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ORIGINAL PAPER

Case–control study of smoking and non-melanoma skin cancer

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Abstract
Objective To investigate the association between cigarette smoking and basal and squamous cell carcinomas (BCC and SCC) of the skin, a clinic-based case–control study was conducted in Tampa, FL.
Methods Patients with histologically confirmed BCC/SCC were recruited from a university dermatology clinic ($n = 215$ BCC, 165 SCC). Controls were comprised of individuals with no history of skin cancer who screened negative for skin cancer upon physical examination at the affiliated cancer screening or primary care clinics ($n = 315$). Information on smoking and other risk factors was obtained from self-administered questionnaires.
Results After adjustment for age, sex, and other skin cancer–risk factors, ever smoking was not associated with BCC (odds ratio (OR) = 1.26, 95% confidence interval (CI) = 0.83–1.92), but was statistically significantly associated with SCC (OR = 1.97, 95% CI = 1.19–3.26), with significant trends observed for SCC associated with increasing cigarettes per day ($p = 0.01$) and pack-years smoked ($p = 0.01$). Among men, smoking ≥20 pack-years was associated with non-significant increased risks of BCC (OR = 1.90, 95% CI = 0.88–4.12) and SCC (OR = 1.97, 95% CI = 0.84–4.66), whereas among women, no association was observed with BCC (OR = 0.98, 95% CI = 0.39–2.46) while a statistically significant three-fold risk was observed with SCC (OR = 3.00, 95% CI = 1.02–8.80).
Conclusion Cigarette smoking is more strongly associated with SCC than BCC, particularly among women.

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Introduction

Non-melanoma skin cancer (NMSC), comprised of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is the most frequently occurring cancer among Caucasians in the United States, with an annual incidence of greater than one million new cases [1]. The prevalence of NMSC is estimated to be five times higher than that of breast or prostate cancer, with 13 million white non-Hispanics and one in five seventy-year-olds having had at least one NMSC [2]. Ultraviolet (UV) radiation exposure is an established environmental risk factor for NMSC, although other factors may play a role in NMSC development.

BCC and SCC are often studied as one disease entity; however, risk factors for BCC and SCC may differ. For example, several studies have observed positive associations between cigarette smoking and SCC [3–8], while findings for the association between smoking and BCC have been less consistent [4, 6, 9–17]. Specifically, eight [3–8, 18, 19] of 12 [3–8, 11, 14, 18–21] previous studies reported positive associations between smoking and SCC, including two prospective studies [5, 6]. However, only three studies included measures of dose–response [4, 7, 8], two of which were conducted among men or women only [7, 8]. Previously reported associations between smoking and BCC have been mostly null, with only three [9, 15, 17] of twelve studies [4, 6, 9, 10, 12–18, 22] observing positive associations.

With the exception of an Australian study [22], previous epidemiologic studies investigating the association between cigarette smoking and NMSC have focused exclusively on either BCC or SCC, limiting the direct comparison of risk factors for the two cancers within the same population. At least two studies indicate that the risk of smoking-associated NMSC may be greater among women [15, 17], yet few studies have presented associations stratified by sex [12, 15, 17], while others were limited to men only [7, 16, 22]. Most studies did not incorporate measures of frequency or duration of smoking frequency, such as total years smoked, cigarettes per day and pack-years. The objective of the current study was to investigate the associations between cigarette smoking and both BCC and SCC, in men and women, and to assess whether there is a dose–response relationship between smoking and BCC/SCC.

Materials and methods

Study population

A clinic-based case–control study was conducted in Tampa, FL. Cases were defined as patients, aged 18 years and older, diagnosed with a histologically confirmed basal or squamous cell carcinoma between March 2007 and December 2008 and were recruited from the University of South Florida (USF) Dermatology Clinic. Control subjects were comprised of patients who underwent a skin cancer screening examination at the H. Lee Moffitt Lifetime Cancer Screening and Prevention Clinic (LCS) or the USF Family Medicine Clinic, located adjacent to the USF Dermatology Clinic. Skin cancer screening patients who screened negative for all forms of skin cancer and reported having no history of skin cancer were included as controls. A subset of patients with suspicious skin lesions detected on the screening examination were referred for a follow-up with a dermatologist, and those who were ultimately determined to be free of skin cancer were included as controls, whereas patients who were diagnosed with a histologically confirmed BCC or SCC as a result of the follow-up examination were included as cases. Those patients who never completed the follow-up examination or were unsuccessfully re-contacted by study staff on three separate occasions were considered lost to follow-up and excluded from the study. Pathology reports were obtained for all cases to verify diagnoses. All participants provided written informed consent, and all study procedures were approved by the institutional review board at the University of South Florida.

Of the 537 NMSC patients approached at the USF Dermatology Clinic, 424 (79%) agreed to participate. There were no statistically significant differences in age or gender between those NMSC patients who agreed to participate and those that refused. Of the 756 patients recruited through the LCS and USF Family Medicine Clinic, 432 (57%) agreed to participate, of whom 281 (65%) screened negative for skin cancer and were included in the study as controls. Of the 151 (35%) who were referred for a follow-up examination with a dermatologist, 95 (63%) were successfully re-contacted and had completed the follow-up examination, 77 of whom were determined not to have skin cancer and were included in the study as controls. The 18 who were determined to have skin cancer based on the follow-up examination included six SCC cases, nine BCC cases, and three cases of melanoma or NMSC not otherwise specified, the latter three of whom were excluded from the study. There were no statistically significant differences in age or gender between those that completed screening follow-up and those that did not. The current analysis was restricted to White participants with complete

information on smoking, resulting in a final sample size of 383 NMSC cases (215 BCC, 165 SCC and 3 Basosquam) and 316 controls.

Exposure assessment

Self-administered questionnaires were used to obtain information on demographics and other skin cancer risk factors including eye, hair, and skin color, alcohol intake, history of blistering sunburn, occupational sun exposure, and tanning ability. Detailed information was also collected on cigarette smoke exposures. Participants were asked whether they had smoked at least 100 cigarettes in their entire lifetime, and those that responded "yes" were considered to be ever smokers. These individuals were then asked their age at smoking initiation, the total number of years smoked (not including any periods of time during which they stopped smoking), and the average number of cigarettes smoked per day, the latter two measures of which were multiplied together to derive total pack-years of cigarette smoking. Smoking status was available for all study participants, whereas information on the other smoking variables was missing for some participants. Information on time since quitting smoking was not available from the study questionnaire.

Statistical methods

Demographic and skin cancer risk factors were compared between NMSC cases and controls using the Chi-square test. Associations between cigarette smoking and NMSC were estimated by odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression. Those demographic and skin cancer factors associated with a NMSC at a significance level of $p < 0.05$ were included as covariates in the logistic regression models: age, sex, education, history of blistering sunburn, job in the sun for at least three months, eye and hair color, alcohol consumption, skin reaction to first sun exposure and skin reaction to repeated sun exposure. Age at smoking initiation was categorized as $\leq$15 and >15 years, and the number of cigarettes smoked per day, number of years smoked, and number of pack-years smoked were categorized as <10, 10–19, and $\geq$20, with never smokers defined as the reference group for all categories of smoking. Tests for trend in risk of NMSC associated with increasing number of total years smoked, cigarettes smoked per day and total pack-years smoked were calculated by assigning ordinal values to each level of the smoking exposure. Analyses were conducted for NMSC overall (including BCC, SCC, and three Basosquam cases) and stratified by type of NMSC (BCC and SCC) and sex.

Associations between smoking-related factors and NMSC were stratified by age and sex to investigate potential effect modification. Statistical significance of the interactions was determined by including interaction terms in the logistic regression models. To investigate the independent effects of age at smoking initiation, cigarettes smoked per day, and years smoked, a separate analysis was conducted, adjusting each factor for one of the others. Specifically, age at smoking initiation was adjusted for pack-years of smoking, cigarettes per day was adjusted for years of smoking, and years of smoking was adjusted for cigarettes per day. To account for collinearity between these factors, analyses were conducted using centered values [23]. Results were considered statistically significant at p-values <0.05. All analyses were performed using the SAS version 9.1.3.

Results

Demographic characteristics and skin cancer risk factors are presented for cases and controls in Table 1. NMSC cases were mostly male (62.1%) and tended to be older (mean age = 63.6 years) and less educated as compared to controls. With the exception of color of untanned skin, all of the skin cancer risk factors examined were statistically significantly associated with NMSC, including a history of blistering sunburn, having ever had a job in the sun for at least 3 months, light eye and hair color, alcohol consumption in the past year, propensity to sunburn, and inability to tan. All factors were associated with BCC and SCC separately and achieved statistical significance with the exceptions of history of blistering sunburn and alcohol consumption in association with BCC, and color of untanned skin in association with both BCC and SCC (Table 1).

Associations between cigarette smoking and NMSC are presented in Table 2. NMSC was statistically significantly associated with multiple measures of cigarette smoking, including ever smoking, smoking $\geq$20 cigarettes per day (OR = 1.63, 95% CI = 1.03–2.57; $p_{trend} = 0.02$), smoking for $\geq$20 years (OR = 1.97, 95% CI = 1.24–3.12; $p_{trend} = 0.01$), and smoking $\geq$20 pack-years (OR = 1.65, 95% CI = 1.01–2.58; $p_{trend} = 0.03$). Similar patterns of association were observed for BCC and SCC separately, although the magnitudes of the associations were greater for SCC, with statistically significant dose–response relationships observed for increasing cigarettes per day ($p_{trend} = 0.01$), total years smoked ($p_{trend} = 0.003$), and pack-years ($p_{trend} = 0.01$) only for this type of NMSC. Ever smoking was associated with a statistically significant increased risk of SCC (OR = 1.97; 95% CI = 1.19–3.26), as was smoking $\geq$20 cigarettes per day (OR = 1.99;

Table 1 Demographic and skin cancer–risk factors among white non-melanoma skin cancer cases and controls

Characteristic	Controls ($n = 315$)	NMSC[a] ($n = 383$)		BCC[a] ($n = 215$)		SCC[a] ($n = 165$)	
	n (%)	*n* (%)	p[b]	*n* (%)	p[b]	*n* (%)	p[b]
Age (years)			<0.0001		<0.0001		<0.0001
18–39	29 (9.2)	10 (2.6)		7 (3.3)		3 (1.8)	
40–49	55 (17.5)	34 (8.9)		24 (11.2)		10 (6.1)	
50–59	109 (34.6)	76 (19.8)		46 (21.4)		30 (18.2)	
60–69	88 (27.9)	131 (34.2)		63 (29.3)		66 (40.0)	
70–80	34 (10.8)	132 (34.5)		75 (34.9)		56 (33.9)	
Sex			<0.0001		<0.0001		<0.0001
Men	117 (37.1)	238 (62.1)		130 (60.5)		105 (63.6)	
Women	198 (62.9)	145 (37.9)		85 (39.5)		60 (36.4)	
Education			<0.0001		0.0004		0.001
≤12 years	32 (10.3)	82 (21.6)		46 (21.6)		35 (21.3)	
>12 years	279 (89.7)	298 (78.4)		167 (78.5)		129 (78.7)	
History of a blistering sunburn			0.02		0.08		0.04
Yes	211 (67.6)	289 (75.9)		160 (74.8)		126 (76.8)	
No	101 (32.4)	92 (24.2)		54 (25.2)		38 (23.2	
Job in the sun for ≥3 months			<0.0001		<0.0001		<0.0001
Yes	85 (27.3)	175 (46.2)		95 (44.4)		77 (47.5)	
No	226 (72.7)	204 (53.8)		119 (55.6)		85 (52.5)	
Eye color			0.001		0.008		0.01
Blue	93 (29.9)	156 (41.4)		86 (40.4)		69 (42.9)	
Green	50 (16.1)	49 (13.0)		24 (11.3)		25 (15.5)	
Hazel	52 (16.7)	76 (20.2)		47 (22.1)		29 (18.0)	
Light brown	36 (11.6)	39 (10.3)		22 (10.3)		16 (9.9)	
Dark brown	80 (25.7)	57 (15.1)		34 (16.0)		22 (13.7)	
Hair color			0.01		0.05		0.02
Black/brown	244 (77.7)	261 (68.9)		150 (70.1)		110 (67.9)	
Blonde/red	70 (22.3)	118 (31.1)		64 (29.9)		52 (32.1)	
Color of untanned skin			0.37		0.40		0.58
White	298 (95.2)	366 (96.6)		206 (96.7)		157 (96.3)	
Brown	15 (4.8)	13 (3.4)		7 (3.3)		6 (3.7)	
Alcohol consumption			0.02		0.11		0.02
≥1 drink in past year	273 (87.2)	304 (80.4)		175 (82.2)		128 (79.0)	
No drinks in past year	40 (12.8)	74 (19.6)		38 (17.8)		34 (21.0)	
Skin reaction to season's 1st sun exposure			<0.0001		<0.0001		0.003
Sunburn with or without blisters	124 (39.9)	223 (58.4)		127 (60.2)		89 (55.3)	
Mild sunburn turns to a tan	144 (46.2)	114 (30.4)		64 (30.3)		50 (31.1)	
Tan or no change in skin color	44 (14.1)	43 (11.5)		20 (9.5)		22 (13.7)	
Skin reaction to repeated sun exposure			0.0001		0.02		<0.0001
It is unable to tan	22 (7.1)	43 (11.5)		15 (7.2)		26 (16.2)	
It can tan if you work at it	102 (32.9)	166 (44.5)		93 (44.5)		73 (45.3)	
It tans easily	186 (60.0)	164 (44.0)		101 (48.3)		62 (38.5)	

[a] *NMSC* non-melanoma skin cancer, *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma

[b] p-values obtained from Chi-square tests

95% CI = 1.07–3.68), having smoked for ≥20 years (OR = 2.55; 95% CI = 1.40–4.65) and ≥20 pack-years (OR = 2.18; 95% CI = 1.67–4.10) (Table 2). The association between smoking and SCC was greater for those who reported starting smoking after age 15 years (OR = 2.08, 95% CI = 1.21–3.56) than for those who

Table 2 Associations between cigarette smoking and non-melanoma skin cancer, Tampa FL, 2006–2008

Cigarette (cigs) smoking exposure	Controls ($n = 315$) n (%)	All non-melanoma skin cancer ($n = 383$)			Basal cell carcinoma ($n = 215$)			Squamous cell carcinoma ($n = 165$)	
		n (%)	OR (95% CI)[a]	OR (95% CI)[b]	n (%)	OR (95% CI)[a]	OR (95% CI)[b]	n (%)	(95% CI)[a]
Smoking status									
Never	161 (51.1)	132 (34.5)	1.00 (reference)	1.00 (reference)	81 (37.7)	1.00 (reference)	1.00 (reference)	51 (30.9)	1.00 (reference)
Ever	154 (48.9)	251 (65.5)	1.46 (1.05–2.03)	1.52 (1.05–2.20)	134 (62.3)	1.27 (0.87–1.86)	1.26 (0.83–1.92)	114 (69.1)	1.77 (1.15–2.73)
Age started smoking									
≤15 years	45 (14.4)	73 (19.3)	1.45 (0.91–2.32)	1.42 (0.85–2.37)	39 (18.4)	1.30 (0.76–2.21)	1.17 (0.65–2.12)	33 (20.1)	1.77 (0.97–3.23)
>15 years	107 (34.2)	174 (45.9)	1.46 (1.02–2.09)	1.57 (1.06–2.35)	92 (43.4)	1.25 (0.83–1.89)	1.30 (0.82–2.05)	80 (48.8)	1.79 (1.12–2.85)
Cigs per day									
<10	45 (14.6)	42 (11.4)	1.09 (0.66–1.83)	1.13 (0.65–1.97)	22 (10.7)	0.91 (0.50–1.67)	0.93 (0.48–1.79)	19 (12.0	1.34 (0.68–2.63)
10–19	39 (12.6)	64 (17.4)	1.52 (0.93–2.49)	1.75 (1.00–3.04)	35 (17.0)	1.30 (0.74–2.29)	1.33 (0.71–2.49)	29 (18.4)	1.91 (1.02–3.57)
≥20	64 (20.7)	129 (35.2)	1.60 (1.07–2.41)	1.63 (1.03–2.57)	68 (33.0)	1.42 (0.89–2.26)	1.43 (0.86–3.40)	59 (37.3)	1.89 (1.13–3.17)
			$p_{trend} = 0.01$	$p_{trend} = 0.02$		$p_{trend} = 0.11$	$p_{trend} = 0.14$		$p_{trend} = 0.01$
Years smoked									
<10	45 (14.6)	51 (13.6)	1.21 (0.74–1.98)	1.29 (0.75–2.22)	31 (14.8)	1.15 (0.66–2.01)	1.14 (0.62–2.09)	20 (12.4)	1.31 (0.68–2.54)
10–19	46 (14.9)	54 (14.4)	1.17 (0.72–1.91)	1.24 (0.73–2.14)	30 (14.4)	1.07 (0.61–1.87)	1.00 (0.53–1.88)	24 (14.8)	1.37 (0.73–2.60)
≥20	57 (18.5)	137 (36.6)	1.90 (1.26–2.87)	1.97 (1.24–3.12)	67 (32.1)	1.54 (0.96–2.47)	1.63 (0.96–2.76)	67 (41.4)	2.42 (1.45–4.03)
			$p_{trend} = 0.004$	$p_{trend} = 0.01$		$p_{trend} = 0.10$	$p_{trend} = 0.11$		$p_{trend} = 0.001$
Pack years									
<10	71 (22.1)	81 (22.1)	1.23 (0.81–1.87)	1.34 (0.85–2.14)	46 (22.3)	1.10 (0.68–1.79)	1.14 (0.67–1.93)	34 (21.5)	1.41 (0.81–2.46)
10–19	26 (12.0)	44 (12.0)	1.62 (0.92–2.87)	1.75 (0.93–3.14)	25 (12.1)	1.43 (0.75–2.73)	1.36 (0.66–2.81)	19 (12.0)	1.94 (0.94–3.99)
≥20	49 (30.0)	110 (30.0)	1.68 (1.09–2.60)	1.65 (1.01–2.58)	54 (26.2)	1.39 (0.84–2.30)	1.41 (0.82–2.47)	54 (34.2)	2.13 (1.24–3.65)
			$p_{trend} = 0.01$	$p_{trend} = 0.03$		$p_{trend} = 0.15$	$p_{trend} = 0.19$		$p_{trend} = 0.004$

[a] Adjusted for age and sex

[b] Adjusted for age, sex, education, blistering sunburn, job in sun, eye color, hair color, alcohol consumption, skin reaction to first sun exposure, and skin reaction to repeated sun exposure

Table 3 Associations between cigarette smoking and non-melanoma skin cancer among men

Cigarette (cigs) smoking exposure	Controls ($n = 117$)	All non-melanoma skin cancer ($n = 238$)		Basal cell carcinoma		Squamous cell carcinoma ($n = 105$)	
	n (%)	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]
Smoking status							
Never	55 (47.0)	66 (27.7)	1.00 (reference)	36 (27.7)	1.00 (reference)	30 (28.6)	1.00 (reference)
Ever	62 (53.0)	172 (72.3)	1.85 (1.06–3.23)	94 (72.3)	1.73 (0.91–3.29)	75 (71.4)	1.76 (0.85–3.64)
Age started smoking							
≤15 years	17 (14.7)	57 (24.2)	2.36 (1.10–5.08)	30 (23.4)	2.03 (0.86–4.83)	26 (24.8)	2.25 (0.85–5.99)
>15 years	44 (37.9)	113 (47.9)	1.72 (0.94–3.13)	62 (48.4)	1.65 (0.83–3.29)	49 (46.7)	1.68 (0.78–3.62)
Cigs per day							
<10	12 (10.4)	20 (8.9)	1.35 (0.53–3.46)	12 (9.7)	1.31 (0.44–3.84)	7 (7.1)	0.82 (0.23–2.95)
10–19	13 (11.3)	36 (15.9)	1.51 (0.65–3.47)	22 (17.7)	1.36 (0.53–3.48)	14 (14.1)	1.77 (0.62–5.04)
≥20	35 (30.4)	104 (46.0)	2.01 (1.06–3.80)	54 (43.6)	1.98 (0.96–4.10)	48 (48.5)	1.84 (0.80–4.24)
			$p_{trend} = 0.03$		$p_{trend} = 0.07$		$p_{trend} = 0.10$
Years smoked							
<10	18 (15.8)	33 (14.3)	1.38 (0.61–3.08)	23 (18.4)	1.56 (0.64–3.82)	10 (9.7)	1.08 (0.36–3.26)
10–19	14 (12.3)	33 (14.3)	1.53 (0.65–3.63)	17 (13.6)	1.07 (0.39–2.96)	16 (15.5)	1.66 (0.57–4.79)
≥20	27 (23.7)	99 (42.9)	2.24 (1.15–4.36)	49 (39.2)	2.16 (1.01–4.66)	47 (45.6)	2.13 (0.92–4.92)
			$p_{trend} = 0.02$		$p_{trend} = 0.07$		
Pack years							
<10	24 (21.1)	45 (19.9)	1.35 (0.66–2.79)	28 (22.6)	1.39 (0.61–3.16)	16 (16.2)	1.09 (0.42–2.83)
10–19	8 (7.0)	29 (12.8)	2.29 (0.85–6.17)	18 (14.5)	1.88 (0.64–5.56)	11 (11.1)	2.30 (0.62–8.48)
≥20	27 (23.7)	86 (38.1)	1.97 (1.00–3.88)	42 (33.9)	1.90 (0.88–4.12)	42 (42.4)	1.97 (0.84–4.66)
			$p_{trend} = 0.03$		$p_{trend} = 0.09$		$p_{trend} = 0.09$

[a] Adjusted for age, sex, education, blistering sunburn, job in sun, eye color, hair color, alcohol consumption, skin reaction to first sun exposure, and skin reaction to repeated sun exposure

started smoking at ages 15 years and younger (OR = 1.77, 95% CI = 0.89–3.51). In contrast, although the sample size was greater for BCC cases, none of the associations between smoking and BCC were statistically significant.

Stratified analyses did not indicate any differences in smoking-related NMSC risk by age (data not shown). Results stratified by sex are presented in Tables 3 and 4. Ever smoking at least 100 cigarettes was associated with NMSC among men (OR = 1.85; 95% CI = 1.06–3.23) with consistent dose–response trends observed for increasing numbers of cigarettes smoked per day ($p_{trend} = 0.03$), total years smoked ($p_{trend} = 0.02$), and pack-years smoked ($p_{trend} = 0.03$; Table 3). Similar magnitudes of associations with cigarette smoking were observed for BCC and SCC among men, although none were statistically significant with the one exception of the association between smoking for ≥20 years and BCC (OR = 2.16; 95% CI = 1.01–4.66). Among women, SCC cases were almost three times more likely to be ever smokers as controls (OR = 2.75, 95% CI = 1.26–6.03), whereas no association was observed with BCC (OR = 0.95, 95% CI = 0.52–1.72) (Table 4). Furthermore, statistically significant dose–response trends were observed for SCC in association with increasing numbers of cigarettes smoked per day ($p_{trend} = 0.01$), total years smoked ($p_{trend} = 0.01$), and pack-years of smoking ($p_{trend} = 0.02$). Similar trends were not observed for any measure of cigarette smoking exposure and BCC among women. None of the tests for interaction between smoking and sex were statistically significant for either BCC ($p_{interaction} = 0.17$ for ever smoking, 0.41 for age at smoking initiation, 0.27 for cigarettes per day, 0.27 for years smoked, 0.21 for pack-years) or SCC ($p_{interaction} = 0.56$ for ever smoking, 0.24 for age at smoking initiation, 0.59 for cigarettes per day, 0.73 for years smoked, and 0.69 for pack-years).

Table 5 presents the associations between smoking and NMSC with adjustment for other smoking factors. No statistically significant associations between age at smoking initiation and NMSC were observed after adjustment for pack-years of smoking. Similarly, associations between increasing numbers of cigarettes smoked per day and NMSC were not statistically significant after adjustment for years smoked. However, increasing numbers of years smoked was significantly associated with both NMSC and SCC after adjustment for cigarettes per day (Table 5).

Table 4 Associations between cigarette smoking and non–melanoma skin cancer among women

Cigarette (cigs) smoking	Controls ($n = 198$)	All non-melanoma skin cancer ($n = 145$)		Basal cell carcinoma ($n = 85$)		Squamous cell carcinoma ($n = 60$)	
	n (%)	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]
Smoking status							
Never	106 (53.5)	66 (45.5)	1.00 (reference)	45 (52.9)	1.00 (reference)	21 (35.0)	1.00 (reference)
Ever	92 (46.5)	79 (54.5)	1.38 (0.82–2.31)	40 (47.1)	0.95 (0.52–1.72)	39 (65.0)	2.75 (1.26–6.03)
Age started smoking							
≤15 years	28 (14.2)	16 (11.2)	0.70 (0.32–1.57)	9 (10.7)	0.45 (0.17–1.20)	7 (11.9)	1.25 (0.39–3.96)
>15 years	63 (32.0)	61 (42.7)	1.77 (1.00–3.11)	30 (35.7)	1.23 (0.64–2.37)	31 (52.5)	3.94 (1.65–9.40)
Cigs per day							
<10	33 (17.0)	22 (15.6)	1.11 (0.54–2.28)	10 (12.2)	0.67 (0.27–1.66)	12 (20.3)	2.13 (0.75–6.06)
10–19	26 (13.4)	28 (19.9)	2.11 (0.99–4.50)	13 (15.9)	1.22 (0.50–2.98)	15 (25.4)	5.88 (1.93–17.87)
≥20	29 (15.0)	25 (17.7)	1.31 (0.63–2.71)	14 (17.7)	1.02 (0.44–2.35)	11 (18.6)	2.70 (0.90–8.82)
			$p_{trend} = 0.18$		$p_{trend} = 0.88$		$p_{trend} = 0.01$
Years smoked							
<10	27 (13.9)	18 (12.6)	1.36 (0.62–2.97)	8 (9.5)	0.74 (0.28–1.95)	10 (17.0)	3.29 (1.10–9.83)
10–19	32 (16.4)	21 (14.7)	1.12 (0.54–2.33)	13 (15.5)	0.96 (0.42–2.21)	8 (13.6)	1.67 (0.52–5.41)
≥20	30 (15.4)	38 (26.6)	1.89 (0.94–3.78)	18 (21.4)	1.22 (0.54–7.56)	20 (33.9)	3.96 (1.49–10.54)
			$p_{trend} = 0.11$		$p_{trend} = 0.71$		$p_{trend} = 0.01$
Pack years							
<10	47 (24.4)	36 (25.5)	1.48 (0.79–2.78)	18 (22.0)	0.97 (0.46–2.04)	18 (30.5)	3.07 (1.20–7.89)
10–19	18 (9.3)	15 (10.6)	1.46 (0.60–3.58)	7 (8.5)	0.89 (0.31–2.58)	8 (13.6)	3.65 (0.98–13.66)
≥20	22 (11.4)	24 (17.0)	1.36 (0.62–2.98)	12 (14.6)	0.98 (0.39–2.46)	12 (20.3)	3.00 (1.02–8.80)
			$p_{trend} = 0.31$		$p_{trend} = 0.91$		$p_{trend} = 0.02$

[a] adjusted for age, sex, education, blistering sunburn, job in sun, eye color, hair color, alcohol consumption, skin reaction to first sun exposure, and skin reaction to repeated sun exposure

Discussion

In this clinic-based case–control study, cigarette smoking was associated with NMSC overall, with statistically significant trends observed for increasing numbers of cigarettes per day, total years and pack-years smoked in association with SCC. When cigarette smoking results were stratified by sex, associations with BCC and SCC were observed among men, with odds ratios approximately equal to 2.0 for the categories of greatest exposure. In contrast, there was no association with BCC among women, whereas a statistically significant 3-fold risk of SCC was observed. Our findings for men and women combined are consistent with previous studies that have observed positive associations between smoking and SCC [3, 4, 6, 18, 19], but conflict with those that observed no associations with SCC [11, 14, 20] and/or BCC [4, 6, 10, 12, 14, 18]. Of the four previous studies conducted among women only, two investigated SCC, both of which observed positive associations with SCC [5, 8], and two investigated BCC [9, 13], only one of which observed a positive association [9]. Of the four previous studies conducted among men only, one [7] of two [7, 21] studies observed a positive association with SCC, and neither of two studies observed an association with BCC [16, 22]. One possible reason for the inconsistency in findings across previous studies of men and women combined may be differences in the gender distribution across studies populations, given that we and others [17, 24] have observed differences in smoking-associated NMSC risk by gender.

Observations from the lung cancer literature provide possible explanations for the observed gender differences in smoking-associated cutaneous SCC. Female current smokers have a 30–60% increased risk of lung adenocarcinoma and 20–50% increased risk of lung squamous carcinomas compared with male current smokers [25]. Women have been shown to have more active CYP enzyme activity in the lung, responsible for metabolizing 70–80% of nicotine, possibly due to upregulation of CYP by estrogen [26]. Women have also been shown to have higher levels of DNA adducts and lower levels of DNA repair capacity (DRC) in the lung compared with men [27]. In addition, a case–control study of DRC and BCC demonstrated that the risk of BCC associated with low DRC among individuals with a history of six or more sunburns was four-fold higher among women than men [28].

Table 5 Associations between smoking variables and non-melanoma skin cancer while simultaneously modeling other smoking-related factors

Variable	Controls $n = 315$	NMSC $n = 383$		BCC $n = 215$		SCC $n = 165$	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Age started smoking[a]							
Never	161 (51.1)	132 (34.5)	1.00 (reference)	81 (37.7)	1.00 (reference)	51 (30.9)	1.00 (reference)
≤15 years	45 (14.4)	73 (19.3)	1.28 (0.74–2.22)	39 (18.4)	1.17 (0.63–2.19)	33 (20.1)	1.47 (0.73–2.97)
>15 years	107 (34.2)	174 (45.9)	1.36 (0.90–2.07)	92 (43.4)	1.17 (0.72–1.89)	80 (48.8)	1.64 (0.95–2.84)
Cigs per day[b]							
Never	161 (51.1)	132 (34.5)	1.00 (reference)	81 (37.7)	1.00 (reference)	51 (30.9)	1.00 (reference)
<10	45 (14.6)	42 (11.4)	1.03 (0.60–1.77)	22 (10.7)	0.94 (0.50–1.76)	19 (12.0)	1.13 (0.55–2.31)
10–19	39 (12.6)	64 (17.4)	1.31 (0.75–2.29)	35 (17.0)	1.29 (0.69–2.41)	29 (18.4)	1.32 (0.63–2.74)
≥20	64 (20.7)	129 (35.2)	1.33 (0.78–2.78)	68 (33.0)	1.45 (0.79–2.67)	59 (37.3)	1.21 (0.61–2.41)
			$p_{trend} = 0.47$		$p_{trend} = 0.38$		$p_{trend} = 0.81$
Years smoked[c]							
Never	161 (51.1)	132 (34.5)	1.00 (reference)	81 (37.7)	1.00 (reference)	51 (30.9)	1.00 (reference)
<10	45 (14.6)	51 (13.6)	1.17 (0.70–1.95)	31 (14.8)	1.08 (0.61–1.93)	20 (12.4)	1.32 (0.67–2.60)
10–19	46 (14.9)	54 (14.4)	1.09 (0.61–1.97)	30 (14.4)	0.93 (0.47–1.83)	24 (14.8)	1.39 (0.64–2.99)
≥20	57 (18.5)	137 (36.6)	1.68 (0.98–2.90)	67 (32.1)	1.25 (0.66–2.37)	67 (41.4)	2.36 (1.20–4.64)
			$p_{trend} = 0.05$		$p_{trend} = 0.54$		$p_{trend} = 0.004$

[a] OR and 95% CI adjusted for number of pack-years, age and sex

[b] OR and 95% CI adjusted for number of years smoked, age and sex

[c] OR and 95% CI adjusted for number of cigarettes smoked per day, age and sex

Although this study did not investigate SCC or exposure to smoking, it raises the possibility that differences in DRC between men and women may partially explain the observed sex differences in the associations between smoking and NMSC.

The current study had some limitations. When results were stratified by current smoking status, smoking 20 or more years was positively associated with both BCC and SCC (data not shown). However, the small number of current smokers limited stratified analyses. Another limitation of the study was the lack of information on time since quitting smoking among former smokers. Additionally, given the clinic-based design, neither the case nor the control groups were population-based samples. However, most cancer registries, including the state of Florida's, do not ascertain cases of cutaneous BCC and SCC, thus limiting access to population-based case ascertainment. The clinic-based design facilitates more efficient recruitment of large numbers of BCC/SCC patients and afforded the additional opportunity of verifying case and control status through physical examination by a nurse practitioner. In previously published case–control studies, the controls were rarely examined to rule out prevalent NMSC. In fact, 5% of the screening patients in the current study were subsequently diagnosed with skin cancer and would have been misclassified as controls without the conduct of a physical examination of the skin. Thus, physical examination of the controls was an important strength of the current study.

Despite the limitations of the current, there are several strengths that should be noted. The clinics included in the current study serve similar underlying populations, with the Moffitt Lifetime Cancer Screening (LCS) Clinic and the USF Dermatology and Family Medicine Clinics located within a mile of each other. Cases and controls had equal access to the clinics, with many of the LCS screening patients referred for follow-up completing their follow-up exams at the USF Dermatology Clinic, and an estimated 28% of the patients being treated for BCC/SCC in the USF Dermatology clinic having records in the USF Family Medicine Clinic. Furthermore, the study controls were representative of the general population with respect to smoking status, given that the proportion of ever-smoker controls in the current study (49%) is similar to that of the general population in Florida (45%) and Hillsborough County (44%), the county in which the study clinics are located [29].

An additional strength of the study includes the ability to adjust for a multitude of skin cancer risk factors is given that many previous studies of smoking and NMSC adjusted only for demographic factors. In addition to age and sex, all smoking analyses in the current study were adjusted for history of blistering sunburns, jobs in the sun, eye and hair

color, tanning ability and alcohol consumption. Furthermore, a sensitivity analysis of the current data restricted to study participants ages 40–69 demonstrated similar associations between smoking and NMSC as observed for the total study population (data not shown).

Information on cigarette smoking was obtained through self-administered questionnaires and may have been subject to recall bias. Although this bias cannot be ruled out, the positive association between smoking and SCC contrasted with the null association between smoking and BCC, both among women, argues against recall bias, given that most patients do not have preconceived notions that smoking is preferentially associated with one NMSC type. In addition, our case–control findings for SCC are consistent with those from two [5, 6] of four [5, 6, 11, 21] prospective studies in which exposure was assessed before the development of disease. Furthermore, clear dose–response relationships between smoking and SCC risk were observed in the current study, consistent with the only three previous studies that incorporated measures of dose–response [4, 7, 8].

In conclusion, cigarette smoking was associated with NMSC, with significantly increased risks associated with increasing dose (cigarettes per day), duration (number of years smoked), and pack-years smoked. Analyses conducted to tease apart the independent effects of duration and dose suggested that years smoked was more strongly associated with NMSC than cigarettes smoked per day. Among men, smoking was modestly associated with both BCC and SCC, whereas strong associations with SCC and no associations with BCC were observed among women. Additional studies are needed to further characterize these gender differences in smoking-associated NMSC, incorporating verification of case–control status through physical examination, detailed smoking exposure assessments, adjustment for known skin cancer–risk factors, and inclusion of possible biomarkers of susceptibility to tobacco-related carcinogens.

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References

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ (2004) Cancer statistics, 2004. CA Cancer J Clin 54:8–29
2. Stern RS (2010) Prevalence of a history of skin cancer in 2007: results of an incidence-based model. Arch Dermatol 146:279–282
3. Aubry F, MacGibbon B (1985) Risk factors of squamous cell carcinoma of the skin. A case-control study in the Montreal region. Cancer 55:907–911
4. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN (2001) Relation between smoking and skin cancer. J Clin Oncol 19:231–238
5. Grodstein F, Speizer FE, Hunter DJ (1995) A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. J Natl Cancer Inst 87:1061–1066
6. Karagas MR, Stukel TA, Greenberg ER, Baron JA, Mott LA, Stern RS (1992) Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin cancer prevention study group. JAMA 267: 3305–3310
7. Perea-Milla LE, Minarro-Del Moral RM, Martinez-Garcia C, Zanetti R, Rosso S, Serrano S, Aneiros JF, Jimenez-Puente A, Redondo M (2003) Lifestyles, environmental and phenotypic factors associated with lip cancer: a case–control study in southern Spain. Br J Cancer 88:1702–1707
8. Pogoda JM, Preston-Martin S (1996) Solar radiation, lip protection, and lip cancer risk in Los Angeles County women (California, United States). Cancer Causes Control 7:458–463
9. Boyd AS, Shyr Y, King LE Jr (2002) Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J Am Acad Dermatol 46:706–709
10. Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, Chinni LM, Gobello T, Mazzanti C, Puddu P, Pasquini P (2001) Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. Arch Dermatol 137:1162–1168
11. Foote JA, Harris RB, Giuliano AR, Roe DJ, Moon TE, Cartmel B, Alberts DS (2001) Predictors for cutaneous basal- and squamous-cell carcinoma among actinically damaged adults. Int J Cancer 95:7–11
12. Freedman DM, Sigurdson A, Doody MM, Mabuchi K, Linet MS (2003) Risk of basal cell carcinoma in relation to alcohol intake and smoking. Cancer Epidemiol Biomarkers Prev 12:1540–1543
13. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE (1990) Risk factors for basal cell carcinoma in a prospective cohort of women. Ann Epidemiol 1:13–23
14. Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, Strange RC, Fryer AA (1997) Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. J R Soc Med 90:371–374
15. Milan T, Verkasalo PK, Kaprio J, Koskenvuo M (2003) Lifestyle differences in twin pairs discordant for basal cell carcinoma of the skin. Br J Dermatol 149:115–123
16. van Dam RM, Huang Z, Rimm EB, Weinstock MA, Spiegelman D, Colditz GA, Willett WC, Giovannucci E (1999) Risk factors for basal cell carcinoma of the skin in men: results from the health professional's follow-up study. Am J Epidemiol 150: 459–468
17. Wojno TH (1999) The association between cigarette smoking and basal cell carcinoma of the eyelids in women. Ophthal Plast Reconstr Surg 15:390–392
18. Ramsay HM, Fryer AA, Hawley CM, Smith AG, Nicol DL, Harden PN (2003) Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. J Am Acad Dermatol 49:397–406
19. Stein L, Urban MI, Weber M, Ruff P, Hale M, Donde B, Patel M, Sitas F (2008) Effects of tobacco smoking on cancer and cardiovascular disease in urban black South Africans. Br J Cancer 98:1586–1592
20. Hogan DJ, Lane PR, Gran L, Wong D (1990) Risk factors for squamous cell carcinoma of the skin in Saskatchewan, Canada. J Dermatol Sci 1:97–101
21. Odenbro A, Bellocco R, Boffetta P, Lindelof B, Adami J (2005) Tobacco smoking, snuff dipping and the risk of cutaneous

squamous cell carcinoma: a nationwide cohort study in Sweden. Br J Cancer 92:1326–1328
22. Kune GA, Bannerman S, Field B, Watson LF, Cleland H, Merenstein D, Vitetta L (1992) Diet, alcohol, smoking, serum beta-carotene, and vitamin A in male nonmelanocytic skin cancer patients and controls. Nutr Cancer 18:237–244
23. Leffondre K, Abrahamowicz M, Siemiatycki J, Rachet B (2002) Modeling smoking history: a comparison of different approaches. Am J Epidemiol 156:813–823
24. Milan T, Pukkala E, Verkasalo PK, Kaprio J, Jansen CT, Koskenvuo M, Teppo L (2000) Subsequent primary cancers after basal-cell carcinoma: a nationwide study in Finland from 1953 to 1995. Int J Cancer 87:283–288
25. Zang EA, Wynder EL (1996) Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 88:183–192
26. Ramchandran K, Patel JD (2009) Sex differences in susceptibility to carcinogens. Semin Oncol 36:516–523
27. Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, Spitz MR (2000) Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 92:1764–1772
28. Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L (1993) DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. Proc Natl Acad Sci USA 90:1614–1618
29. Johnson T, Yu B, Murray M, Huang Y (2007) Florida behavioral risk factor surveillance system (BRFSS) data report 2007. Florida Department of Health, Tallahassee