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Smoking And Early-Onset Basal Cell Carcinoma

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SMOKING AND EARLY-ONSET BASAL CELL CARCINOMA

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Abstract

Background – Smoking has been identified as a risk factor for many cancers. While many studies have investigated the association between smoking and basal cell carcinoma (BCC), the results have been inconsistent, and no study has evaluated this association among a young population.

Methods – Early-onset BCC cases (n=374) and controls with minor benign skin conditions (n=384) under age 40 were identified through Yale Dermatopathology. Participants over 18 years old were asked whether they ever smoked (defined as ever smoked at least 100 cigarettes) during an in-person interview. Those who responded affirmatively were then asked about their smoking history. We calculated odds ratios (OR) and 95% confidence intervals (CI) for the association between smoking and early-onset BCC using unconditional multivariate logistic regression.

Results – Current smokers had significantly lower odds of having early-onset BCC compared to non-smokers (OR=0.43, 95% CI=0.24-0.77). There was no evidence for a clear dose-response effect by pack-years, but there was a statistically significant inverse association for younger age at smoking initiation (OR for below median vs non-smokers=0.62, 95% CI=0.40-0.96). We did not find evidence that alcohol consumption, site of skin biopsy or sex were effect modifiers of the association between smoking and BCC.

Conclusions – Overall, we observed an inverse association between smoking status and early-onset BCC. Replication in other populations is important to further clarify this association.

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Introduction

Basal cell carcinoma (BCC) is a type of nonmelanoma skin cancer (NMSC), which is the most common form of skin cancer, and the most frequently occurring form of all cancers[1]. In the U.S., the most recent estimates from 2012 suggest 5.4 million NMSCs are diagnosed each year, and 80% of NMSCs are BCCs[1]. The incidence rate of BCC is still increasing.[2] Previously, many studies have shown that the incidence of NMSC increases with age, which reflects cumulative ultraviolet radiation (UV) from sun exposure and damage over time.[3,4] However, in recent years, studies have shown that the incidence is increasing among people under the age of 40, especially women, which indicated that novel environmental and lifestyle factors may be associated with increased risk of BCC as well[5].

Smoking has been identified as a risk factor for many human cancers, but it is still an undetermined risk factor for BCC. Past studies on smoking and BCC are inconsistent, and smoking-related associations may vary by tumor histology and anatomical site. In 2012, two meta-analyses of the association between smoking and BCC had different conclusions, with one finding a positive association and one being null.[6,7] However, this was likely due to inclusion of different studies and different measures of smoking (e.g. ever vs. never, current vs. former vs. never smokers). Since 2012, four studies, including a meta-analysis of prospective studies in 2018, found that smoking was associated with a reduced risk of BCC[8–11]. The potential reasons for the conflicting results among previous studies may be due to different measures of smoking, confounding, and loss to follow-up. Furthermore, some studies have investigated the potential for detection bias to influence the diagnosis of BCCs by smoking status, as non-smokers may seek medical care more than smokers and therefore having BCC's detected more frequently.[11,12]

One potential mechanism for smoking being a risk factor for BCC is that smoke contains several classes of compounds with carcinogenic or cocarcinogenic activity that may act as skin carcinogens.[13] Furthermore, tobacco smoke can decrease cutaneous blood flow and suppress immune responses, which can increase the risk of skin cancer[13]. On the other hand, the inverse association between smoking and BCC reported in several studies may be explained by smoking protecting the skin from the inflammatory reaction induced by UV radiation and thereby decreasing the risk of skin cancer[14].

To our knowledge, there is no prior research specifically in a young population, so the association between smoking and early-onset BCC is still unexplored. Based on the uncertainty of this association overall for BCC, we investigated the relationship between cigarette smoking and early-onset BCC among young people in the Yale Study of Skin Health in Young People, a case-control study conducted in Connecticut. In addition, our study is unlikely to suffer from the potential detection bias of other designs, as our population of young people had a much lower overall incidence of BCC and our controls were seen by a dermatologist under age 40 for a benign skin condition and therefore could have had a BCC detected.

Methods

Yale Study of Skin Health in Young People

The Yale Study of Skin Health in Young People was a case-control study of early-onset BCC conducted in Connecticut between July 2007 and December 2010, investigating lifestyle factors associated with BCC[15]. BCC cases were identified through Yale University's

Dermatopathology database. Control subjects were individuals with non-UV-related benign skin conditions randomly sampled from the same database and frequency matched to BCC cases on age at biopsy (5-year age groups), gender, and biopsy site (head/neck, trunk, extremity). A total of 389 cases (participation rate=72.8%) and 458 controls (participation rate=60.7%) enrolled in the study. Participants completed a face-to-face interview and several mailed self-administered questionnaires. Yale University's Institutional Review Board approved the study and participants (or guardians) provided written informed consent.

Data Collection

The structured interview contained questions on sociodemographic characteristics, outdoor UV exposure (incidental exposure, intentional sunbathing, outdoor activities), indoor tanning (ever/never, number of sessions), history of sunburns, alcoholic drinks, family history of skin cancer, as well as self-reported phenotype characteristics (eye, skin, and hair color). Interviewers were blinded to case-control status until the end of the interview, when participants were asked about their personal history of cancer.

Participants over 18 years old were asked whether they ever smoked; defined as ever smoked at least 100 cigarettes. Those who responded affirmatively were then asked about the average number of cigarettes per day. Pack years were calculated by taking the average number of cigarettes per day times total years smoked then divided by 20. Individuals who were non-smokers were assigned a zero value for pack years. Participants were also asked the age that they first started smoking, and participants who were non-smokers were assigned zero.

Statistical Analysis

Our analytic sample was limited to non-Hispanic whites without Gorlin Syndrome, which predisposes individuals to multiple BCCs early in life[16]: 377 cases (96.9%) and 390 controls (85.2%). Nine participants (3 cases and 6 controls) less than 18 years of age at the time of interview were also excluded, as they were not asked about smoking history since they were under the legal age for smoking. This left 758 individuals (374 cases and 384 controls) for analysis.

We used descriptive statistics (Chi-square test, Wilcoxon rank-sum test, and Student's t-test) to evaluate differences between cases and controls. Multivariate unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between smoking status and early-onset BCC in the whole sample, and in each sex separately. In addition to smoking status, we also examined the frequency of smoking (pack years) and age starting smoking in relation to early-onset BCC via multivariate unconditional logistic regression. We categorized pack-years into three categories: non-smoker, below or equal to median pack-years, and above the median; with the median based on the distribution in the controls. Similarly, a three-level categorical variable was created for age starting smoking. We evaluated the linear trend of pack-years using an ordinal categorical variable.

All models were adjusted for study frequency matching variables (gender, age at diagnosis, and body site of biopsy), and the following characteristics which either changed risk estimates by at least 10% or were associated with early-onset BCC in our population (skin color, education, alcohol consumption, hours spent outdoors in warm months, sunburns, indoor tanning, skin reaction on long exposure to sun, and family history of skin cancer).

We tested the interactions between smoking status (non-smoker, former, current) and alcohol intake, sex, and body site of biopsy by including the cross-product terms in the multivariate models. All descriptive and multivariate analyses were conducted using SAS Version 9.4 (SAS. Cary, NC), and reported p-values are two-sided.

Results

Among 758 participants, 69.7% were female and the median age at skin biopsy was approximately 36 years (Table 1). The body site of the biopsy was significantly different between cases and controls. Controls were more likely to have black/dark brown hair color, less very fair skin color, compared to cases. Compared to controls, BCC cases were more likely to have a higher level of education, lower BMI, longer outdoor sun exposure in warm months, more sunburns, and a family history of skin cancer.

Controls were more likely to be current smokers than BCC cases (Table 1). However, current smokers made up a relatively small proportion of study participants (8% of cases and 16.7% of controls). Controls had a higher pack year history than cases. The majority of study participants were non-smokers (62.3% of cases and 51.6% of controls).

Multivariate ORs were calculated for BCC in relation to smoking status in the overall population and each gender separately (Table 2). Among all participants, current smoking was inversely associated with early-onset BCC compared to never smoking (OR=0.43, 95% CI=0.24-0.77). There was no statistically significant interaction (p interaction=0.627) by gender, and the magnitude of the ORs for current smoking was similar for women and men, but only reached statistical significance among women (OR=0.44, 95% CI=0.21-0.92). There was an inverse

association for former smokers in the full sample, but this did not reach statistical significance (OR=0.72; 95% CI=0.50-1.06).

We also investigated whether the frequency of smoking and the age started smoking were associated with early-onset BCC (Table 3). Compared to non-smokers, those with below the median pack year history had significantly lower odds of early-onset BCC (OR=0.55, 95% CI=0.36-0.85), but those with above the median pack years had similar odds of BCC to non-smokers (OR=0.80, 95%CI = 0.51-1.26). There was no evidence for a linear trend with pack years (p-trend=0.616). For age started smoking, we observed decreased odds of BCC for people in the below the median age of started smoking compared to non-smokers (below median: OR=0.62, 95% CI=0.40-0.96). There was a borderline association with above the median age started smoking compared to non-smokers (OR=0.66, 95% CI=0.43-1.01).

There was no evidence that alcohol consumption or body site of biopsy were effect modifiers of the association between smoking status (non-smoker, former, current) and early-onset BCC (data not shown).

Discussion

In this case-control study of BCC among young people, current smoking was inversely associated with early-onset BCC. There was no evidence for a clear dose-response effect by pack-years, but we did see a statistically significant inverse association for younger age at smoking initiation. We did not find evidence that alcohol consumption, site of biopsy or sex were effect modifiers of the association between smoking and BCC.

Our finding of lower odds of early-onset BCC among current smokers are similar to the latest studies for BCC among all ages[8–11]. However, we should note that the most recent meta-analysis only included prospective studies and the newest individual study with over 1 million women in the UK that found an inverse association[8]. Therefore the 2018 meta-analysis estimates are driven by that population. Previously, two other meta-analyses had conflicting findings, with one reporting a positive association and one reporting a null association[6,7], but they included different studies (4 studies and only evaluated prospective designs in Song et al. and 23 studies in Lenoardi-Bee et al.). In addition to including different designs, Lenoardi-Bee et al. may have observed a positive relationship between smoking and the risk of BCC as they included studies that only adjusted for age and sex and did not have robustly controlled multivariate models.

While our power to look at difference by sex was limited due to the small number of males in our population, there was no evidence of effect modification and the associations for smoking and BCC were of similar magnitude and direction in males and females. As other have assessed this counter-intuitive inverse association, the hypothesis of detection bias has been posited, in which never smokers who are more likely to have more regular skin checks than current smokers, would have a greater chance of being diagnosed with BCC[10,11]. Our cases did tend to have a higher education level than controls, so it is possible they could have greater economic resources and be more health-conscious. However, based on our design, all people had been seen by a dermatologist under age 40 so the detection bias should have been largely avoided in our study. In addition, since all our participants were under age 40 overall incidence of BCC would have been low further reducing the possibility of undetected BCC by smoking status.

The biggest difference between our study and previous studies is that we not only investigated the association of BCC and status of smoking (non-smoker, former smoker, current smoker), but

also explored the association between pack-years of smoking and age at first smoking with BCC. Our results were very similar to the research of Jean et al.[17] For the smoking frequency in our study, there was only a significant association in the low frequency group, and there was no dose response between smoking and the risk of early-onset BCC. Jean et al. also did not find a relationship between pack-years of smoking and BCC. For the age at first smoking, younger age of initiation of smoking was significantly associated with early-onset BCC while older age was just borderline statistically significant, and this result was similar to the research of Jean et al.

Previously, smoking has been identified as a risk factor for cancers of lung, bladder, and cervix and several studies have found that smoking increased the risk of squamous cell carcinoma (SCC) of the skin [6–8,11]. Regarding the inverse association between smoking and BCC, several possible biological mechanisms may explain it. First, nicotine administration via transdermal delivery system can suppress the cutaneous inflammatory response to skin irritants, thus nicotine may protect smokers from long-term UV radiation-induced inflammation[18]. Furthermore, nicotine can alter differentiation of keratinocytes via increasing keratinocyte adhesion[19]. However, at present these mechanisms are speculative and we lack a clear understanding of why smoking would influence the development of two types of skin cancers (BCC versus SCC) differently.

A limitation of our case-control study is the inability to establish temporality of the association. We also had a relatively small number of current smokers in our study population, making it difficult to fully explore dose-response effects. Furthermore, past smoking frequency in our study may suffer from poor recall though this should be similar among cases and controls. Additionally, our study was conducted only in Connecticut, and our study participants were well-educated, so this may affect the generalizability of our results to a broader population.

Our study also had several strengths. First of all, this was the first study to explore the association between smoking and early-onset BCC in a young population. Moreover, we captured extensive information on major skin risk factors and UV-related activities, which allowed us to comprehensively control for potential confounders. Detection bias was also likely avoided by our study design of all cases and control being seen by a dermatology. Compared to most previous studies investigating the association between smoking and BCC, we not only had the variable of smoking status (never, former, current), but also had other dimensions of smoking.

In conclusion, compared with non-smokers, current smokers had lower odds of early-onset BCC, but there was no evidence of a dose-response relationship by pack-years. Younger age at initiation of smoking was associated with lower odds of early-onset BCC. While we did observe an inverse association between smoking and early-onset BCC, it is important to not overlook the overall data on smoking increasing the risk of many other diseases with high morbidity and mortality, including several cancers, heart disease, stroke, COPD, and diabetes[20]. Therefore, smoking should not be promoted to reduce risk of BCC; however, nicotine may be of further interest to investigate mechanistically in relation to BCC. Furthermore, replication in large, prospective studies is important to further clarify this potential association with early-onset BCC.

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Table 1. Selected characteristics of BCC cases and controls in Yale Study of Skin Health in Young people (N=758)

Characteristic	BCC Cases (N = 374) N[a] (%)	Controls (N = 384) N[a] (%)	P-value[b]
Age (y), Median (IQR)	36.4 (33.3-38.5)	36.8 (32.9-38.5)	0.812
Female	256 (68.5%)	272 (70.8%)	0.475
Body site of biopsy			<0.001
Head	201 (53.7%)	160 (41.7%)	
Extremity	72 (19.3%)	124 (32.3%)	
Trunk	101 (27.0%)	100 (26.0%)	
Smoking Status			<0.001
Non-smoker	233 (62.3%)	198 (51.6%)	
Former smoker	111 (29.7%)	122 (31.8%)	
Current Smoker	30 (8.0%)	64 (16.7%)	
Pack-years	0 (0-3)	0 (0-5)	0.004
Age started smoking	17 (16-18)	16 (15-18)	0.377
Education			0.017
≤ Some college	103 (27.5%)	139 (36.2%)	
College graduate	113 (30.2%)	116 (30.2%)	
≥ Some graduate school	158 (42.3%)	129 (33.6%)	
Hair color			<0.001
Black/dark brown	101 (27.1%)	159 (41.4%)	
Light brown	134 (35.9%)	152 (39.6%)	
Blonde/fair	99 (26.5%)	63 (16.4%)	
Red	39 (10.5%)	10 (2.6%)	
Skin color (inner upper arm)			<0.001
Olive	15 (4.0%)	76 (19.8%)	
Fair	210 (56.2%)	232 (60.4%)	
Very fair	149 (39.8%)	76 (19.8%)	
Body mass index, kg/m^2			<0.001
≤ 25.0	243 (65.0%)	203 (52.9%)	
25-29.9	91 (24.3%)	106 (27.6%)	
≥ 30.0	40 (10.7%)	75 (19.5%)	
Alcohol Drinker	283 (76.3%)	276 (72.1%)	0.186
Family history of skin cancer	245 (65.5%)	149 (38.8%)	<0.001
Ever indoor tanning	246 (66.0%)	249 (64.3%)	0.749
Outdoor sun exposure in warm months (h), median (IQR)	8793.2 (6476.3-11135.5)	7915.2 (6113.9-10466.7)	0.017
Sunburns (n), median (IQR)	6 (1-16)	3 (1-9)	<0.001

[a]Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

[b]Chi-square test for categorical variables, Wilcoxon rank sum test for continuous variables

Table 2. Odds ratios for early-onset BCC among all subjects (n=758) and women (n=528) & men (n=233) according to the status of smoking

	Non-smoker	Former smoker	Current smoker	$P_{interaction}$
Overall				
N	431	233	94	
Cases/controls	233/198	111/122	30/64	
Unadjusted OR (95% CI)	1.00	0.77 (0.56-1.06)	0.40 (0.25-0.64)	
Adjusted OR (95% CI)[a]	1.00	0.72 (0.50-1.06)	0.43 (0.24-0.77)	
Women				
N	293	177	58	
Cases/controls	156/137	83/94	17/41	
Unadjusted OR (95% CI)	1.00	0.78 (0.53-1.13)	0.36 (0.20-0.67)	
Adjusted OR (95% CI)[a]	1.00	0.72 (0.47-1.12)	0.44 (0.21-0.92)	0.627
Men				
N	139	56	38	
Cases/controls	77/61	28/28	13/23	
Unadjusted OR (95% CI)	1.00	0.79 (0.43-1.48)	0.45 (0.21-0.96)	
Adjusted OR (95% CI)[a]	1.00	0.77 (0.34-1.78)	0.46 (0.15-1.41)	

[a] Adjusted for age, gender (for overall sample model), body site of biopsy (head, extremity, trunk), skin color (olive, fair, very fair), education (some college or less, college graduate, some graduate school), alcohol consumption (drink at least once a week for 6 months or more), hours spent outdoors in warm months (continuous), sunburns (continuous), indoor tanning (ever vs never), reaction on long exposure to sun (very brown and deeply tanned, moderately tanned, only mildly tanned due to peeling, only freckled, not tan), and family history of skin cancer (yes, no)

Table 3. Odds ratios for early-onset BCC among all subjects (n=758) according to the frequency of smoking and the age started smoking

	Cases/controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	P-trend[a]
Smoking Frequency				
Non-smoker	233/198	1.00	1.00	0.616
Below median (≤ 5.6 pack-years)	65/91	0.61 (0.42-0.88)	0.55 (0.36-0.85)	
Above median (> 5.6 pack-years)	74/81	0.69 (0.48-0.99)	0.80 (0.51-1.26)	
Age started smoking				
Non-smoker	233/198	1.00	1.00	-
Below median (≤ 16 years old)	67/99	0.58 (0.40-0.83)	0.62 (0.40-0.96)	
Above median (> 16 years old)	74/87	0.72 (0.50-1.04)	0.66 (0.43-1.01)	

[a] Adjusted for age, gender (for overall sample model), body site of biopsy (head, extremity, trunk), skin color (olive, fair, very fair), education (some college or less, college graduate, some graduate school), alcohol consumption (drink at least once a week for 6 months or more), hours spent outdoors in warm months (continuous), sunburns (continuous), indoor tanning (ever vs never), reaction on long exposure to sun (very brown and deeply tanned, moderately tanned, only mildly tanned due to peeling, only freckled, not tan), and family history of skin cancer (yes, no)