Research Article

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Smoking and Cutaneous Melanoma: Findings from the QSkin Sun and Health Cohort Study

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Abstract

Background: Previous studies suggest that smokers have lower risks of cutaneous melanoma than nonsmokers, but data from population-based prospective studies are scarce. We investigated associations between smoking and melanoma in a cohort study purpose-designed to investigate skin cancer outcomes.

Methods: Participants with no prior history of melanoma (n = 38,697) completed a risk factor survey at baseline (2011). Patients were followed through linkage to the cancer registry. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between smoking (including intensity, duration, time since quitting) and melanoma using multivariate Cox proportional hazards regression, accounting for death as a competing event.

Results: During a mean follow-up of 3.5 years, invasive melanomas developed in 247 participants. Compared with never smokers, former smokers (but not current smokers) had lower risks of invasive melanoma (HR 0.76; 95% CI, 0.57–1.01). Among former smokers, risks were lower with greater quantity of cigarettes smoked (HR 0.75; 95% CI, 0.56–0.98 per 10 cigarettes/day). No association was observed with duration of smoking while longer time since quitting was associated with a relative risk of melanoma that was not significantly different from the null (HR 1.18; 95% CI, 0.91–1.51, for every 10 years since quitting).

Conclusions: We observed complex associations between smoking and melanoma, with some suggestion that former smokers had lower risks than never or current smokers. The apparent inverse association among former smokers may be due to residual confounding, although surveillance bias or biological effects cannot be excluded entirely.

Impact: Smoking does not increase the risk of cutaneous melanoma. *Cancer Epidemiol Biomarkers Prev; 27(8); 874–81.* *©2018 AACR.*

Introduction

The International Agency for Research on Cancer (IARC) has declared smoking as a cause of 18 cancers (1). Although no cancers of the skin are currently included in this list, there is strengthening evidence that smoking is a cause of cutaneous squamous cell carcinoma (SCC; ref. 2). The association between smoking and melanoma remains unclear despite considerable investigation. Two previous meta-analyses reported moderate inverse associations between smoking and melanoma, although both noted important limitations with the literature. The first used a dichotomized measure of smoking (ever vs. never) which failed to separate the effect of current and former smoking (3). The second reported significant publication bias due to selective reporting in the included studies (4).

Cohort studies have reported mixed findings. Blakeley and colleagues reported inverse associations between current smoking and melanoma, but that study did not report any findings for former smokers (5). The Swedish Construction Workers and the U.S. Radiologic Technologists study cohort reported inverse associations between both current and former smoking and melanoma (6, 7). A prospective cohort study of cancer mortality and incidence showed a significant inverse association between current smoking and melanoma incidence in women but not in men, whereas a null association was reported among former smokers in both sexes (8). The Health Professionals Follow-up Study reported an inverse association between current and former smoking and melanoma in men (3), whereas the Nurses' Health Study (women only; ref. 3) reported null associations in both current and former smokers. Findings from case–control studies have been mixed, reporting both positive and negative associations (9, 10).

Several design and analysis features of previous prospective studies exploring this potential association have rendered the findings open to questions of bias and confounding, meaning that the question of whether smoking increases or decreases the risk of melanoma has not been answered definitively. For example, no previous cohorts have collected information on potentially important factors such as skin phototype (burning/tanning). In terms of analysis, various studies have shown that analyzing multiple measures of smoking history individually is inefficient and may lead to over- or underestimation of risk by failing to account for variability in smoking history (11, 12). Moreover, the influence of various sources of bias have rarely been investigated,

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despite their acknowledged importance (13, 14). For example, detection bias could arise if smokers underwent fewer physician skin checks than nonsmokers, resulting in apparently lower melanoma incidence among smokers. Similarly, smokers have higher all-cause mortality than nonsmokers, which might contribute to an apparent lower melanoma incidence among smokers due to competing risks of death.

We sought to investigate further the role of cigarette smoking in the development of cutaneous melanoma using data from a large population-based cohort study purpose-designed to investigate skin cancer outcomes. In particular, we aimed to explore possible dose–response relationships with duration or intensity of smoking, and time since quitting smoking, while taking full account of the potential confounding effects of established risk factors for melanoma.

Materials and Methods

Study population

The QSkin Sun and Health Study (QSkin) is a prospective cohort study of 43,794 men and women randomly sampled from the Queensland population in 2011, who were between ages 40 and 69 years at study entry. Detailed information regarding participant recruitment and other study characteristics has been reported elsewhere (15). We restricted our analysis to participants of European ancestry who completed the smoking questions in the baseline questionnaire. Prior to baseline, we excluded those with a confirmed diagnosis of both *in situ* and invasive melanoma ($n = 126$); or invasive melanoma only ($n = 867$); or *in situ* melanoma only ($n = 764$), leaving 38,697 participants for analysis.

This study has received approval from the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute. Each participant provided written informed consent to take part in the study.

Exposure assessment

At baseline participants self-completed a questionnaire asking about demographic items, general medical history, pigmentary characteristics, history of sun exposure, sun protection behavior, and history of skin cancer. They were further asked to report the number of times they had undergone regular skin checks by a doctor over the past 3 years. Participants were asked to report their smoking history; those who had smoked daily for at least 6 months were asked further questions including age at smoking initiation, the age at which they stopped smoking permanently (among former smokers), the amount they smoked per day while smoking, and the total number of years during which they had smoked. Repeatability for smoking measures was nearly perfect (weighted $\kappa = 0.97$; 95% CI, 0.92–1.00; ref. 16).

Follow-up

In addition to historical data obtained from the cancer registry prior to baseline, participants were followed prospectively for the first occurrence of histologically confirmed *in situ* or invasive melanoma by record linkage to the Queensland Cancer Registry (notification has been mandatory since 1982 and is virtually complete). Surveillance commenced from date of enrollment (2010–2011) through 30 June 2014. Deaths in the cohort were identified through linkage with the National Death Index.

Statistical analysis

The primary outcome was incident invasive melanoma. Participants contributed person-years to the analysis from date of consent until one of the following endpoints: histologically confirmed *in situ* or invasive melanoma, death or end of follow-up (June 30, 2014), whichever occurred first. In our primary analysis, *in situ* melanomas occurring during follow-up were censored on the date of diagnosis. However, we performed sensitivity analyses by (i) including *in situ* melanoma in the case group (i.e., cases = any diagnosis of melanoma, *in situ* or invasive) and (ii) by treating history of *in situ* melanoma as a time-varying covariate, whereby participants so diagnosed remained at risk for a subsequent invasive melanoma but were treated as a different risk set post *in situ* diagnosis.

We performed competing risks regression analyses to account for possible increased mortality hazards among smokers. We used the Fine-Gray approach to calculate overall and gender-specific subdistribution hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between measures of smoking and risk of melanoma in the presence of death as a competing risk (17).

We selected potential confounders based on prior knowledge and the published literature, but we also looked at pairwise associations in our data. Our final multivariate models were adjusted for age, sex, natural skin color, tanning tendency, number of moles at age 21, past history of excised skin cancers, past history of destructive skin cancer treatments, family history of melanoma, history of sunburn as a child, and cumulative lifetime sun exposure.

To test for trends in dose response, we included categorical smoking variables (intensity, duration, and time since quitting) in each model as continuous terms, and assigned a value to each ordinal category equal to the median of its continuous distribution within that category and then modeled each categorical dimension as a continuous term. We performed additional analyses assessing each measure of smoking as a continuous variable while simultaneously adjusting for other measures of smoking. To avoid multi-collinearity, we centered all continuous measures of smoking (rescaled to the mean; ref. 18). Pack-years smoked was used to adjust for dose smoked while estimating the effect of time since quitting due to strong correlation between duration and time since quitting. To explore possible nonlinear dose effects of continuous measures of smoking, we used generalized additive models with cubic splines fixed at 3 degrees of freedom. We used R software for these generalized additive models (CRAN package mgcv) and SAS 9.4 software (SAS Institute, Cary, NC) for all other statistical analyses.

Results

The average follow-up duration was 3.5 years (minimum 2.4 years, maximum 3.6 years). Of the 38,697 eligible participants, 247 developed a first incident invasive melanoma during follow-up (139 men, 108 women) and 394 developed a first incident *in situ* melanoma (236 men, 158 women), 445 participants died (Fig. 1). The mean age at study entry was 56 years, 10% were current smokers and 36% former smokers. Compared with never smokers, current smokers were younger (mean 54 years vs. 56 years), more likely to be males and less likely to have achieved higher levels of education (Table 1). Current smokers were also less likely than never smokers to report having a skin type that

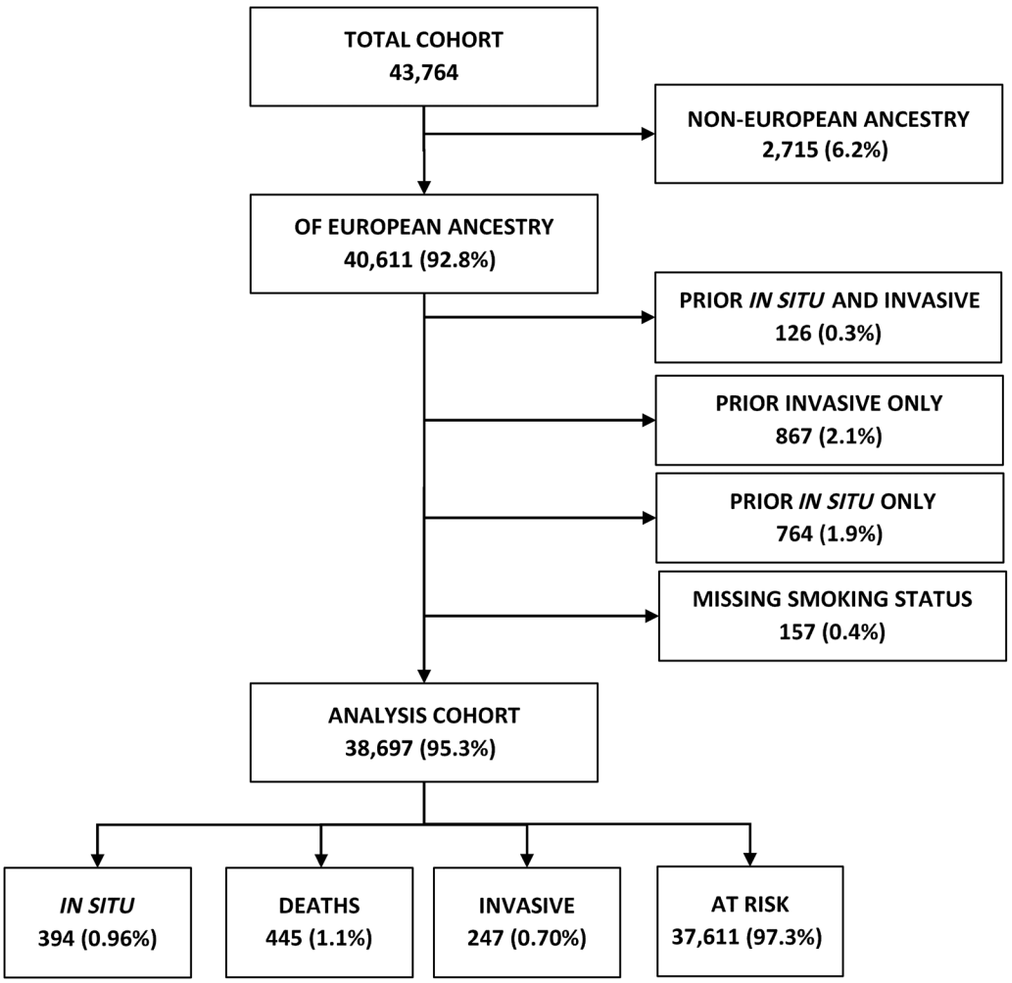

Figure 1.
Flow diagram describing the analysis sample of the QSkin cohort ($n = 43{,}764$) and outcomes after 3.5 years of follow-up.

burns easily, and were more likely to report having skin that tans deeply. On average, current smokers smoked for a significantly longer duration than former smokers (mean 36.5 years vs. 19.8 years, respectively), but both groups reported similar smoking intensity (mean 18 vs. 19 cigs/day, respectively).

After adjusting for potential confounding factors, ever smokers were less likely than never smokers to develop invasive melanoma (HR 0.80; 95% CI, 0.62–1.05; Table 2). We also observed lower risks of invasive melanoma among ever smokers in analyses of intensity and time since quitting, but not with duration or age at smoking initiation.

When analyzed by smoking status, we observed no association between current (HR 1.01; 95% CI, 0.64–1.61), and former smoking (HR 0.76; 95% CI, 0.57–1.01) with melanoma. The lower risks of invasive melanoma among ever smokers were also observed in analyses of smoking intensity and time since quitting. There was no association between age at smoking initiation and duration and invasive melanoma, but there was a significant inverse trend with increasing smoking intensity ($P_{\text{trend}} = 0.001$).

We observed unusual trends among former smokers whereby the inverse association was significant among recent quitters and then gradually decreased toward the null. Although this pattern suggests a nonlinear trend, the test for nonlinearity was not statistically significant. The association between smoking and melanoma did not differ materially across strata of cumulative sun exposure (Supplementary Table S1). The inverse association among former smokers was similar for women and men.

To further assess the linearity in dose response with incremental change in each continuous dimension of smoking, linear terms for smoking duration, intensity, and time since quitting were modeled simultaneously with an indicator variable for smoking status (Table 3). When duration and intensity were included simultaneously in the model, intensity was associated with significantly lower risks of melanoma among former smokers (HR 0.74; 95% CI, 0.56–0.98, for every 10 cigarettes/day). We observed a similar inverse trend among current smokers, although the association was not statistically significant (HR 0.81; 95% CI, 0.55–1.51, for every 10 cigarettes/day). Smoking intensity remained significantly inversely associated with melanoma even

Table 1. Baseline characteristics of QSkin study participants by smoking status

		Smoking status at baseline			
Parameter	**Total (*n* = 38,697) *n* (%)**	**Never (*n* = 21,035) *n* (%)**	**Former (*n* = 13,935) *n* (%)**	**Current (*n* = 3727) *n* (%)**	**Chi-square *P*-value**
Age at entry, mean (SD)	56.1 (8.2)	55.7 (8.2)	57.1 (8.1)	54.3 (7.7)	<0.0001[a]
Age group					
40–49	10237 (26.5)	5909 (28.1)	3096 (22.2)	1232 (33.1)	<0.0001
40–59	14669 (37.9)	7852 (37.3)	5263 (37.8)	1553 (41.7)	
60–69	13791 (35.6)	7274 (34.6)	5576 (40.0)	941 (25.3)	
Sex					
Females	21000 (54.3)	12550 (59.7)	6590 (47.3)	1860 (49.9)	<0.0001
Males	17697 (45.7)	8485 (40.3)	7345 (52.7)	1867 (50.1)	
Further education					
No school certificate	2978 (7.7)	1266 (6.0)	1210 (8.7)	502 (13.5)	<0.0001
School certificate	5997 (15.5)	3059 (14.5)	2281 (16.4)	657 (17.6)	
Completed high school	7051 (18.2)	3873 (18.4)	2418 (17.3)	760 (20.4)	
Trade/certificate/diploma	10821 (27.9)	5502 (26.2)	4292 (30.8)	1027 (27.5)	
University degree	9086 (23.5)	6078 (28.9)	2613 (18.7)	395 (10.6)	
Missing	2764 (7.2)	1257 (5.9)	1121 (8.0)	386 (10.4)	
Private health insurance					
No	26110 (67.5)	15618 (74.3)	8877 (63.7)	1527 (41.0)	<0.0001
Yes	12588 (32.5)	5346 (25.4)	4995 (35.8)	2180 (58.5)	
Missing	154 (0.4)	71 (0.3)	63 (0.6)	20 (0.5)	
Skin color					
Fair	23534 (60.8)	13014 (61.9)	8322 (59.7)	2198 (58.9)	<0.0001
Medium	12433 (32.1)	6685 (31.8)	4570 (32.8)	1178 (31.6)	
Olive/dark	2538 (6.6)	1237 (5.9)	977 (7.0)	324 (8.7)	
Missing	192 (0.5)	99 (0.5)	66 (0.5)	27 (0.7)	
Eye color					
Blue/grey	15255 (39.4)	8281 (39.4)	5490 (39.4)	1484 (39.8)	0.40
Green/hazel	14683 (37.9)	8063 (38.3)	5210 (37.4)	1410 (37.8)	
Brown/black	8246 (21.3)	4447 (21.2)	3029 (21.7)	770 (20.7)	
Missing	513 (1.3)	244 (1.2)	206 (1.5)	63 (1.7)	
Hair color					
Dark brown/black	15981 (41.5)	8817 (41.9)	5738 (41.2)	1426 (38.3)	<0.0001
Light brown	14743 (38.3)	7992 (37.9)	5356 (38.4)	1395 (37.4)	
Blonde	5550 (14.4)	2922 (13.9)	1982 (14.2)	646 (17.3)	
Red/auburn	2220 (5.8)	1203 (5.7)	784 (5.6)	233 (6.3)	
Missing	203 (0.5)	101 (0.5)	75 (0.5)	27 (0.7)	
Burning tendency					
No burns	3350 (8.7)	1570 (7.5)	1278 (9.2)	502 (13.5)	<0.0001
Burns a little	16680 (43.1)	8765 (41.7)	6213 (44.6)	1702 (45.7)	
Burns moderately	13021 (33.6)	7353 (34.9)	4588 (32.9)	1080 (28.9)	
Burns badly	5443 (14.1)	3241 (15.4)	1782 (12.8)	420 (11.3)	
Missing	203 (0.5)	106 (0.5)	74 (0.5)	23 (0.6)	
Tanning tendency					
No tan	2489 (6.4)	1464 (6.9)	780 (5.6)	245 (6.6)	<0.0001
Tan lightly	8097 (20.9)	4857 (23.1)	2514 (18.1)	726 (19.5)	
Tan moderately	19252 (49.7)	10463 (49.7)	7093 (50.9)	1696 (45.5)	
Tan deeply	8584 (22.1)	4094 (19.5)	3460 (24.8)	1030 (27.6)	
Missing	275 (0.71)	157 (0.7)	88 (0.6)	30 (0.8)	
Freckles at age 21 years (face)					
None	17884 (46.2)	9337 (44.4)	6778 (48.6)	1769 (47.5)	<0.0001
A few	12177 (31.5)	6847 (32.5)	4219 (30.3)	1111 (29.8)	
Some	6085 (15.7)	3474 (16.5)	2026 (14.5)	585 (15.7)	
Many	2362 (6.1)	1272 (6.1)	850 (6.1)	240 (6.4)	
Missing	189 (0.5)	105 (0.5)	62 (0.4)	22 (0.6)	
Nevus category at age 21					
None	10740 (27.8)	5470 (26.0)	4087 (29.3)	1183 (31.7)	<0.0001
A few	20100 (51.9)	11148 (53.0)	7123 (51.1)	1829 (49.1)	
Some	5677 (14.7)	3227 (15.3)	1922 (13.8)	528 (14.2)	
Many	1158 (2.9)	676 (3.2)	388 (2.8)	94 (2.5)	
Missing	1022 (2.6)	514 (2.4)	515 (2.9)	93 (2.5)	
Sunburns as a child					
Never	7253 (18.7)	4083 (19.4)	2469 (17.7)	701 (18.8)	<0.0001
1–5	16003 (41.4)	8915 (42.4)	5631 (40.4)	1457 (39.1)	
6–10	6228 (16.1)	3355 (15.9)	2301 (16.5)	572 (15.4)	
11+	5578 (14.4)	2778 (13.2)	2158 (15.5)	642 (17.2)	
Missing	3635 (9.4)	1904 (9.1)	1376 (9.9)	355 (9.5)	

(Continued on the following page)

Table 1. Baseline characteristics of QSkin study participants by smoking status (Cont'd)

Parameter	Total ($n = 38,697$) *n* (%)	Smoking status at baseline: Never ($n = 21,035$) *n* (%)	Former ($n = 13,935$) *n* (%)	Current ($n = 3727$) *n* (%)	Chi-square *P*-value
Skin checks by a doctor (past 3 years)					
No	10236 (26.4)	5178 (24.6)	3805 (27.3)	1253 (33.6)	<0.0001
Yes	27616 (71.4)	15440 (73.4)	9824 (70.5)	2352 (63.1)	
Missing	845 (2.2)	417 (1.9)	306 (2.2)	122 (3.3)	
AKs[b]/skin cancers destructively treated prior to baseline					
None	17252 (44.8)	9130 (43.4)	6122 (43.9)	2000 (53.7)	<0.0001
1–5	10412 (27.1)	5880 (27.9)	3687 (26.5)	845 (22.7)	
6 +	10840 (28.2)	5913 (28.1)	4063 (29.2)	864 (23.2)	
Missing	193 (0.5)	112 (0.5)	63 (0.4)	18 (0.5)	
Family history of melanoma					
No	24132 (62.4)	13181 (62.6)	8796 (63.1)	2155 (57.8)	<0.0001
Yes	8892 (22.9)	5067 (24.1)	2962 (21.3)	863 (23.2)	
Missing	5673 (14.7)	2787 (13.3)	2177 (15.6)	709 (19.0)	
Duration (years) of smoking, mean (SD)	23.32 (13.2)	36.48 (9.2)	19.78 (11.8)	N/A	<0.0001
Intensity of smoking (cigarettes/day), mean (SD)	19.29 (12.5)	18.71 (9.6)	19.44 (13.2)	N/A	0.002

[a]*P*-value for significant difference using Ryan–Einot–Gabriel–Welsch multiple range test.
[b]AKs, actinic keratosis.

after including time since quitting in the model. Longer time since quitting was associated with a relative risk of melanoma that was not significantly different from the null (HR 1.18; 95% CI, 0.91–1.51, for every 10 years since quitting). In contrast, we saw no significant associations between smoking duration and melanoma risk in any analyses. We did not observe statistically significant nonlinear dose effects for smoking duration, intensity or time since quitting ($P = 0.09$, 0.06, and 0.8, respectively, for testing for departure from linearity (Supplementary Figs. S1–S3).

We performed further analysis by combining current smokers and recent quitters ($\leq$10 years), which increased the number of melanoma cases among current smokers by approximately 40%. This analysis made essentially no difference to the observed risk in current smokers (HR 0.99; 95% CI, 0.66–1.24), whereas the inverse association observed in former smokers was somewhat attenuated (HR 0.86; 95% CI, 0.64–1.15).

We conducted sensitivity analyses in which we included as cases those participants who were diagnosed with *in situ* melanomas and those diagnosed with invasive melanoma (Supplementary Table S2). These analyses resulted in slightly attenuated associations with ever smoking but the direction of association remained unchanged. Finally, we performed two additional sensitivity analyses, first by ignoring any *in situ* melanoma diagnoses during follow-up, and second by treating a diagnosis of *in situ* melanoma as a time-dependent covariate (Supplementary Table S3). These analyses made essentially no difference to the estimates we have reported in Table 2.

Discussion

We investigated the association between cigarette smoking and incidence of melanoma in a prospective cohort study of more than 38,000 participants. We found no evidence that smoking increases the risk of melanoma; indeed, our analysis suggests that former smokers may have lower risks of melanoma than never smokers, although this assessment is offered cautiously. Overall, the inverse association was apparent among former smokers but not in current smokers, and although not always statistically significant, the reductions in risk in former smokers appeared greater with longer durations or greater intensity of smoking. Taken together, these headline findings are similar to those from previous cohort studies (6, 8, 19) and meta-analyses (3, 4), which have mostly reported moderately lower risks of melanoma among smokers. We observed nonsignificant dose–response trends; smoking intensity and duration decreased the risk whereas longer time since quitting was associated with a relative risk of melanoma that was not significantly different from the null. Again, these observations are consistent with previous studies which reported diminished risks of invasive melanoma with longer durations of smoking and greater quantity of tobacco smoked (6, 20).

We explored whether these findings might be explained by the confounding effects of other factors, because in this cohort, smoking was significantly associated with a large number of factors that are known to influence a person's risk of melanoma (including sex, education, private health insurance, pigmentation phenotypes, burning and tanning tendency, and history of prior actinic skin damage and sun exposure). We therefore adjusted for these factors in our analyses, but risk estimates changed little between minimally adjusted and fully adjusted models. Recall bias is unlikely since smoking exposures were captured prior to melanoma development and in the 3 years of follow-up, smoking status is unlikely to have changed appreciably. Loss to follow-up is also unlikely to explain these findings as notifications to the cancer registry are mandatory in Queensland, and registration is virtually complete. It has been suggested previously that the inverse associations between smoking and melanoma in cohort studies might be explained by competing risks of deaths from smoking-related diseases (21). In a simulation study, it was argued that smokers are at increased risk of acquiring various smoking-related diseases, and thus may die at younger ages before being diagnosed with age-dependent conditions such as melanoma. This explanation was certainly possible in our dataset, as we observed a substantially higher cumulative mortality among current smokers compared with never smokers (2.6% vs. 0.7%, respectively). We therefore conducted a competing risks analysis to account for this effect, but observed that the inverse relationship between smoking and melanoma was essentially unchanged. However, in spite of very high repeatability of smoking measures

Table 2. The association between measures of smoking and incidence of invasive melanoma

		Minimally adjusted model[a]	Fully adjusted model[b]		
Parameter	**Cases/person-years**	**Total cohort HR (95% CI)**	**Total cohort HR (95% CI)**	**Males HR (95% CI)**	**Females HR (95% CI)**
Smoking status					
Never smoker[c]	151/73321	1.00	1.00	1.00	1.00
Ever smoker	96/61347	0.72 (0.55–0.92)	0.80 (0.62–1.05)	0.87 (0.62–1.22)	0.71 (0.46–1.09)
Ex-smoker	75/48417	0.66 (0.50- 0.88)	0.76 (0.57–1.01)	0.79 (0.55–1.15)	0.71 (0.45–1.13)
Current smoker	21/12930	0.81 (0.51–1.27)	1.01 (0.64–1.61)	1.26 (0.72–2.20)	0.69 (0.29–1.60)
P-value		0.01	0.1	0.2	0.3
Age (years) at starting smoking					
Never	151/73321	1.00	1.00	1.00	1.00
≤16	32/26107	0.53 (0.36–0.78)	0.63 (0.43–0.93)	0.69 (0.44–1.09)	0.50 (0.22–1.12)
>16	63/34517	0.81 (0.60–1.09)	0.93 (0.69–1.26)	1.03 (0.69–1.53)	0.82 (0.52–1.31)
P-value[d]		0.053	0.07	0.1	0.5
Duration (years) of smoking					
Never	151/73321	1.00	1.00	1.00	1.00
≤10	23/13243	0.86 (0.56–1.34)	0.91 (0.58–1.42)	0.97 (0.53–1.75)	0.85 (0.42–1.71)
11–20	27/14102	0.86 (0.57–1.30)	1.01 (0.67–1.52)	1.16 (0.71–1.91)	0.73 (0.34–1.60)
21–30	15/13698	0.51 (0.30–0.87)	0.61 (0.36–1.05)	0.63 (0.32–1.22)	0.60 (0.24–1.49)
>30	29/19347	0.58 (0.38–0.86)	0.71 (0.47–1.07)	0.77 (0.47–1.28)	0.61 (0.29–1.27)
P_{trend}[d]		0.049	0.1	0.2	0.4
Intensity of smoking (cigarettes/day)					
Never	151/73321	1.00	1.00	1.00	1.00
≤10	37/18491	0.99 (0.66–1.42)	1.14 (0.79–1.64)	1.08 (0.63–1.83)	1.20 (0.73–1.98)
11–20	41/24678	0.71 (0.50–1.01)	0.79 (0.56–1.13)	0.96 (0.63–1.47)	0.49 (0.24–1.04)
>20	16/16825	0.38 (0.22–0.63)	0.47 (0.28–0.79)	0.57 (0.32–1.02)	0.23 (0.05–0.93)
P_{trend}[d]		0.001	0.001	0.054	0.006
Pack-years of smoking					
Never	151/73321	1.00	1.00	1.00	1.00
≤10	36/19247	0.94 (0.65–1.35)	1.01 (0.69–1.46)	0.98 (0.58–1.65)	1.04 (0.61–1.78)
11–20	18/13034	0.63 (0.39–1.03)	0.75 (0.46–1.22)	0.99 (0.57–1.73)	0.34 (0.11–1.07)
21–30	19/9546	0.88 (0.54–1.42)	1.01 (0.62–1.64)	1.03 (0.55–1.91)	1.00 (0.44–2.29)
>30	20/17428	0.42 (0.26–0.68)	0.54 (0.34–0.86)	0.65 (0.38–1.10)	0.30 (0.09–0.95)
P_{trend}[d]		0.003	0.02	0.1	0.045
Years since quitting (past smokers)					
Never	151/73321	1.00	1.00	1.00	1.00
≤10	8/11892	0.33 (0.16–0.67)	0.36 (0.17–0.78)	0.42 (0.17–1.03)	0.29 (0.07–1.17)
11–20	17/11892	0.68 (0.41–1.13)	0.82 (0.49–1.37)	0.81 (0.41–1.57)	0.86 (0.39–1.88)
21–30	21/14209	0.66 (0.42–1.05)	0.75 (0.47–1.18)	0.74 (0.41–1.34)	0.76 (0.37–1.58)
>30	28/10045	1.01 (0.66–1.50)	1.01 (0.67–1.53)	1.34 (0.69–1.86)	0.76 (0.33–1.74)
P_{trend}[d]		0.01	0.044	0.049	0.5

[a]Models were adjusted for age and sex.

[b]Models were adjusted for age, sex, natural skin color, tanning tendency, number of moles at age 21, past history of skin cancer surgically removed, past history of skin cancer destructively removed, history of sunburn as a child, cumulative sun exposure, and family history of melanoma.

[c]"Never smoker" was the reference category for all analyses.

[d]P_{trend} values do not include reference group (*P*-value for the exact Cochran–Armitage trend test).

in this cohort (16), we cannot completely exclude the possibility of residual confounding due to measurement error. For example, our repeatability study showed a moderate-to-high agreement for measures of phenotypic characteristics whereas measures of sun exposure had lower levels of agreement.

The key question is whether the observed inverse association reflects a "protective effect" of smoking on development of melanoma, or whether there are alternative noncausal explanations. It is likely that never smokers have more medical surveillance and earlier detection of disease compared with smokers as a consequence of a generally healthier lifestyle (2). In our dataset, a greater proportion of never smokers than ever smokers self-reported that they had undergone a skin screening examination by a doctor in the 3 years prior to enrollment (75% vs. 66%, respectively). Thus, it is possible that increased opportunities for melanoma detection contributed to a higher incidence of melanoma amongst never smokers, thereby creating a spurious inverse association with smoking status (22). We have previously found evidence for such an effect for basal cell carcinomas in this cohort, but not for squamous cell carcinomas (2). Longer follow-up of the cohort would resolve this question, because invasive melanomas would eventually come to clinical attention, even among people with low health awareness.

If confounding and bias do not fully explain the inverse associations, then potential biological mechanisms ought to be considered for completeness. Nicotine, one of the constituents of tobacco smoke, has anti-inflammatory properties (23, 24) and nicotine administration via a transdermal delivery system suppresses the cutaneous responses to known inflammatory stimuli such as UV-B (25). Moreover, a recent Mendelian randomization study tested whether smoking-related genetic variants were associated with melanoma risk, and found inverse associations with variants located on chromosome 15q25.1 (26). Although this intriguing finding is outwardly supportive of the inverse associations we observed, that study suffered from limited sample size and multiple testing, and so cautious interpretation is required. Despite these speculations, the discordant associations we observed for current and former smoking run counter to any

Table 3. The association between smoking and invasive melanoma: simultaneous modeling of qualitative and quantitative smoking measures

Model		Overall HR[a] (95% CI)	Males HR[a] (95% CI)	Females HR[a] (95% CI)
A	Current smoker	1.06 (0.41–2.72)	1.82 (0.62–5.4)	0.26 (0.03–2.09)
	Intensity of smoking (per 10 cigarettes/day)[b]	0.81 (0.55–1.51)	1.41 (0.88–2.26)	0.40 (0.18–0.90)
	Duration of smoking (per 10 years)[b]	0.99 (0.61–1.63)	0.78 (0.47–1.32)	1.49 (0.40–5.50)
B	Former smoker	0.68 (0.50–0.93)	0.74 (0.50–1.09)	0.47 (0.24–0.94)
	Intensity of smoking (per 10 cigarettes/day)[b]	0.74 (0.56–0.98)	0.82 (0.60–1.10)	0.49 (0.27–0.92)
	Duration of smoking (per 10 years)[b]	0.88 (0.73–1.06)	0.81 (0.64–1.01)	1.06 (0.75–1.49)
C	Former smoker	0.65 (0.47–0.90)	0.72 (0.48–1.08)	0.46 (0.23–0.90)
	Intensity of smoking (per 10 cigarettes/day)[b]	0.75 (0.56–0.98)	0.80 (0.59–1.09)	0.53 (0.29–0.97)
	Time since quitting smoking (per 10 years)[b]	1.22 (1.01–1.48)	1.23 (0.99–1.54)	1.15 (0.81–1.65)
D	Former smoker	0.68 (0.49–0.93)	0.70 (0.47–1.05)	0.71 (0.43–1.28)
	Duration of smoking (per 10 years)[b]	0.99 (0.68–1.43)	0.78 (0.49–1.26)	1.40 (0.75–2.56)
	Time since quitting smoking (per 10 years)[b]	1.29 (0.89–1.85)	1.06 (0.66–1.68)	1.66 (0.90–3.10)
E	Former smoker	0.67 (0.49–0.93)	0.73 (0.48–1.08)	0.53 (0.26–1.02)
	Pack-years of smoking	0.90 (0.74–1.11)	0.92 (0.73–1.15)	0.77 (0.52–1.13)
	Time since quitting smoking (per 10 years)[b]	1.18 (0.91–1.51)	1.18 (0.87–1.59)	1.08 (0.68–1.69)

[a]Models were adjusted for age, sex, natural skin color, tanning tendency, number of moles at age 21, past history of skin cancer surgically removed, past history of skin cancer destructively removed, history of sunburn as a child, cumulative sun exposure, and family history of melanoma.
[b]Continuous measures were centred and estimates of HR were obtained using separate models that each included an indicator of ever/never smoking.

biological mechanism of which we can conceive and suggest that the observed associations are explained by other factors.

Our study has some limitations. Follow-up duration was short, and the number of melanoma cases was limited, so some analyses were constrained by sample size, particularly in current smokers who represented a small proportion of the overall study population. For example, we could not stratify our analysis by history of skin checks or melanoma thickness. Although QSkin shares several design features with previous studies, such as large sample size and complete follow-up through data linkage, the cohort is unique in having been purpose-designed to investigate skin cancer and having sampled participants from the general population. At baseline, we collected comprehensive data on key phenotypic and sun exposure variables, allowing greater control of potential confounding than earlier prospective investigations. Finally, we used a variety of statistical techniques to explore in more detail possibly complex associations between smoking and melanoma (i.e., modeling simultaneously several dimensions of smoking) and excluding possible bias from competing risks of death. These new data therefore extend the insights gained from previous studies, and resolve some (but not all) of the uncertainties in this association.

In summary, we found no evidence that cigarette-smoking increases the risk of cutaneous melanoma. The inconsistent findings relating to current and former smokers, and the mixed evidence regarding dose–response relationships, make the interpretation of these results difficult and argues against biological effects. We infer that the observed lower risk of melanoma associated with smoking is probably due to some residual confounding as well as some surveillance bias among never-smokers. However, a possible biological effect cannot be completely ruled out. Even if melanoma risks were confirmed to be lower among smokers however, there would be no justification in advocating smoking on "preventive" grounds given the well-documented adverse health effects.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033–4.
2. Dusingize JC, Olsen CM, Pandeya NP, Subramaniam P, Thompson BS, Neale RE, et al. Cigarette smoking and the risks of basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol 2017;137:1700–8.
3. Song F, Qureshi AA, Gao X, Li T, Han J. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol 2012;41:1694–705.
4. Li Z, Wang Z, Yu Y, Zhang H, Chen L. Smoking is inversely related to cutaneous malignant melanoma: results of a meta-analysis. Br J Dermatol 2015;173:1540–3.

5. Blakely T, Barendregt JJ, Foster RH, Hill S, Atkinson J, Sarfati D, et al. The association of active smoking with multiple cancers: national census-cancer registry cohorts with quantitative bias analysis. Cancer Causes Control 2013;24:1243–55.
6. Odenbro A, Gillgren P, Bellocco R, Boffetta P, Hakansson N, Adami J. The risk for cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma in relation to tobacco use and body mass index. Br J Dermatol 2007;156:99–105.
7. Freedman DM, Sigurdson A, Doody MM, Rao RS, Linet MS. Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. Cancer Causes Control 2003;14:847–57.
8. DeLancey JO, Hannan LM, Gapstur SM, Thun MJ. Cigarette smoking and the risk of incident and fatal melanoma in a large prospective cohort study. Cancer Causes Control 2011;22:937–42.
9. De Hertog SA,Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, et al. Relation between smoking and skin cancer. J Clin Oncol 2001;19:231–8.
10. Kessides MC, Wheless L, Hoffman-Bolton J, Clipp S, Alani RM, Alberg AJ. Cigarette smoking and malignant melanoma: a case-control study. J Am Acad Dermatol 2011;64:84–90.
11. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. Cancer Epidemiol Biomark Prev 2006;15:517–23.
12. Lubin JH, Caporaso N, Wichmann HE, Schaffrath-Rosario A, Alavanja MC. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. Epidemiology (Cambridge, Mass) 2007;18:639–48.
13. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;170:244–56.
14. Heckman CJ. Enhancing skin cancer screening through behavioral intervention. JAMA Dermatol 2014;150:363–5.
15. Olsen CM, Green AC, Neale RE, Webb PM, Cicero RA, Jackman LM, et al. Cohort profile: the QSkin Sun and Health Study. Int J Epidemiol 2012; 41:929–i.
16. Morze CJ, Olsen CM, Perry SL, Jackman LM, Ranieri BA, O'Brien SM, et al. Good test-retest reproducibility for an instrument to capture self-reported melanoma risk factors. J Clin Epidemiol 2012;65: 1329–36.
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Statist Assoc 1999;94:496–509.
18. Leffondre K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: a comparison of different approaches. Am J Epidemiol 2002;156:813–23.
19. Freedman DM, Sigurdson A, Doody MM, Mabuchi K, Linet MS. Risk of basal cell carcinoma in relation to alcohol intake and smoking. Cancer Epidemiol Biomark Prev 2003;12:1540–3.
20. Song F, Qureshi AA, Gao X, Li T, Han J. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol 2012;41: 1694–705.
21. Thompson CA, Zhang ZF, Arah OA. Competing risk bias to explain the inverse relationship between smoking and malignant melanoma. Eur J Epidemiol 2013;28:557–67.
22. Hiatt RA, Fireman B. The possible effect of increased surveillance on the incidence of malignant melanoma. Prev Med 1986;15: 652–60.
23. Ingram JR. Nicotine: does it have a role in the treatment of skin disease? Postgrad Med J 2009;85:196–201.
24. Mills CM. Cigarette smoking, cutaneous immunity, and inflammatory response. Clin Dermatol 1998;16:589–94.
25. Kalra R, Singh SP, Pena-Philippides JC, Langley RJ, Razani-Boroujerdi S, Sopori ML. Immunosuppressive and anti-inflammatory effects of nicotine administered by patch in an animal model. Clin Diagn Lab Immunol 2004;11:563–8.
26. Wu W, Liu H, Song F, Chen LS, Kraft P, Wei Q, et al. Associations between smoking behavior-related alleles and the risk of melanoma. Oncotarget 2016;7:47366–75.