See related commentary on pg 1614

Cigarette Smoking and the Risks of Basal Cell Carcinoma and Squamous Cell Carcinoma

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Sunlight is the principal environmental risk factor for keratinocyte cancers, but other carcinogens have also been implicated, including tobacco smoke. Findings have been conflicting, however. We investigated associations between cigarette smoking and incidence of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) in QSkin, a prospective study of skin cancer (N = 43,794). Smoking history was self-reported at baseline; newly diagnosed BCCs and SCCs were ascertained through data linkage and verified by histopathology reports. We restricted analyses to white participants who at baseline reported no past history of skin cancer excisions and no more than five destructively treated actinic skin lesions. We fitted Cox proportional hazards models, adjusted for known confounders. Compared with never smokers, current smokers had significantly lower risks of BCC (hazard ratio = 0.6; 95% confidence interval = 0.4–0.9) but significantly higher risks of SCC (hazard ratio = 2.3; 95% confidence interval = 1.5–3.6). Former smokers had similar risks for BCC and SCC as never smokers. Among smokers, we observed no dose-response trends with duration of smoking, intensity, or time since quitting. On further analysis, current smokers had fewer skin examinations and procedures than never smokers, suggesting greater opportunities for detection among never smokers. Strengths include large sample size, prospective design, and virtually complete follow-up; however, histologic details were missing for a proportion of excised tumors. In conclusion, current smokers had a lower incidence of BCC (possibly because of detection bias) but higher rates of SCC.

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INTRODUCTION

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), collectively named keratinocyte carcinomas (KCs), are the most common malignancies worldwide (Cakir et al., 2012). Although UVR exposure is established as the major causal factor for KCs, the role of smoking, which is the strongest modifiable risk factor for many human cancers (El Ghissassi et al., 2009), is not yet understood. New evidence continues to expand the list of tobacco-related cancers; however, the potential role of cigarette smoking in relation to cutaneous malignancies remains inconclusive, with previous epidemiological studies reporting both positive and negative associations.

Two meta-analyses reported pooled estimates of the association between smoking and the risk of KCs and drew different conclusions. The first reported that ever smokers of both sexes had slightly increased risks of both BCC and SCC compared with never smokers (Song et al., 2012). The second concluded that smoking increases the risk of SCC but not BCC (Leonardi-Bee et al., 2012). More recently, the findings from a 16-year prospective study of 1,621 adults residing in Nambour, Queensland, Australia were published, reporting a nonsignificant inverse association between current smoking and BCC compared with never smokers (Hughes et al., 2014) but no association with SCC (McBride et al., 2011).

Possible reasons for the inconsistencies between previous studies include using different approaches to analyze smoking exposure (ever vs. never, current vs. former vs. never), failure to account for various dimensions of smoking history (e.g., duration, intensity), inadequate control of potential confounding factors, and loss to follow-up in prospective studies. In addition, most studies have not explored other potential sources of bias, such as detection biases that appear to underlie BCC surveillance in high-incidence populations (Valery et al., 2004).

Given the uncertainty of these associations, we sought to investigate the relationship between cigarette smoking and risk of BCC and SCC using data from a large, population-based cohort study that captured detailed information at baseline on phenotype, sun exposure, and medical history,

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HR, hazard ratio; KC, keratinocyte carcinoma; SCC, squamous cell carcinoma

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in addition to other items necessary to explore potential detection biases.

RESULTS

Baseline demographic characteristics of the study cohort according to smoking status are presented in Table 1. Overall, 10% and 35% of the study cohort were current and ex-smokers, respectively; data for smoking status were missing for 61 people. Current smokers were younger (mean age = 53 years vs. 54 years, respectively), more likely to be men (46% vs. 37%, respectively), less likely to have private health insurance (39% vs. 73%, respectively) and less likely to hold a university degree (13% vs. 33%, respectively) than never smokers. Current smokers were also less likely than never smokers to report having undergone destructive treatments for actinic skin lesions or skin cancers ($P < 0.001$) and were less likely to have had their skin checked by a doctor before baseline.

During a median follow-up period of 3.0 years, 640 participants developed at least one histologically confirmed BCC, and 193 developed at least one histologically confirmed invasive SCC. In addition, there were 316 participants with a Medicare claim for at least one KC event for whom no confirmatory histopathological reports were obtained. BCCs occurred mainly on the head/neck (48%), with 35% occurring on the trunk and 17% on the limbs, whereas most SCCs occurred on the limbs (47%) and head/neck (42%), with 11% on the trunk. Compared with never smokers, current smokers at baseline had significantly lower risks of developing BCC (hazard ratio [HR] = 0.64, 95% confidence interval [CI] = 0.44−0.93); ex-smoking was not significantly associated (Table 2). We observed no significant linear trend in risk of BCC with increasing smoking intensity or duration (P trend = 0.06 and 0.11, respectively) among smokers. Because individuals with a past history of actinic skin damage have markedly higher risks of subsequent KC (Whiteman et al., 2016), which may modify any association between smoking and KC risk, we also performed analyses stratified by past history of treatment for actinic skin lesions (no lesions, n = 13,322 vs. one to five lesions, n = 5,506). Among those with no past history of destructive treatments for skin lesions, current smoking had a nonsignificant but inverse association with BCC compared with never smoking (HR = 0.85; 95% CI = 0.54−1.33). Among those with one to five skin lesions, however, the risks of BCC were significantly lower among current smokers compared with never smokers (HR = 0.43, 95% CI = 0.21−0.88). The interaction between smoking status and history of destructive treatments for skin lesions did not reach statistical significance, however.

We conducted further stratified analyses to evaluate other potential instances of effect modification (Figures 1 and 2). We found that the association between current smoking and BCC differed by body site, with lower risks observed for BCC occurring on the trunk and limbs compared with the head/neck (Figure 1). Stratification by self-reported history of skin checks by a doctor in the past 3 years showed a significant inverse association between current smoking and BCC in people who reported one or more skin checks but a null association in people who reported never having their skin checked (Table 3 and Figure 1). None of the interactions described above (i.e., by body site of BCC or history of skin checks by a doctor) reached statistical significance, however. We found no differences in risk of BCC by sex, age, skin color, tanning tendency, freckles at age 21 years, or having a skin biopsy during follow-up.

We found that current smokers at baseline had significantly higher SCC incidence compared with never smokers (HR = 2.30, 95% CI = 1.46−3.62) (Table 4), and the risks remained significantly elevated after adjusting for the independent effects of duration and intensity (see Supplementary Table S1 online). Unlike BCC, the risks of SCC associated with smoking varied only modestly according to self-reported history of destructive treatments for skin lesions. The association between current smoking and SCC varied slightly according to self-reported history of skin checks, and consistent with the pattern seen for BCC, risk of SCC was lower among people with a history of skin checks (Table 3 and Figure 2). Stratified analyses by body site showed a significantly increased risk of SCC on the limbs but not on the trunk or head/neck among current smokers (Figure 2). Again, the interaction terms did not reach statistical significance. Sensitivity analyses including intraepithelial carcinoma/keratoacanthoma as SCC cases did not result in any material difference to the associations we observed between smoking status and SCC (see Supplementary Table S2 online).

We found no evidence of dose-response effects for any of the continuous measures of smoking with respect to BCC or SCC once the qualitative effect of smoking was incorporated in the model (see Supplementary Table S1). Furthermore, using nonlinear terms of smoking measures did not improve the model fit (data not shown).

Finally, we conducted sensitivity analyses to test the possible effects of missing pathology data on the association between smoking and risks of BCC and SCC. The directions of association were unchanged, although the magnitude varied depending on whether we assigned all participants with missing pathology data as *BCC cases* (adjusted HR, current vs. never smoker = 0.84; 95% CI = 0.63−1.11) or *non-cases* (adjusted HR, current vs. never smoker = 0.64; 95% CI = 0.44−0.93), or else randomly assigned 75% of all participants missing pathology data as *BCC cases* (adjusted HR, current vs. never smoker = 0.81; 95% CI = 0.61−1.08) (see Supplementary Table S3 online). We performed similar sensitivity analysis for SCC; the positive associations between current smoking and SCC remained significant under each scenario (see Supplementary Table S3).

DISCUSSION

We have prospectively investigated the association between smoking and the risk of developing a first BCC or SCC in a large population-based cohort while taking account of the potential confounding influence of demographic and phenotypic characteristics and sun exposure history. Overall, we found that current smokers with no prior history of any excisions for skin cancer were significantly less likely than never smokers to be diagnosed with a new BCC during follow-up but were significantly more likely to be diagnosed with a new SCC. We found no significant associations between former smoking and BCC or SCC. Unlike other cancers, for which clear dose-response relationships with

Table 1. Baseline characteristics of 18,828 QSkin study participants, overall and stratified by smoking status[1]

	Smoking Status				
	Total (N = 18,828)	Never (n = 10,222)	Former (n = 6,675)	Current (n = 1,870)	Chi-Square *P*-Value
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Age in years at entry (mean, SD)	54.2 (8.2)	53.8 (8.2)	55.3 (8.2)	52.8 (7.6)	<0.001[2]
Age group in years					
40–49	6,535 (34.7)	3,771 (36.9)	1,965 (29.5)	772 (41.3)	<0.001
40–59	7,134 (37.9)	3,797 (37.2)	2,574 (38.6)	733 (39.2)	
60–69	5,159 (27.4)	2,654 (25.9)	2,126 (31.9)	365 (19.5)	
Sex					
Female	10,983 (58.3)	6,472 (63.3)	3,472 (52.1)	1,007 (53.6)	<0.001
Male	7,845 (41.7)	3,750 (36.7)	3,193 (47.9)	873 (46.4)	
Further education					
No school certificate	1,315 (7.5)	524 (5.4)	542 (8.8)	244 (14.5)	<0.001
School certificate	2,607 (14.8)	1,351 (13.9)	949 (15.4)	298 (17.6)	
Higher school	3,470 (19.7)	1,872 (19.3)	1,197 (19.4)	386 (22.9)	
Trade/certificate/diploma	5,434 (30.8)	2,743 (28.2)	2,133 (34.5)	541 (32.0)	
University degree	4,808 (27.3)	3,224 (33.2)	1,359 (22.9)	219 (12.9)	
Private health insurance					
No	6,442 (34.3)	2,798 (27.5)	2,474 (37.3)	1,141 (60.9)	<0.001
Yes	12,324 (65.7)	7,393 (72.5)	4,168 (62.7)	732 (39.1)	
Skin color					
Fair	9,981 (53.3)	5,584 (54.9)	3,445 (51.9)	923 (49.4)	<0.001
Medium	7,054 (37.7)	3,746 (36.9)	2,569 (38.7)	715 (38.3)	
Olive/dark	1,688 (9.0)	833 (8.2)	619 (9.3)	229 (12.3)	
Eye color					
Blue/grey	6,886 (37.0)	3,720 (36.8)	2,445 (37.2)	695 (37.4)	0.68
Green/hazel	7,137 (38.4)	3,932 (38.9)	2,480 (37.8)	706 (38.0)	
Brown/black	4,573 (24.6)	2,460 (24.3)	1,642 (24.98)	457 (24.6)	
Hair color					
Dark brown/black	8,372 (44.70)	4,603 (45.3)	2,952 (44.5)	789 (42.2)	0.01
Light brown	7,106 (37.9)	3,833 (37.7)	2,545 (38.4)	704 (37.7)	
Blonde	2,602 (13.9)	1,366 (13.4)	924 (13.9)	304 (16.3)	
Red/auburn	658 (3.5)	371 (3.6)	214 (3.2)	73 (3.9)	
Burning tendency					
No burns	2,066 (11.0)	967 (9.5)	777 (11.7)	313 (16.7)	<0.001
Burns a little	8,874 (47.4)	4,704 (46.2)	3,228 (48.7)	908 (48.5)	
Burns moderately	5,853 (31.2)	3,338 (32.8)	2,002 (30.2)	500 (26.7)	
Burns badly	1,947 (10.4)	1,171 (11.5)	621 (9.4)	150 (8.0)	
Tanning tendency					
No tan	702 (3.8)	420 (4.1)	210 (3.2)	70 (3.8)	<0.001
Tan lightly	3,205 (17.1)	1,963 (19.3)	937 (14.1)	300 (16.1)	
Tan moderately	9,755 (52.1)	5,379 (52.9)	3,477 (52.5)	870 (46.6)	
Tan deeply	5,066 (27.0)	2,411 (23.7)	2,005 (30.3)	626 (33.6)	
Freckles at age 21 years (face)					
None	9,981 (53.2)	5,169 (50.8)	3,732 (56.2)	1,041 (55.6)	<0.001
A few	5,726 (30.5)	3,274 (32.2)	1,889 (28.4)	544 (29.0)	
Some	2,320 (12.4)	1,325 (13.0)	786 (11.7)	217 (11.6)	
Many	720 (3.8)	404 (4.0)	244 (3.7)	71 (3.8)	
Sunburns as a child					
Never	4,178 (24.3)	2,311 (24.7)	1,427 (23.7)	428 (24.8)	<0.001
1–5	8,086 (47.1)	4,469 (47.7)	2,809 (46.6)	785 (45.6)	
6–10	2,761 (16.1)	1,517 (16.2)	982 (16.3)	254 (14.7)	
11+	2,155 (12.5)	1,073 (11.5)	815 (13.5)	256 (14.9)	
AKs/skin cancers destructively treated before baseline					
None	13,322 (62.7)	7,065 (61.0)	4,718 (62.3)	1,501 (74.2)	<0.001
1-5	5,506 (25.9)	3,157 (27.3)	1,947 (25.7)	379 (18.7)	
6 +	2,413 (11.4)	13,59 (11.7)	906 (12.0)	144 (7.1)	

Abbreviations: AK, actinic keratoses; SD, standard deviation.
[1]Numbers may not sum to total because of missing data.
[2]*P*-value for significant difference using Ryan-Einot-Gabriel-Welsch multiple range test.

Table 2. The association between different dimensions of smoking and basal cell carcinoma, stratified by self-reported history of destructive treatments for skin lesions before baseline[1]

	Total (N = 18,828)		No Destructive Treatments for Skin Lesions Before Baseline (n = 13,322)		One to Five Destructive Treatments for Skin Lesions Before Baseline (n = 5,506)	
Parameter	**Case/Person-Years**	**HR (95% CI)**	**Cases/Person-Years**	**HR (95% CI)**	**Cases/Person-Years**	**HR (95% CI)**
Smoking status[2]						
Never smoker	384/30,199	1.00	187/21,003	1.00	197/9,196	1.00
Ever smoker	255/25,259	0.81 (0.68–0.97)	142/18,447	0.87 (0.68–1.12)	113/6,813	0.79 (0.61–1.03)
Ex-smoker	217/19,684	0.85 (0.71–1.03)	112/14,005	0.88 (0.68–1.14)	105/5,680	0.86 (0.66–1.12)
Current smoker	38/5,575	0.64 (0.44–0.93)	30/4,442	0.85 (0.54–1.33)	8/1,133	0.43 (0.21–0.88)
P-value		<0.001		<0.001		0.075
Age in years when started smoking						
Never	384/30,199	1.00	187/21,003	1.00	197/9,196	1.00
<15	29/3,303	0.85 (0.56–1.26)	15/2,528	0.81 (0.46–1.41)	14/775	0.97 (0.54–1.76)
15–16	71/7,457	0.78 (0.58–1.03)	37/5,462	0.79 (0.53–1.17)	34/1,994	0.79 (0.53–1.21)
>16	151/14,268	0.83 (0.68–1.03)	87/10,269	0.93 (0.70–1.24)	64/3,999	0.77 (0.56–1.05)
P-trend		0.942		0.503		0.449
Duration of smoking in years						
Never	384/30,199	1.00	187/21,003	1.00	197/9,196	1.00
≤10	70/5,441	1.05 (0.79–1.38)	34/3,627	1.09 (0.73–1.62)	36/1,814	0.97 (0.66–1.43)
11–20	49/6,063	0.66 (0.47–0.91)	23/4,377	0.59 (0.37–0.95)	26/1,686	0.75 (0.48–1.18)
21–30	66/5,946	0.90 (0.67–1.22)	36/4,556	0.97 (0.65–1.44)	30/1,389	0.92 (0.58–1.45)
>30	66/7,514	0.71 (0.53–0.96)	46/5,650	0.90 (0.62–1.31)	20/1,864	0.54 (0.33–0.91)
P-trend		0.115		0.976		0.064
Intensity of smoking (cigarettes/day)						
Never	384/30,199	1.00	187/21,003	1.00	197/9196	1.00
≤10	90/7,903	0.98 (0.76–1.25)	45/5,661	1.01 (0.71–1.43)	45/2242	0.99 (0.69–1.41)
11–20	98/10,117	0.76 (0.59–0.98)	59/7,411	0.86 (0.61–1.20)	39/2,706	0.70 (0.47–1.02)
21–30	45/4,610	0.75 (0.52–1.06)	21/3,386	0.66 (0.39–1.10)	24/1,228	0.88 (0.54–1.43)
>30	19/2,098	0.59 (0.34–1.04)	15/1,629	0.93 (0.51–1.70)	4/470	0.13 (0.01–0.97)
P-trend		0.064		0.505		0.972
Pack-years of smoking						
Never	384/30,199	1.00	187/21,003	1.00	197/9,196	1.00
≤10	90/8,059	0.93 (0.72–1.19)	43/5,619	0.93 (0.64–1.32)	47/2,440	0.93 (0.65–1.32)
11–20	61/5,619	0.92 (0.69–1.24)	29/4,069	0.89 (0.58–1.35)	32/1,550	0.99 (0.66–1.49)
21–30	33/4,117	0.66 (0.44–0.98)	22/3,104	0.81 (0.49–1.34)	11/1,014	0.53 (0.27–1.04)
>30	64/6,692	0.70 (0.51–0.96)	43/5,103	0.87 (0.58–1.28)	21/1,589	0.56 (0.33–0.97)
P-trend		0.075		0.765		0.985
Years since quitting (past smokers)						
Never	384/30,199	1.00	187/21,003	1.00	197/9,196	1.00
≤10	47/5,297	0.82 (0.59–1.14)	26/4,081	0.80 (0.51–1.26)	21/1,215	0.95 (0.58–1.53)
11–20	56/5,387	0.83 (0.61–1.14)	33/3,946	1.01 (0.68–1.52)	23/1,441	0.66 (0.39–1.10)
21–30	65/5,546	0.88 (0.66–1.19)	27/3,856	0.74 (0.47–1.17)	38/1,690	1.04 (0.70–1.54)
>30	48/3,355	0.86 (0.61–1.23)	25/2,039	0.98 (0.60–1.61)	23/1,316	0.76 (0.46–1.25)
P-trend		0.546		0.709		0.958

Abbreviations: CI, confidence interval; HR, hazard ratio.

[1]Models were adjusted for age, sex, private health insurance, education status, natural skin color, tanning ability, number of freckles, history of sunburn as a child, and cumulative sun exposure. *Never smoker* was the reference category for all analyses. *P*-trend values do not include reference group (*P*-value for the exact Cochran-Armitage trend test).

[2]One person with basal cell carcinoma had missing smoking status.

increasing duration and intensity of smoking exposure have been observed (van Osch et al., 2016), we saw no trends with duration of smoking, intensity, or time since quitting in our cohort.

Our findings of lower risk of BCC among current smokers are similar to those of previous cohort studies that reported null or inverse associations (Freedman et al., 2003; Hughes et al., 2014; Song et al., 2012). Case-control studies have been heterogeneous and reported both positive and negative associations (Boyd et al., 2002; De Hertog et al., 2001; Marehbian et al., 2007; Rollison et al., 2012). It is unlikely that the associations reported here are due to confounding, because we controlled for sun exposure and phenotypic and other skin cancer risk factors, although some analyses suggested differences according to health-promoting behaviors. When we stratified by recent history of skin checks, we saw no effect of current smoking on BCC risk among those who never had their skin checked, but we saw a significantly

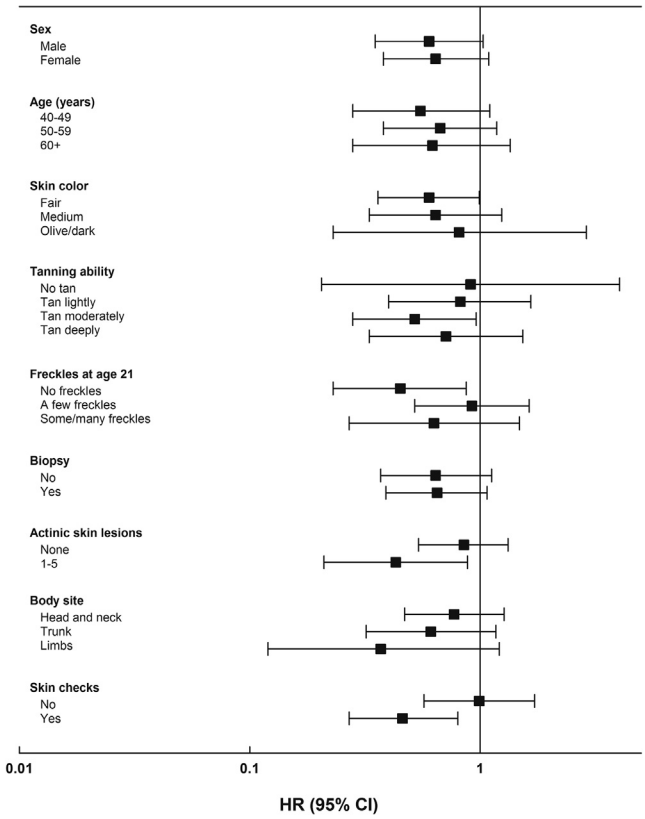

Figure 1. Results of stratified analyses on the association between current smoking at baseline and risk of basal cell carcinoma. The square represents the HR of the association between current smoking and risk of basal cell carcinoma, and the lines represent the 95% confidence intervals of the association. CI, confidence interval; HR, hazard ratio.

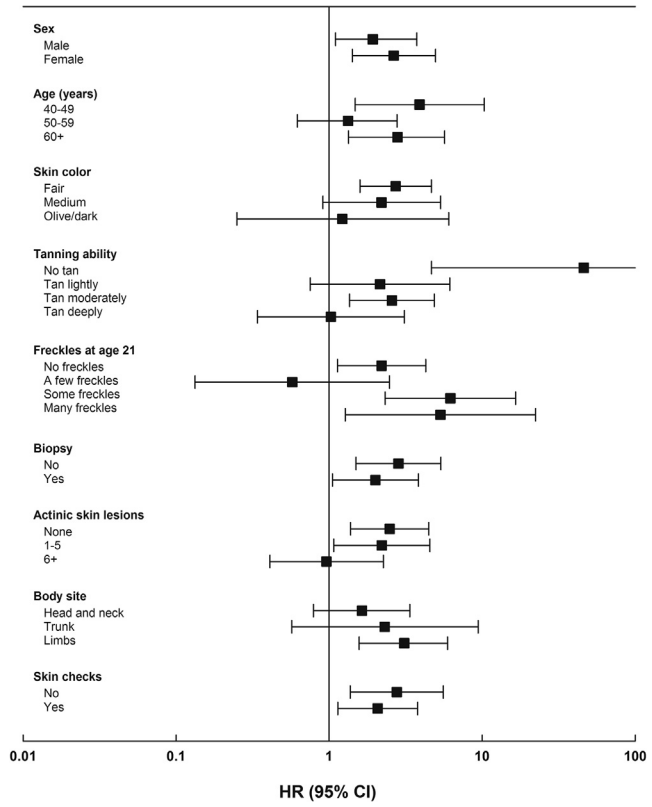

Figure 2. Results of stratified analyses on the association between current smoking at baseline and risk of squamous cell carcinoma. The square represents the HR of the association between current smoking and risk of basal cell carcinoma, and the lines represent the 95% confidence intervals of the association. The upper range of the confidence interval for some strata was too large and was truncated while trying to keep the same scale. CI, confidence interval; HR, hazard ratio.

protective effect of current smoking among those who had undergone a skin check. Our assessment is that the inverse association between current smoking and BCC is likely explained, at least in part, by detection bias, in which never smokers who undergo regular skin checks are more likely to be diagnosed with indolent BCCs than current smokers. This fits with the baseline data presented in Table 1. Never smokers were more highly educated, more likely to have private health insurance, and more likely to have skin checks than current smokers; thus they were more likely to have health-promoting behaviors. This is consistent with previous research, which has shown that incidence of BCC varies according to the methods of surveillance (Valery et al., 2004).

In our cohort we found a strongly positive significant association between current smoking and SCC, consistent with earlier reports from the female Nurses' Health Study (Song et al., 2012), male Health Professional Follow-Up Study (Song et al., 2012), and others (De Hertog et al., 2001; Grodstein et al., 1995). The Nambour cohort in Queensland (McBride et al., 2011) and the Swedish Construction Workers cohort (Odenbro et al., 2005) reported nonsignificant increased associations between smoking and SCC. The association may not have reached significance in the Nambour study because of the relatively small sample size, and the Swedish Construction Workers study did not control for potential confounding effects of sun exposure and phenotypic factors. Other possible sources of inconsistency across studies include using different approaches to define smoking status and failing to account for potential sources of bias (particularly detection bias). In addition, most previous studies did not analyze different dimensions of smoking, nor did they adjust for skin cancer risk factors at baseline.

We found little evidence of confounding, because the risk estimates remained stable after adjustment and stratification. Moreover, the observed association between smoking and SCC is not likely due to information bias, because follow-up was high and our sensitivity analyses, in which we variously included participants with missing pathology data as cases or non-cases, resulted in similar risk estimates. We cannot, however, exclude the possibility of detection bias, which may have resulted in an underestimate of the effect. The risks of SCC associated with smoking were modestly lower among those who had ever had their skin checked by a doctor (HR = 2.08) than among those with no prior history of skin checks (HR = 2.77). The difference between these estimates was not statistically significant, however. Thus, although there may be some detection effect for SCC, the magnitude appears less than that observed for BCC. This accords with the known differences between BCC and SCC detection, because it has

Table 3. Smoking status and risk of basal cell carcinoma and squamous cell carcinoma, stratified by self-reported history of skin checks by a doctor (yes/no) in the past 3 years[1]

	Skin Never Checked by a Doctor				Skin Ever Checked by a Doctor			
	BCC		SCC		BCC		SCC	
Parameter	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Smoking status among people with fewer than five destructive treatments for skin lesions before baseline								
Never smoker	101	1.00	27	1.00	283	1.00	59	1.00
Former smoker	64	0.83 (0.58–1.18)	27	1.05 (0.55–1.83)	153	0.88 (0.71–1.10)	46	1.07 (0.70–1.64)
Current smoker	19	0.99 (0.57–1.72)	16	2.77 (1.37–5.68)	19	0.49 (0.29–0.84)	18	2.08 (1.14–3.79)
Smoking status among people with no history of destructive treatments for skin lesions before baseline								
Never smoker	61	1.00	19	1.00	126	1.00	26	1.00
Former smoker	46	0.97 (0.63–1.50)	17	0.82 (0.39–1.74)	66	0.83 (0.59–1.26)	25	1.33 (0.71–2.47)
Current smoker	16	1.16 (0.62–2.20)	13	2.61 (1.15–5.91)	14	0.66 (0.34–1.27)	11	2.24 (0.95–5.28)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma.

[1]Models were adjusted for age, sex, private health insurance, education status, natural skin color, tanning ability, number of freckles, history of sunburn as a child, and cumulative sun exposure.

been shown previously that incidence of BCC (but not SCC) varies according to the methods of surveillance (Valery et al., 2004).

There are several possible biological mechanisms for how smoking may induce cutaneous malignancies, although none explains why the effect would be restricted to current smokers or be specific for SCC but not BCC. Although the toxic constituents of tobacco products have been reported to down-regulate gene expression of the Notch pathway (an important gene inhibiting the growth of KCs) (Nicolas et al., 2003; Panelos and Massi, 2009), why this would differentially influence SCC and BCC development is unclear. Nicotine, the main constituent of cigarette smoke, acts systemically to suppress the immune system (Sopori, 2002), which might conceivably be associated more strongly with SCC than BCC. These mechanistic explanations remain entirely speculative, however.

A limitation of our study is reliance on self-reported exposure information and smoking history, which is potentially subject to misclassification. Arguing against this is our previous demonstration of a very high degree of repeatability for smoking measures in this cohort (Morze et al., 2012). A further limitation was the reasonably high level of missing pathology data among participants who were known to have undergone treatment for a KC. We addressed this in a series of sensitivity analyses in which participants with missing pathology data were randomly assigned various states. In none of these sensitivity analyses were our conclusions markedly altered.

Our study has several strengths. The large sample size allowed us to restrict our analyses to participants with no prior history of treatment for any skin lesion. We captured comprehensive data at baseline on key phenotypic and exposure variables for skin cancer, which permitted careful control of confounders and reduced potential recall bias. Further strengths were the complete follow-up of skin cancer events in the cohort through data linkage and pathologic testing confirmation for most diagnoses. We were also able to conduct stratified analyses, including for health-promoting behaviors reported previously to be associated with smoking status (Wheless et al., 2009). Finally, our analyses enabled the assessment of associations with a range of smoking dimensions measures independent of the effects of ever smoking.

In conclusion, our data accord with the emerging consensus that BCC and SCC have very different associations with smoking. We found that current smoking is associated with lower risk of BCC, possibly as a result of detection bias due to lower rates of screening among smokers, although a lower risk of BCC in smokers cannot be ruled out. Because our findings for BCC may be influenced by screening practices that are specific to Queensland, our findings may not be generalizable to other populations. The significantly increased risk of SCC among current smokers we report may be causal, because the association is consistent with evidence from other cohort studies, and we have demonstrated temporality and specificity. However, because of the lack of association among ex-smokers, the lack of a dose-response relationship with intensity and duration of smoking, and no compelling biologic mechanism, we urge cautious interpretation of our findings.

METHODS

Study population

The QSkin Sun and Health Study (QSkin) comprises a cohort of 43,794 men and women aged 40 to 69 years sampled randomly from the Queensland population in 2011. Detailed information of participant recruitment has been described elsewhere (Olsen et al., 2012).

This study was approved by 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 completed a questionnaire about demographic items, general medical history, pigmentary characteristics,

Table 4. The association between different dimensions of smoking and squamous cell carcinoma, stratified by self-reported history of destructive treatments for skin lesions at baseline[1]

	Total (N = 18,828)		No Destructive Treatments for Skin Lesions Before Baseline (n = 13,322)		One to Five Destructive Treatments for Skin Lesions Before Baseline (n = 5,506)	
Parameter	**Cases/Person-Years**	**HR (95% CI)**	**Cases/Person-Years**	**HR (95% CI)**	**Cases/Person-Years**	**HR (95% CI)**
Smoking status						
Never smoker	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
Ever smoker	107/25,480	1.26 (0.92–1.73)	66/18,542	1.36 (0.88–2.09)	41/6,938	1.20 (0.75–1.92)
Ex-smoker	73/19,889	1.05 (0.74–1.48)	42/14,086	1.10 (0.68–1.77)	31/5,803	1.03 (0.62–1.71)
Current smoker	34/5,591	2.30 (1.46–3.62)	24/4,456	2.49 (1.38–4.47)	10/1,135	2.21 (1.07–4.56)
P-value		<0.001		<0.001		0.001
Age in years when started smoking						
Never	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
<15	12/3,322	0.98 (0.48–1.98)	5/2,538	0.55 (0.16–1.80)	7/784	1.70 (0.69–4.10)
15–16	36/7,505	1.42 (0.92–2.18)	23/5,471	1.70 (0.96–3.00)	13/2,033	1.17 (0.59–2.32)
>16	59/14,416	1.26 (0.87–1.18)	38/10,340	1.41 (0.86–2.30)	21/4,076	1.14 (0.66–1.97)
P-trend		0.664		0.240		0.438
Duration of smoking in years						
Never	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
≤10	16/5,518	1.12 (0.64–1.95)	8/3,659	1.25 (0.58–2.70)	8/1,858	0.96 (0.42–2.16)
11–20	17/6,109	0.87 (0.49–1.56)	10/4,394	0.94 (0.43–2.02)	7/1,715	0.79 (0.33–1.90)
21–30	23/6,015	1.24 (0.74–2.09)	15/4,585	1.37 (0.69–2.71)	8/1,430	1.18 (0.51–2.67)
>30	50/7,538	1.60 (1.07–2.40)	33/5,662	1.74 (1.01–2.98)	17/1,876	1.61 (0.88–2.97)
P-trend		0.117		0.239		0.219
Intensity of smoking in cigarettes/day						
Never	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
≤10	32/7,982	1.51 (0.98–2.32)	20/5,688	1.73 (0.97–3.09)	12/2,294	1.32 (0.69–2.54)
11–20	35/10,212	1.04 (0.67–1.60)	19/7,467	1.04 (0.57–1.89)	16/2,745	1.08 (0.58–2.04)
21–30	19/4,657	1.03 (0.57–1.84)	14/3,391	1.22 (0.58–2.56)	5/1,265	0.82 (0.32–2.13)
>30	16/2,103	1.32 (0.67–2.61)	10/1,636	1.25 (0.51–3.04)	6/467	1.76 (0.61–5.07)
P-trend		0.546		0.897		0.897
Pack-years of smoking						
Never	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
≤10	25/8,150	1.15 (0.71–1.85)	14/5,654	1.26 (0.65–2.42)	11/2,496	1.03 (0.51–2.08)
11–20	21/5,679	1.32 (0.80–2.18)	15/4,087	1.81 (0.97–3.35)	6/1,592	0.82 (0.34–1.95)
21–30	14/4,149	1.04 (0.55–1.97)	8/3,124	1.06 (0.44–2.53)	6/1,025	1.12 (0.43–2.87)
>30	41/6,731	1.24 (0.79–1.94)	26/5,123	1.16 (0.62–2.15)	15/1,609	1.51 (0.78–2.93)
P-trend		0.953		0.505		0.367
Years since quitting, ex-smokers						
Never	86/30,654	1.00	45/21,224	1.00	41/9,430	1.00
≤10	16/5,337	1.08 (0.59–1.96)	11/4,095	1.19 (0.54–2.58)	5/1,242	1.09 (0.42–2.81)
11-20	12/5,455	0.62 (0.31–1.25)	6/3,983	0.50 (0.17–1.41)	6/1,472	0.79 (0.31–2.05)
21-30	26/5,615	1.34 (0.83–2.17)	15/3,876	1.35 (0.70–2.62)	11/1,740	1.33 (0.65–2.69)
>30	18/3,382	0.96 (0.54–1.70)	10/2,048	1.16 (0.54–2.46)	8/1,333	0.77 (0.32–1.86)
P-trend		0.664		0.597		0.975

Abbreviations: CI, confidence interval; HR, hazard ratio.

[1]Models were adjusted for age, sex, private health insurance, education status, natural skin color, tanning ability, number of freckles, history of sunburn as a child, cumulative sun exposure. Never smoker was the reference category for all analyses. *P*-trend values do not include reference group (*P*-value for the exact Cochran-Armitage trend test).

history of sun exposure, sun protection behaviors, and history of skin cancer. Participants were asked, *About how many separate skin cancers (but not moles or warts) have you ever had cut off your skin?* and separately, *About how many sunspots or skin cancers have you ever had frozen or burnt off your skin?* They were also asked to report the number of times they had their skin deliberately checked by a doctor during the past 3 years. Items relating to phenotype had moderate to very high repeatability (kappa coefficients = 0.51–0.87); agreement was also very high for the questions on past surgical and nonsurgical treatments of skin cancer (weighted kappa = 0.79 and 0.83, respectively) (Morze et al., 2012). With respect to smoking, participants were asked whether they had ever

smoked tobacco daily for at least 6 months. Ever smokers were then asked questions about the average number of cigarettes smoked per day while smoking, their age at initiation, and the total number of years during which they had smoked. Former smokers were asked the age at which they had stopped smoking. Repeatability for smoking status (current, former, and never smoker) was almost perfect (weighted kappa = 0.97, 95% CI = 0.92−1.00), as were other smoking parameters (Morze et al., 2012).

Follow-up

Participants were followed up for the first occurrence of histologically confirmed invasive SCC or BCC through record linkage to health databases. We first linked the dataset to the Australian national health insurance scheme (Medicare) to identify participants who had received treatment for skin cancer, including biopsies and excisions. We then linked this list of treated participants to data held by the pathology laboratories servicing the Queensland population to obtain detailed histology reports for the skin lesions so identified. All pathology reports were reviewed and coded by qualified investigators.

BCC and SCC endpoints were recorded from the date of consent through to June 30, 2014. We excluded lip SCCs from our analyses (n = 51), because these lesions have a different etiology that cutaneous SCCs (Perea-Milla Lopez et al., 2003). People with common low-grade lesions such as keratoacanthoma, intraepidermal carcinoma, Bowen's disease, which individually have a very small risk of progressing to SCC (Weedon et al., 2010; Zalaudek et al., 2012), were included in the non-case group in our primary analyses; however, we also included them in the SCC case group in sensitivity analyses. We obtained mortality data for the cohort through linkage with the National Death Index that records the date and cause of all deaths occurring in Australia.

Statistical analysis

The aims of the analyses were to quantify the association between smoking and risk of first incident BCC or SCC. We restricted our analysis to white participants who met the following inclusion criteria: (i) no reported past history of excisions for skin cancer, (ii) no more than five sunspots or skin cancers (hereafter referred to as *actinic skin lesions*) treated by freezing or burning reported, and (iii) no record of melanoma in the Queensland Cancer Registry at time of recruitment. The final sample for analysis numbered 18,828 participants (see Supplementary Figure S1 online).

We used Cox proportional hazards regression analysis to examine the association between various measures of smoking and risk of first BCC or first invasive SCC. We calculated each person's follow-up duration as the time from the date of consent up until either the date of first histologically confirmed BCC or invasive SCC, or the date of death, or the end of follow-up (June 30, 2014), whichever occurred first. In our primary analysis, we excluded those participants who had a Medicare claim for at least one KC event but for whom no confirmatory histopathological reports were obtained (termed *missing pathology cases*). We performed three sets of sensitivity analyses by firstly assigning those with missing pathology data as non-cases, secondly assigning them as cases, and finally by randomly assigning 75% of participants with missing pathology data as BCC cases and 25% as SCC cases (based on the BCC-to-SCC ratio of 3:1 observed in our data).

We modeled BCC and SCC separately. We first analyzed the association between smoking status (never, ex-, and current smoker) and risk of incident BCC or incident SCC. Potential confounders included self-reported factors from the baseline questionnaire and other factors identified through record linkage to health databases. Using the DAGitty program (Textor et al., 2011), we constructed directed acyclic graphs to identify a minimum sufficient adjustment set of confounding factors to estimate the total effect of smoking on BCC or SCC. Our final models were adjusted for age, sex, private health insurance, education status, natural skin color, tanning ability, number of freckles, history of sunburn as a child, and cumulative sun exposure.

Because smoking is a multidimensional exposure, statistical models that examine only the association between smoking status and health outcome, and that fail to consider important contributors to total smoking exposure, have been deemed inefficient (Thomas, 1988). Therefore, we also investigated possible effects of smoking duration and intensity and time since quitting. We first used a standard approach in which never smokers were included as the reference category and continuous measures of smoking were categorized into ordinal categories at their approximate quartile cut-points. The tests for linear trend for ordinal categorical variables (restricted to ever smokers) were assessed by assigning a median value to each category and modeling as continuous variables in the model.

To further assess possible effects of smoking intensity, duration, and time since quitting independently of the effects of ever smoking, we fitted models that included a term for smoking status (current/never smoker) and a term for the centered (rescaled to the mean) continuous measures of either duration or intensity of smoking (Leffondre et al., 2002). This approach avoids multicollinearity. We also assessed potential nonlinear associations with dose by fitting generalized additive models with smoothed functions for the continuous measures of duration and intensity of smoking. We used SAS 9.4 software (SAS Institute, Cary, NC) for all statistical analyses except generalized additive models, which were conducted using R software.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.03.027.

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