	(0.19–0.95)
50+ years	12	0.75	0.82	(0.46–1.48)	3	0.42	0.41	(0.13–1.27)
	p-trend = 0.32				p-trend = 0.43			

[a] Adjusted for BMI, education, occupation and latitude

smoking at baseline in 1982 who re-enrolled in a new cohort in 1992 had stopped smoking during the intervening 10 year period. We were able to address this in the incidence cohort with time-varying updated smoking information. However, participants in the mortality study who were classified as current smokers based on their behavior in 1982 remained in this category even if they quit smoking. The effect of this misclassification would be to bias the hazard ratio associated with "current" smoking towards that for former smoking. The actual consequence would be small in this study, since the inverse association with former smoking is almost as strong in men and stronger in women than that with current smoking. Additional limitations are the small number of current smokers in the incidence analyses and lack of direct information related to sun exposure behaviors. While we were able to control for latitude as a proxy for sun exposure, this variable does not capture individual behaviors that affect sun exposure.

In conclusion, our findings are consistent with previous studies which showed decreased risk of melanoma incidence associated with smoking. The absence of clear dose–response relationships with respect to duration of smoking and cigarettes per day complicates interpretation of these results.

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