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Tobacco Smoking and Cutaneous Squamous Cell Carcinoma: A 16 -Year Longitudinal Population-Based Study

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Abstract

Background—Although tobacco smoking is commonly cited as a risk factor for cutaneous squamous cell carcinoma (SCC), the evidence from previous clinical and case-control studies is conflicting. We therefore aimed to prospectively examine the role of tobacco smoking in the development of SCC of the skin in a population-based study.

Methods—Study participants were 1287 adults aged 25 to 75 years in 1992, randomly selected from the Nambour community, with no previous history of SCC. Standard skin pigment and sun-sensitivity profiles were obtained at baseline. Detailed prospective information on sun exposure, smoking and skin cancer occurrence (histologically-confirmed) was collected over a 16-year period, 1992-2007.

Results—Of 1287 participants, 43% were male, and average age was 48 years. A total of 188 first cutaneous SCCs were identified during the study period. After adjustment for other known risk factors, neither former nor current smokers were at raised risk of SCC: RR 1.1, 95%CI 0.8, 1.5 and RR 1.1, 95%CI 0.7, 1.5, respectively, compared with lifelong non-smokers, nor were there any dose-response relationships with amount smoked or duration of smoking and risk of SCC.

Conclusions—In this Australian follow-up study tobacco smoking did not increase the risk of SCC of the skin.

Impact—These prospective adjusted data provide strong evidence which suggests that cutaneous SCC should not be on the list of tobacco-related cancers.

Keywords

smoking; skin cancer; cutaneous squamous cell carcinoma; cohort study; population-based

Introduction

Tobacco smoking is widely held to be a risk factor for cutaneous SCC (1-4). The evidence to support this is not strong or consistent however. While several studies have reported moderately raised SCC risks in former and current smokers compared with non-smokers (1-3, 5-7), others, including a large Swedish population-based cohort study with 756 SCC cases among 337 311 Swedish men (8), have found no association between tobacco smoking

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and cutaneous SCC (4, 9). Sun exposure has been either not accounted for, or inadequately so, in the majority of previous studies (5, 6, 8, 10). In addition, several previous studies have been hospital-based rather than community-based (1, 4, 5) and therefore results have less generalisability, and may have been distorted by higher smoking prevalence and different habits of clinical controls compared with the general population (1, 4, 7). Of studies reporting a positive association between smoking and SCC, few found any relationship of SCC to the number of cigarettes smoked (2, 4).

Evaluation of the potential role of tobacco smoking in the development of cutaneous SCC in humans is necessary in view of both laboratory experiments on animal models (11) and epidemiological research linking smoking with other dermatological conditions, including poor wound healing, premature skin aging, acne, psoriasis, and hair loss (12). Tobacco smoke contains many mutagenic compounds including oxidants, radicals, and polycyclic aromatic hydrocarbons (13) and the cutaneous effects of smoking are thought to be mediated through alterations in the normal balance between cell proliferation, differentiation and apoptosis, or through impaired immune function, all factors that are important in carcinogenesis.

The aim of this study was to examine prospectively and comprehensively the association between smoking habit and the incidence of primary cutaneous SCC taking full account of other established risk factors, especially sun exposure.

Methods

Participants

The participants of this study were drawn from the Nambour Skin Cancer Study population whose establishment in 1986 has been described in detail elsewhere (14). Briefly, a random sample of 2095 residents of Nambour (latitude 26°S) aged between 20 and 69 had skin examinations conducted by dermatologists in 1986 and completed a detailed questionnaire regarding personal characteristics and skin phenotype (14). In 1992 they were invited to take part in a 5-year field trial of daily sunscreen application and beta-carotene supplementation for skin cancer prevention and 1621 participants agreed and were fully examined for skin cancer by dermatologists at trial baseline (15). To be eligible for inclusion in this analysis of tobacco smoking and SCC, participants must have had a full skin examination in 1992 and must have given written informed consent for their ongoing study participation.

Data collection

Participants provided information regarding their current and past smoking habits, including duration (total years of smoking) and intensity (average number of cigarettes smoked per day), at baseline in 1992 and regularly during the follow-up period: in 1998, 2000, 2002, 2003, and 2007. They also reported their occupation and leisure sun exposure (using the categories: mainly outdoors; mixed outdoor/indoor; mainly indoors), life-course sun exposure measures, and lifetime sunburns. Other personal information such as usage of anti-inflammatory drugs (NSAIDs) was also determined. The study outcome was first histologically-confirmed cutaneous SCC occurring after baseline skin examination in 1992 up to 31 December 2007. From 1992-2007, records of any skin cancer, including SCC, biopsied or removed were obtained from the relevant pathology laboratories with participants' consent.

Statistical Analyses

People with SCC of the lip and those with a history of skin SCC prior to 1992 were excluded from study. A participant's lifetime exposure with regard to smoking status and

smoking pack-years was estimated at end of follow-up as exposure measures at baseline did not always accurately reflect smoking during the subsequent study period of approximately 17 years. Thus for each unaffected participant in the cohort, cumulative amount of tobacco smoked was estimated in pack-years as the product of smoking duration in years (between age of starting, and age of permanent quitting or age at cessation of active participation/ end of study) and the average number of cigarettes smoked per day. For those with incident cutaneous SCC, smoking status at, and cumulative pack-years up to, the time of diagnosis were determined. Initial analyses examined the differences between lifelong non-smokers, former smokers and current smokers in terms of phenotypic and demographic factors, occupation, leisure, recent sun exposure (prior 2 years), cumulative ultraviolet (UV) exposure estimated from study questionnaires regarding lifecourse sun exposure, and sun-protective behaviours.

Multivariate Poisson regression was performed for all risk factors and for both former and current smokers including in relation to cumulative pack-years of smoking to establish the relative risk of developing a new SCC during the person-years accumulated from baseline to end of active follow-up or to the end of 2007, or to development of SCC for cases. After routine univariate analyses, potential confounding variables were entered simultaneously into a multivariate Poisson regression model. Age, sex, skin colour, NSAID use and sunscreen randomization within the Nambour Trial were entered into the model regardless of statistical significance. Backward elimination was used to collapse levels of variables where appropriate and where there was no significant decrease in log-likelihood. Thus optimal models were arrived at. Cox proportional hazards analyses were also conducted to examine time to first SCC among current smokers and former smokers compared with non-smokers. All analyses were carried out using SAS (Cary, NC, USA).

Results

Characteristics of study population

There were 1287 participants (557 males, 43%) with an average age of 48 years after excluding 52 participants, 3 (2 males, 1 female) who had been diagnosed with SCC of the mucocutaneous lip, and 49 (31 males, 63% and 18 females, 37%) with a history of skin SCC prior to 1992, and a further 334 participants who did not consent to active follow-up by questionnaire since complete smoking history was not obtained. There were 89 deaths and 298 withdrawals from active questionnaire completion during the study period, however all participants had provided smoking data prior to death or withdrawal from questionnaire completion. A total of 188 first cutaneous SCCs were identified during the study period (1992 to 2007).

Smoking status was defined as that at the time of diagnosis of SCC or end of consent to active follow-up. For only 81 participants (6% of total) was their status at this time different from their smoking status at baseline in 1992: 5 (0.3%) had taken up smoking, 59 (4.5%) had changed from current to former smokers, while 17 (1.3%) former smokers had resumed smoking. The characteristics of lifelong non-smokers (n=729) and former and current smokers (n=438 and 120, respectively) (Table 1) showed that a higher proportion of women (67%) than men (33%) were lifelong non-smokers ($p<0.001$) and current smokers were significantly younger on average than both non-smokers and former smokers (mean ages: non-smokers 62 years, former smokers 63 years and current smokers 57 years, $p< 0.05$). A significantly higher proportion of former smokers characterised their skin colour as olive (10% versus 7.5% of current smokers and 5% of non-smokers, $p=0.03$) and a significantly higher proportion of former and current smokers worked in mainly outdoor occupational activities and/or undertook mainly outdoor leisure activities compared with non-smokers (Table 1). High sun exposure was reported more frequently by former and current smokers

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compared with non-smokers ($p<0.001$) and the proportion of those with many lifetime sunburns was also higher for former and current smokers (Table 1).

Former versus current smokers

Former smokers (mean age at baseline: 50 years) were older than current smokers (mean age at baseline: 44 years) and although they smoked similar numbers of cigarettes each day (18 on average for former smokers and 19 for current), the average number of pack-years smoked by the 438 former smokers was lower at 17 pack-years (median 10) than the 120 current smokers who smoked an average of 35 pack-years (median 31) ($p<0.05$), reflecting current smokers' longer duration of smoking compared with former smokers (i.e. 38 years versus 20 years respectively, $p<0.05$).

Smoking and SCC

After adjustment for age, sex, skin color, average lifetime UV exposure, allocation to sunscreen application within the Nambour Trial and NSAID use, there was no significant relationship between former smoking (RR 1.1, 95%CI 0.8, 1.5) or current smoking and SCC (RR1.1, 95%CI 0.7, 1.5) (Table 2) when compared with lifelong non-smokers. Similarly, for former smokers, there was no relationship between SCC and time since smoking cessation (data not shown). For the Poisson regression analysis, the risk over total person-years was considered rather than the time to event as for Cox regression. The average person-years at risk in this study were 13.8 (median 15.9, minimum 0.1 and maximum 15.9 years).

A Cox proportional hazards analysis which accounted for time to SCC was also performed. Again there was no significant difference in time to SCC between non-smokers, former smokers and current smokers. The adjusted hazard ratio (HR) for former smokers was 1.0 (95%CI 0.7, 1.4) and for current smokers it was 1.5 (95%CI 0.9, 2.5).

Stratified analyses were performed to examine the relative risk of SCC according to levels of sun exposure for former and current smokers compared with non-smokers. The lack of effect of smoking on the risk of SCC was confirmed for groups who had reported low and moderate/high recent sun exposure (prior 2 years) (Table 2). In those randomised to discretionary sunscreen treatment (n=643) the adjusted relative risks were RR1.1 (95%CI 0.7, 1.6) for former smokers and RR 1.0 (95%CI 0.5, 2.0) for current smokers and in those randomised to daily sunscreen treatment (n=644): RR 1.2 (95%CI 0.8, 1.8) for former smokers and RR 1.4 (95%CI 0.6, 3.1) for current smokers.

Risk of SCC did not vary with cumulative pack-years smoked, duration of past smoking, or intensity of current smoking ($p=0.52$) (Table 3). As a final step, we also investigated those 71 participants who developed more than one SCC in the follow-up period, and again found no association between smoking, past or current, and subsequent or multiple SCCs.

Discussion

We have examined prospectively in a large population-based cohort the association between smoking habit and the incidence of primary cutaneous SCC taking full account of other established risk factors. None of the measures of exposure to tobacco smoking, namely smoking intensity, duration, or pack-years, were related to SCC and there were no dose-response trends. In particular risks of SCC were less than unity for those in the highest categories of pack-years smoked and intensity of smoking. Our finding that neither current nor past tobacco smoking increased the risk of SCC is in agreement with the findings of three cohort studies (8, 10, 16). Two other cohort studies that have examined the association reported moderately strong associations between tobacco smoking and skin SCC (2, 3) however. Findings from case-control studies have been inconsistent: two studies reported a

two to three fold increased risk of SCC associated with current smoking (1, 4), whereas others found no significant association (5, 6, 17). Most of the previous studies that have examined the association, however, did not measure important potential confounders including skin color or sun exposure history (18) , and this may account for the observed heterogeneity in study findings. For example we noted a correlation between smoking history and both recent sun exposure and frequent lifetime sunburns, and others have observed that outdoor workers have higher rates of smoking than indoor workers (19), demonstrating the importance of adequate adjustment for these potential confounding in analyses of the relationship between SCC and smoking history. We were also able to adjust for sun-protective behaviours which were related to smoking history in our study, since smokers were less likely to practice sun-protection. Current smoking has previously been shown to be associated with a disinclination for health-promoting behaviors (20), though previous studies have either not collected this information or did not consider it in their analyses.

Besides the prospective design and comprehensive risk factor data collected, other strengths of this study included very high case ascertainment and complete follow-up of 77% of the population (298/1287=23% lost to follow-up). Histologically-confirmed SCCs were ascertained through an extensive surveillance system comprising dermatological examinations, questionnaires, doctors' records and independent reports from pathology laboratories. We thus consider misclassification of participants due to misdiagnosis or missed diagnosis of skin cancer unlikely. Importantly, we excluded from our analyses mucocutaneous lip SCCs which have an etiology distinct from cutaneous SCC and are known to be associated with tobacco smoking (7, 21). Only one previous study explicitly excluded lip SCCs from their analyses (1); most studies either included lip SCCs or did not state whether they were included as cases.

Acknowledged limitations of these analyses are the reliance on recalled sun exposure measures that may have resulted in misclassification since the reproducibility of such data is modest (22). Smoking history is also subject to recall bias, although our confirmation of smoking status through follow-up and taking repeated histories over the decades of this study should have eliminated most misclassification amongst non-smokers, former and current smokers. Finally, despite the complete lack of dose-response relationships observed here, it is acknowledged that a very weak positive association between smoking and cutaneous SCC cannot be entirely ruled out based on this single prospective study.

Thus we consider the possible reasons for the lack of any association between smoking and SCC in this Australian study in contrast to the positive association found by others are firstly, that there may be no causal relationship, and the previous findings have reflected methodologic shortcomings such as inclusion of lip SCCs or incomplete adjustment for the clear confounding effect of sun exposure. Secondly the high levels of ambient sun exposure in Australia may override a weak causal effect of smoking if it exists, or thirdly, the prevalence of smoking in the study population may not have been high enough to detect a weak causal effect of smoking on SCC. On balance, however, we believe the null findings presented here and the lack of dose-response trends, are likely to represent the true situation.

In conclusion we found no evidence that tobacco smoking is associated with cutaneous SCC in this long-term population-based investigation based in Australia, after exclusion of mucocutaneous lip SCC from study and after careful assessment of and adjustment for potential confounding by sun exposure and sun protection behaviors.

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Table 1

Characteristics of study population according to smoking habits (n=1287)

	NON-SMOKERS N=729		FORMER SMOKERS N=438		CURRENT SMOKERS N=120		
	Count	**%**	**Count**	**%**	**Count**	**%**	**P value**
Sex							<0.001
Women	487	*67*	187	*26*	56	*8*	
Men	242	*43*	251	*45*	64	*11*	
Skin colour							0.03
Fair	414	*58*	240	*34*	57	*8*	
Medium	276	*57*	156	*32*	54	*11*	
Olive	39	*43*	42	*47*	9	*10*	
Propensity to sunburn (1992)							0.47
Always burn	153	*60*	84	*33*	19	*7*	
Burn then tan	505	*56*	309	*34*	84	*9*	
Only tan	71	*53*	45	*34*	17	*13*	
Occupational sun exposure (1992)							0.001
Mainly outdoors	106	*45*	103	*44*	27	*11*	
Indoors & outdoors	270	*57*	157	*33*	46	*10*	
Mainly indoors	352	*61*	178	*31*	47	*8*	
Leisure type (1992)							0.01
Mainly outdoors	275	*52*	208	*39*	49	*9*	
Indoors & outdoors	329	*59*	182	*32*	51	*9*	
Mainly indoors	123	*64*	48	*25*	20	*10*	
Recent sun exposure							
Hardly ever	291	*62*	139	*30*	36	*8*	<0.001
<50% time	375	*57*	224	*34*	62	*9*	
>50% time	62	*39*	75	*47*	22	*14*	
Lifetime sunburns							
≤ 1 sunburn	129	*65*	53	*27*	16	*8*	0.06

	NON-SMOKERS N=729		FORMER SMOKERS N=438		CURRENT SMOKERS N=120		P value
	Count	%	Count	%	Count	%	
2-5 sunburns	286	*57*	169	*34*	44	*9*	
>5 sunburns	314	*53*	216	*37*	60	*10*	

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Table 2

Smoking status and incident cutaneous SCC 1992 to 2007, stratified by level of recent sun exposure (n=1287)

	No SCC (n=1099)		≥1 SCC (n=188)		95% CI		
Variable	**Count**	**%**	**Count**	**%**	**RR**	**LL**	**UL**
Smoking status *							
Non-smoker	629	*86*	100	*14*	1.00		
Former smoker	366	*84*	72	*16*	1.17	0.87	1.57
Current smoker	104	*87*	16	*13*	1.15	0.68	1.94
Smoking status * *							
Non-smoker	629	*86*	100	*14*	1.00		
Former smoker	366	*84*	72	*16*	1.11	0.65	1.52
Current smoker	104	*87*	16	*13*	1.12	0.82	1.50
LOW SUN EXPOSURE†							
Non-smoker	226	*91*	25	*9*	1.00		
Former smoker	118	*85*	21	*15*	1.49	0.8	2.79
Current smoker	34	*94*	2	*6*	0.94	0.21	4.1
MODERATE AND HIGH RECENT SUN EXPOSURE†							
Non-smoker	363	*83*	74	*17*	1.00		
Former smoker	248	*83*	51	*17*	0.99	0.67	1.46
Current smoker	70	*83*	14	*17*	1.27	0.67	2.39

*Age-adjusted relative risk shown

**Adjusted for age, sex, skin colour, recent sun exposure (prior 2 years), sunscreen treatment in Trial and NSAID use.

†Adjusted for age, sex, skin colour, lifetime sun exposure, sunscreen treatment in Trial and NSAID use.

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Table 3

Smoking dose, duration of past smoking and intensity of current smoking in relation to risk of new SCC, 1992 to 2007 (n=1287)

	No SCC (n=1099)		≥1 SCC (n=188)		95% CI		
Variable	**Count**	**%**	**Count**	**%**	**RR**	**LL**	**UL**
Pack-years							
<1 pack-year	674	*86*	106	*14*	1.00		
1 to 20 pack-years	251	*84*	47	*16*	1.24	0.86	1.79
> 20 pack-years	174	*83*	35	*17*	0.97	0.61	1.55
Duration of past smoking							
0 years	631	*86*	100	*14*	1.00		
1 to 10 years	145	*84*	27	*16*	1.29	0.82	2.03
11 to 20 years	107	*88*	14	*12*	0.98	0.55	1.76
>20 years	207	*82*	47	*18*	1.11	0.73	1.67
Intensity of current smoking							
0 cigarettes per day	629	*86*	100	*14*	1.00		
1 to 15 cigarettes per day	207	*82*	46	*18*	1.42	0.98	2.07
15 to 30 cigarettes per day	206	*87*	31	*13*	0.91	0.58	1.45
>30 cigarettes per day	55	*83*	11	*17*	0.74	0.34	1.59

All estimates adjusted for age, sex, skin colour, lifetime sun exposure, sunscreen treatment in Trial and NSAID use.