Cigarette Smoking and the Risk of Cutaneous Melanoma: A Case-Control Study

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Keywords

Cigarette smoking · Melanoma · Risk factors · Case-control study

Abstract

Objective: Previous studies regarding cigarette smoking causing a lower risk of melanoma are inconclusive. Here, we re-examined melanoma risk in relation to cigarette smoking in a large, case-control study. **Methods:** In total 1,157 patients with melanoma diagnosed between 2003 and 2011 in the Netherlands and 5,595 controls from the Nijmegen Biomedical Study were included. Information concerning smoking habits and known risk factors for melanoma were obtained through self-administered questionnaires. Logistic regression analyses stratified by gender were performed to study the risk of cigarette smoking on melanoma risk, adjusted for age, marital status, highest level of education, skin type, sun vacation, use of solarium, time spent outdoors, and sun protective measures. **Results:** Among men, current and former smokers did not have a higher risk of melanoma compared to never smokers: adjusted odds ratio (OR) = 0.56 (95% confidence interval [CI]: 0.40–0.79) and adjusted OR = 0.50 (95% CI: 0.39–0.64), respectively. With an increasing number

of years smoked the risk of melanoma decreased: <20 years: OR = 0.61 (95% CI: 0.46–0.80); 21–40 years: OR = 0.50 (95% CI: 0.37–0.68); >40 years: OR = 0.26 (95% CI: 0.15–0.44). No clear trend was found for the number of cigarettes smoked. Results for females were less clear and not statistically significant (current smoker: adjusted OR = 0.96, 95% CI: 0.74–1.26, former smoker: adjusted OR = 0.89, 95% CI: 0.73–1.08). **Conclusion:** This study shows a strong inverse association between cigarette smoking and melanoma risk in men. Fundamental laboratory research is necessary to investigate the biological relation between smoking cigarettes and melanoma.

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Introduction

Cutaneous melanoma has been the most rapidly increasing malignancy over the last 50 years, particularly in countries with a predominantly fair-skinned population [1]. At the same time, the survival rate has greatly improved. This is mainly due to the early detection of melanoma [2–4]. The most important known risk factors for the development of melanoma are genetic predisposition,

Fig. 1. Flowchart of Materials and Methods.

skin type, and intermittent exposure to UV radiation [5, 6].

Tobacco smoke is a known risk factor for several types of cancers [7]. Cigarette smoking is also known to come with an increased risk of premature skin aging, psoriasis, poor wound healing, and squamous cell carcinoma [8]. Previous studies have explored the effect of smoking on the risk of cutaneous melanoma, but evidence is inconsistent [9–24]. Seven of these studies, which are mainly prospective cohort studies, reported an inverse relationship between current smoking and melanoma [9, 11–13, 15, 17, 19]. It is suggested that the nicotine in cigarette smoke protects the skin from the inflammatory reaction induced by UV radiation and therefore reduces melanoma risk [25, 26]. Also, a different lifestyle of smokers versus non-smokers might be associated with a reduced melanoma risk in cigarette smokers, as smokers are suggested to spend more time indoors [27].

The other nine studies did not find a significant association between cigarette smoking and melanoma [10, 14, 16, 18, 20–24, 28]. Possible explanations for these results are the small sample size in several of these studies and residual confounding.

In the current study we investigated the association between cigarette smoking and primary melanoma risk in a large case-control study in the Netherlands.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000502129 for all online suppl. material) [29] (Fig. 1).

Results

The patient and lifestyle characteristics of patients and controls are presented in Table 1 for males and Table 2 for females, based on observed data as well as imputed data. Male and female patients were slightly older than controls, were more often living together with a partner, had a lower level of education, had more often a skin type I or II, more frequent sunburns, and more usage of solarium and sun protective measures. Therefore, the multivariable analyses were adjusted for age, marital status,

Table 1. Patient and lifestyle characteristics of male patients and controls

Males	Patients (n = 440)	Patients (after imputation)	Controls (n = 2,548)	Controls (after imputation)	OR (95% CI) ¹
Age at completion of questionnaire, years	57.5±12.5		55.2±16.5		1.00 (1.00–1.02)
<i>Smoking status</i>					
Never	155 (35.2)		652 (25.6)		reference
Current	57 (13.0)		424 (16.6)		0.57 (0.41–0.78)
Former	228 (51.8)		1,472 (57.8)		0.65 (0.52–0.82)
<i>Duration of smoking²</i>					
Never smoker	155 (35.2)		652 (25.6)		reference
<20 years	119 (27.0)		692 (27.2)		0.72 (0.56–0.94)
21–40 years	94 (21.4)		596 (23.4)		0.66 (0.50–0.88)
>40 years	20 (4.5)		227 (8.9)		0.37 (0.23–0.61)
<i>Cigarettes per day</i>					
Never smoker	155 (35.2)		652 (25.6)		reference
<10	106 (24.1)		755 (29.6)		0.59 (0.45–0.77)
10–20	109 (24.8)		696 (27.3)		0.66 (0.50–0.86)
>20	28 (6.4)		206 (8.1)		0.57 (0.37–0.88)
<i>Marital status</i>					
Single	45 (10.3)	46 (10.5)	535 (21.0)	535 (21.0)	reference
With partner	391 (88.9)	394 (89.5)	2,008 (79.0)	2,013 (79.0)	2.30 (1.67–3.18)
Missing	4 (1.0)		5 (0.2)		
<i>Education</i>					
Less than secondary school	101 (23.0)	102 (23.2)	565 (22.2)	568 (22.3)	reference
Secondary school	146 (33.2)	146 (33.2)	677 (26.6)	680 (26.7)	1.21 (0.93–1.56)
More than secondary school	192 (43.6)	192 (43.6)	1,294 (50.8)	1,300 (51.0)	1.46 (1.16–1.85)
Missing	1 (0.3)		12 (0.5)		
<i>Skin type</i>					
I, II	203 (46.1)	203 (46.1)	912 (35.8)	914 (35.9)	reference
III	231 (52.5)	231 (52.5)	1,481 (58.1)	1,484 (58.2)	0.70 (0.57–0.86)
IV–VI	6 (1.3)	6 (1.3)	146 (5.7)	150 (5.9)	0.18 (0.08–0.41)
Missing	0 (0.0)		9 (0.4)		
<i>Skin reaction after 1 h unprotective sun exposure</i>					
Not burned	46 (10.5)	46 (10.5)	574 (22.5)	577 (22.6)	reference
A little bit red	254 (57.7)	254 (57.7)	1,523 (59.8)	1,531 (60.1)	2.08 (1.50–2.89)
Burned	140 (31.8)	140 (31.8)	437 (17.2)	440 (17.3)	4.00 (2.80–5.71)
Missing	0 (0.0)		14 (0.5)		
<i>Solarium usage during lifetime</i>					
Never	201 (45.7)	202 (45.9)	1,440 (56.5)	1,457 (57.2)	reference
<2 cycles	195 (44.3)	196 (44.5)	795 (31.2)	799 (31.4)	1.76 (1.42–2.18)
2–5 cycles	36 (8.2)	36 (8.2)	215 (8.4)	216 (8.5)	1.21 (0.82–1.78)
>5 cycles	6 (1.4)	6 (1.4)	71 (2.8)	76 (3.0)	0.61 (0.26–1.44)
Missing	2 (0.5)		27 (1.1)		
<i>Time spent outdoors weekdays <18 years (hours per day)</i>					
<2 h	253 (57.5)	256 (58.2)	1,437 (56.4)	1,472 (57.8)	reference
2–4 h	113 (25.7)	117 (26.6)	700 (27.5)	721 (28.3)	0.91 (0.72–1.16)
>4 h	65 (14.8)	67 (15.2)	324 (12.7)	355 (13.9)	1.09 (0.81–1.46)
Unknown	9 (2.0)		87 (3.4)		

Table 1 (continued)

Males	Patients (n = 440)	Patients (after imputation)	Controls (n = 2,548)	Controls (after imputation)	OR (95% CI) ¹
<i>Time spent outdoors weekends/holidays <18 years (hours per day)</i>					
<2 h	48 (10.9)	48 (10.9)	249 (9.8)	258 (10.1)	reference
2–4 h	303 (68.9)	307 (69.8)	1,783 (70.0)	1,856 (72.8)	0.88 (0.63–1.23)
>4 h	79 (18.0)	85 (19.3)	385 (15.1)	434 (17.0)	1.04 (0.71–1.54)
Unknown	10 (2.3)		131 (5.1)		
<i>Time spent outdoors weekdays >18 years (hours per day)</i>					
<2 h	286 (65.0)	289 (65.7)	1,673 (65.7)	1,699 (66.7)	reference
2–4 h	109 (24.8)	111 (25.2)	595 (23.4)	606 (23.8)	1.07 (0.84–1.36)
>4 h	38 (8.6)	40 (9.1)	233 (9.1)	243 (9.5)	0.97 (0.68–1.38)
Unknown	7 (1.6)		47 (1.8)		
<i>Time spent outdoors weekends/holidays >18 years (hours per day)</i>					
<2 h	88 (20.0)	89 (20.2)	570 (22.4)	590 (23.2)	reference
2–4 h	295 (67.0)	301 (68.4)	1,578 (61.9)	1,663 (65.3)	1.20 (0.93–1.55)
>4 h	46 (10.5)	50 (11.4)	255 (10.0)	295 (11.6)	1.09 (0.75–1.60)
Unknown	11 (2.5)		145 (5.7)		
<i>Sun vacation <18 years (weeks per year)</i>					
None	251 (57.0)	251 (57.0)	1,467 (57.6)	1,510 (59.3)	reference
1–2 weeks	110 (25.0)	110 (25.0)	547 (21.5)	567 (22.3)	1.17 (0.92–1.50)
3–4 weeks	65 (14.8)	65 (14.8)	407 (16.0)	429 (16.8)	0.91 (0.68–1.21)
>4 weeks	14 (3.2)	14 (3.2)	39 (1.5)	42 (1.6)	1.90 (1.00–3.62)
Missing	0 (0.0)		88 (3.5)		
<i>Sun vacation >18 years (weeks per year)</i>					
None	87 (19.8)	87 (19.8)	568 (22.3)	607 (23.8)	reference
1–2 weeks	180 (40.9)	180 (40.9)	923 (36.2)	957 (37.6)	1.30 (0.98–1.72)
3–4 weeks	164 (37.3)	164 (37.3)	882 (34.6)	929 (36.5)	1.23 (0.93–1.63)
>4 weeks	9 (2.0)	9 (2.0)	53 (2.1)	55 (2.2)	1.12 (0.53–2.36)
Missing	0 (0.0)		122 (4.8)		
<i>Sun protective measures <18 years</i>					
Never	38 (8.6)	41 (9.3)	229 (9.0)	302 (11.9)	reference
Rarely/sometimes	273 (62.0)	295 (67.0)	1,441 (56.6)	1,742 (68.4)	1.24 (0.81–1.91)
Often/always	92 (20.9)	104 (23.6)	419 (16.4)	504 (19.8)	1.47 (0.90–2.39)
Missing	37 (8.4)		459 (18.0)		
<i>Sun protective measures >18 years</i>					
Never	12 (2.7)	15 (3.4)	93 (3.6)	123 (4.8)	reference
Rarely/sometimes	186 (42.3)	200 (45.5)	1,216 (47.7)	1,418 (55.7)	1.26 (0.64–2.48)
Often/always	213 (48.4)	225 (51.1)	891 (35.0)	1,007 (39.5)	1.95 (1.00–3.82)
Missing	29 (6.6)		348 (13.6)		

Data are presented as *n* (%) or mean ± SD unless otherwise indicated. ¹ The imputed data were used for analyses. ² Data of patients and controls who smoke or had smoked and did not specify their smoking behavior in duration of smoking or number of cigarettes per day were not imputed.

skin type, highest level of education, time spent outdoors, sun vacations, use of solarium, and sun protective measures.

The adjusted ORs of melanoma associated with cigarette smoking for males and females are presented in Table 3. Both current and former male smokers did not have a higher risk of melanoma compared to never smokers.

Current smokers had an adjusted OR of 0.56 (95% CI: 0.40–0.79) and former smokers had an adjusted OR of 0.50 (95% CI: 0.39–0.64). In addition, with an increasing number of years smoked the risk of melanoma decreased: <20 years: OR = 0.61 (95% CI: 0.46–0.80); 21–40 years: OR = 0.50 (95% CI: 0.37–0.68); >40 years: OR = 0.26 (95% CI: 0.15–0.44). No clear trend was found for the number

Table 2. Patient and lifestyle characteristics of female patients and controls

Females	Patients (n = 717)	Patients (after imputation)	Controls (n = 3,047)	Controls (after imputation)	OR (95% CI) ¹
Age at completion of questionnaire, years	52.9±13.2		50.2±17.1		1.01 (1.01–1.02)
<i>Smoking status</i>					
Never	319 (44.5)		1,341 (44.0)		reference
Current	111 (15.5)		480 (15.8)		0.97 (0.77–1.24)
Former	287 (40.0)		1,226 (40.2)		0.98 (0.82–1.12)
<i>Duration of smoking²</i>					
Never smoker	319 (44.5)		1,341 (44.0)		reference
<20 years	219 (30.5)		770 (25.3)		1.20 (0.99–1.45)
21–40 years	112 (15.6)		475 (15.6)		0.99 (0.78–1.26)
>40 years	24 (3.3)		142 (4.7)		0.71 (0.45–1.11)
<i>Cigarettes per day</i>					
Never smoker	319 (44.5)		1,341 (44.0)		reference
<10	245 (34.2)		887 (29.1)		1.16 (0.96–1.40)
10–20	107 (14.9)		514 (16.9)		0.88 (0.69–1.11)
>20	25 (3.5)		126 (4.1)		0.83 (0.53–1.30)
<i>Marital status</i>					
Single	137 (19.1)	139 (19.4)	1,079 (35.4)	1,084 (35.6)	reference
With partner	575 (80.2)	578 (80.6)	1,959 (64.3)	1,963 (64.4)	2.28 (1.86–2.79)
Missing	5 (0.7)		9 (0.3)		
<i>Education</i>					
Less than secondary school	172 (24.0)	172 (24.0)	646 (21.2)	650 (21.3)	reference
Secondary school	260 (36.3)	260 (36.3)	880 (28.9)	883 (29.0)	1.11 (0.89–1.38)
More than secondary school	285 (39.7)	285 (39.7)	1,507 (49.5)	1,514 (49.7)	0.71 (0.58–0.88)
Missing	0 (0.0)		14 (0.5)		
<i>Skin type</i>					
I, II	378 (52.7)	378 (52.7)	1,386 (45.5)	1,394 (45.7)	reference
III	331 (46.2)	331 (46.2)	1,522 (50.0)	1,526 (50.1)	0.80 (0.68–0.94)
IV–VI	8 (1.1)	8 (1.1)	125 (4.1)	127 (4.2)	0.24 (0.11–0.48)
Missing	0 (0.0)		14 (0.5)		
<i>Skin reaction after 1 h unprotective sun exposure</i>					
Not burned	66 (9.2)	66 (9.2)	582 (19.1)	585 (19.2)	reference
A little bit red	398 (55.5)	398 (55.5)	1,801 (59.1)	1,810 (59.4)	1.95 (1.48–2.57)
Burned	253 (35.3)	253 (35.3)	646 (21.2)	652 (21.4)	3.46 (2.58–4.64)
Missing	0 (0.0)		18 (0.6)		
<i>Solarium usage during lifetime</i>					
Never	168 (23.4)	169 (23.6)	1,015 (33.3)	1,034 (33.9)	reference
<2 cures	403 (56.2)	403 (56.2)	1,176 (38.6)	1,190 (39.1)	2.07 (1.70–2.53)
2–5 cures	126 (17.6)	126 (17.6)	614 (20.2)	620 (20.3)	1.24 (0.97–1.60)
>5 cures	19 (2.7)	19 (2.6)	201 (6.2)	203 (6.7)	0.58 (0.35–0.95)
Missing	1 (0.1)		41 (1.3)		
<i>Time spent outdoors weekends/holidays <18 years (hours per day)</i>					
<2 h	96 (13.4)	97 (13.5)	460 (15.1)	479 (15.7)	reference
2–4 h	420 (58.6)	434 (60.5)	1,801 (59.1)	1,874 (61.5)	1.13 (0.88–1.44)
>4 h	182 (25.4)	186 (25.9)	633 (20.8)	694 (22.8)	1.31 (0.99–1.72)
Unknown	19 (2.6)		153 (5.0)		
<i>Time spent outdoors weekdays >18 years (hours per day)</i>					
<2 h	494 (68.9)	498 (69.5)	2,146 (70.4)	2,209 (72.5)	reference
2–4 h	133 (18.5)	133 (18.5)	499 (16.4)	520 (17.1)	1.16 (0.93–1.44)
>4 h	82 (11.4)	86 (12.0)	304 (10.0)	318 (10.4)	1.17 (0.90–1.52)
Unknown	8 (1.1)		98 (3.2)		

Table 2 (continued)

Females	Patients (n = 717)	Patients (after imputation)	Controls (n = 3,047)	Controls (after imputation)	OR (95% CI) ¹
<i>Time spent outdoors weekends/holidays >18 years (hours per day)</i>					
<2 h	162 (22.6)	168 (23.4)	697 (22.9)	727 (23.9)	reference
2–4 h	438 (61.1)	451 (62.9)	1,863 (61.1)	1,934 (63.5)	1.00 (0.82–1.22)
>4 h	91 (12.7)	98 (13.7)	345 (11.3)	386 (12.7)	1.06 (0.80–1.41)
Unknown	26 (3.6)		142 (4.7)		
<i>Sun vacation <18 years (weeks per year)</i>					
None	378 (52.7)	378 (52.7)	1,705 (56.0)	1,744 (57.2)	reference
1–2 weeks	192 (26.8)	192 (26.8)	740 (24.3)	761 (25.0)	1.17 (0.96–1.42)
3–4 weeks	121 (16.9)	121 (16.9)	500 (16.4)	518 (17.0)	1.08 (0.86–1.36)
>4 weeks	26 (3.6)	26 (3.6)	21 (0.7)	24 (0.8)	4.62 (2.43–8.78)
Missing	0 (0.0)		81 (2.7)		
<i>Sun vacation >18 years (weeks per year)</i>					
None	123 (17.2)	123 (17.2)	584 (19.2)	606 (19.9)	reference
1–2 weeks	341 (47.6)	341 (47.6)	1,271 (41.7)	1,327 (43.6)	1.28 (1.02–1.60)
3–4 weeks	215 (30.0)	215 (30.0)	1,017 (33.4)	1,062 (34.9)	1.00 (0.78–1.28)
>4 weeks	38 (5.3)	38 (5.3)	51 (1.7)	52 (1.7)	3.37 (2.08–5.48)
Missing	0 (0.0)		124 (4.1)		
<i>Sun protective measures <18 years</i>					
Never	36 (5.0)	40 (5.6)	138 (4.5)	198 (6.5)	reference
Rarely/sometimes	389 (54.3)	438 (61.1)	1,436 (47.1)	1,730 (56.8)	1.23 (0.82–1.85)
Often/always	204 (28.5)	239 (33.3)	897 (29.4)	1,119 (36.7)	1.10 (0.74–1.63)
Missing	88 (12.3)		576 (18.9)		
<i>Sun protective measures >18 years</i>					
Never	6 (0.8)	7 (1.0)	35 (1.1)	62 (2.0)	reference
Rarely/sometimes	239 (33.3)	260 (36.3)	1,112 (36.5)	1,317 (43.2)	1.66 (0.58–4.77)
Often/always	432 (60.3)	450 (62.8)	1,446 (47.5)	1,668 (54.7)	2.34 (0.77–7.12)
Missing	40 (5.6)		454 (14.9)		

Data are presented as *n* (%) or mean ± SD unless otherwise indicated. ¹ The imputed data were used for analyses. ² Data of patients and controls who smoke or had smoked and did not specify their smoking behavior in duration of smoking or number of cigarettes per day were not imputed.

of cigarettes smoked. All results in females were less clear. Current smokers had an adjusted OR of 0.96 (95% CI: 0.74–1.26) compared to never smokers, whereas former smokers had an adjusted OR of 0.89 (95% CI: 0.73–1.08).

Discussion

The aim of this study was to investigate the association between cigarette smoking and risk of developing a primary melanoma. From the results it can be concluded that cigarette smoking does not increase the risk of melanoma. Among males, cigarette smoking might even decrease the risk of melanoma. In addition, the melanoma risk appeared to decrease with a longer duration of cigarette smoking. No clear trend was found with increasing

number of cigarettes smoked per day. In females, the results of all analyses were less clear and not statistically significant.

These results for both males and females are largely in accordance with several previous studies [9, 11–13, 15, 17]. However, none of the previous studies found an inverse association between cigarette smoking and melanoma risk as strong as that observed among males in our study. Also, studies have been published without an inverse association between cigarette smoking and risk of melanoma [10, 14, 16, 18, 22, 28]. Possible explanations for these conflicting observations might be a smaller number of subjects, another time frame with different smoking behavior, and the lack of melanoma-associated confounders (number of nevi, number of atypical nevi, and genetic predisposition). Also, possibly fewer studies

Table 3. Adjusted odds ratios of melanoma associated with cigarette smoking

	Adjusted OR ¹ (95% CI)	
	males	females
<i>Smoking status</i>		
Never	reference	reference
Current	0.56 (0.40–0.79)	0.96 (0.74–1.26)
Former	0.50 (0.39–0.64)	0.89 (0.73–1.08)
<i>Duration of smoking</i>		
Never smoker	reference	reference
<20 years	0.61 (0.46–0.80)	1.18 (0.95–1.46)
21–40 years	0.50 (0.37–0.68)	0.90 (0.70–1.17)
>40 years	0.26 (0.15–0.44)	0.55 (0.34–0.89)
<i>Cigarettes per day</i>		
Never smoker	reference	reference
<10	0.50 (0.37–0.67)	1.11 (0.90–1.36)
10–20	0.52 (0.39–0.70)	0.79 (0.61–1.02)
>20	0.44 (0.28–0.69)	0.80 (0.49–1.29)

¹ OR adjusted for age, marital status, skin type, highest level of education, time spent outdoors, sun vacations, use of solarium, and sun protective measures.

with an inverse association between cigarette smoking and melanoma are published because of ethical issues regarding the possible harmful effect on health care.

Several possible explanations for the observed inverse relation between cigarette smoking and the risk of melanoma have been suggested. A low socioeconomic status is linked to higher smoking prevalence [30] and people of lower socioeconomic status have less exposure to specific lifestyle factors associated with melanoma risk, such as recreational UV exposure and tanning, which may decrease melanoma incidence [31]. Also, smokers presumably spend more time indoors and therefore have less UV exposure [27]. In addition, because of an overall healthier lifestyle it is likely that never smokers have more medical surveillance and earlier detection of disease compared with smokers. Therefore, smokers might have fewer full body skin examinations by a physician compared to never smokers, which results in a delayed detection of melanoma. In our study, we adjusted all risk estimates for the level of education as approximation for socioeconomic status and for the time people spend outdoors. However, we cannot fully exclude the possible effect of other factors associated with cigarette smoking (residual confounding).

It is hypothesized that smoking may protect melanocytes from the inflammatory reaction induced by long-

term UV radiation [25, 26]. This effect of smoking may be partially caused by the long-term effect of nicotine. Cigarette smoke contains many reactive oxygen species, but also UV irradiation causes the production of reactive oxygen species, which are responsible for induction of proinflammatory cytokines. The anti-inflammatory effects of nicotine are mediated by $\alpha 7$ nicotinic acetylcholine receptors, which are also located on cells of the immune system, like macrophages [32]. They inhibit the release of proinflammatory cytokines (TNF α , IL-6, and IL-8) via the cholinergic anti-inflammatory pathway and promote the release of anti-inflammatory cytokines.

In addition, nicotine causes vasoconstriction of peripheral blood vessels including those of the skin, possibly by reduced prostacyclin production [33, 34], which affects the inflammatory response in the skin.

Recently, it has been discovered that genetic predisposition exists for smoking behavior [35, 36]. In a subsequent study an inverse association between smoking behavior-related genetic variants in the chromosome 15q25.1 region and risk of melanoma, especially in males, was observed [37]. This suggests that smoking behavior-related single nucleotide polymorphisms play a role in melanoma development and might indicate that smoking is indeed causally related to melanoma risk.

The inverse association between cigarette smoking and melanoma was most prominently seen in males. These results are consistent with results reported by previous studies [9, 12, 15, 17]. A recent twin study with intravenous infusions of nicotine and cotinine (the most important metabolite of nicotine) showed that nicotine and cotinine metabolism is higher in women compared to men. In addition, use of an oral contraceptive further accelerates nicotine and cotinine metabolism [38, 39]. The gender difference was also detected in recent studies among smokers, showing that the ratio of the nicotine metabolite trans-3'-hydroxycotinine to cotinine in blood or urine is significantly higher in women, supporting the abovementioned faster metabolism in women compared to men [40, 41]. These changes in metabolism seem to be due to hormonal differences. Also, evidence exists that the activity of a member of the cytochrome p450 proteins (CYP) superfamily of enzymes, the CYP2A6 enzyme, is induced by sex hormones and there is recent in vitro evidence for the induction of human CYP2A6 by estrogen acting on the estrogen receptor [42]. Women are suggested to have more active CYP enzyme activity and therefore metabolize more nicotine which reduces the anti-inflammatory effect of nicotine in relation to melanoma development, which means that the melanoma-protecting ef-

fect in women is less pronounced [43]. These gender differences in metabolism could explain the observed strong inverse association between cigarette smoking and melanoma risk in men compared to the lesser effect observed in women.

The main strengths of this population-based study include its large number of subjects and the extensive collection of exposure information with the ability to adjust for the most important confounders. Our questionnaire information represents the best possible approach regarding sun behavior by using different variables as a proxy for intermittent and cumulative sun exposure. A previous study showed that self-reported information on melanoma risk factors is fairly well reproducible and is useful in research settings [44].

There are also limitations. Information on smoking behavior and confounding factors was retrieved after the diagnosis of melanoma. Therefore, recall bias cannot be excluded. However, we have no reason to believe that patients and controls answer questions regarding smoking habits differently, because the public's awareness of the association between cigarette smoking and melanoma is probably very low. Patients might have answered the questions regarding sun behavior in a different way compared to controls because of their higher awareness of melanoma risk factors. Unfortunately, for this study we were not able to include information concerning the presence of atypical nevi, number of nevi, and genetic predisposition, which are important risk factors for melanoma [45]. Also, the cohort time periods are not concomitant across the two cohorts of patients and controls, which may cause a risk of bias. Societal attitudes towards lifestyle and smoking habits might have changed and could therefore influence response behavior because of social desirability. Furthermore, with a response rate of 42% in the control population, a selection bias might be introduced. The response rate for the questionnaire was slightly higher for older age categories than for younger age categories [29]. However, compared to our patients, there is no great difference in mean age. Among patients who had smoked, there is some missing data regarding the number of years of cigarette smoking and number of cigarettes per day, which could introduce bias. However, lack of this information is not dependent on the extent of smoking. Systematic bias is therefore not to be expected, but the observed effect might be less strong.

In conclusion, we observed that cigarette smoking does not increase the risk of developing a primary melanoma. Male smokers might have a decreased risk of melanoma. In females the results were less pronounced. Giv-

en the limitations of this study and possible residual confounding no direct clinical impact can be reduced from these results. Encouraging smoking cessation remains of utmost importance. However, if one of the components of tobacco smoke causes a protective effect on the development of melanoma, this might be of meaning for high-risk patients in the future. To investigate a (causal) biological mechanism underlying the association between smoking cigarettes and melanoma risk and to identify which component(s) of cigarette smoke might be protective, fundamental laboratory studies are necessary.

Key Message

Cigarette smoking does not increase melanoma risk.

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Statement of Ethics

All patients and controls gave written informed consent. The authors have no ethical conflicts to disclose.

Disclosure Statement

There are no conflicts of interest.

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