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SMOKELESS TOBACCO AND RISK OF HEAD AND NECK CANCER: EVIDENCE FROM A CASE-CONTROL STUDY IN NEW ENGLAND

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Abstract

Current studies suggesting that smokeless tobacco use increases the risk of head and neck cancer are hampered by small numbers. Consequently, there remains uncertainty in the magnitude and significance of this risk. We examined the relationship between smokeless tobacco use and head and neck squamous cell carcinoma (HNSCC) in a population-based case-control study with 1,046 cases and 1,239 frequency-matched controls. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI), adjusting for age, gender, race, education level, cigarette smoking, and alcohol consumption. A non-significant elevated association between having ever used smokeless tobacco and HNSCC risk (OR = 1.20, 95% CI: 0.67, 2.16) was observed. Individuals who reported 10 or more years of smokeless tobacco use had a significantly elevated risk of HNSCC (OR = 4.06, 95% CI: 1.31, 12.64), compared to never users. In an analysis restricted to never cigarette smokers, a statistically significant association was observed between ever use of smokeless tobacco and the risk of HNSCC (OR = 4.21, 95% CI: 1.01, 17.57). These findings suggest that long term use of smokeless tobacco increases the risk of HNSCC.

Keywords

smokeless tobacco; head and neck cancer; case-control

Introduction

An estimated 8.6 million Americans aged 12 or older (3.4 percent) actively used smokeless tobacco in 2009.[1] This use was most common among men aged 18 – 24, non-Hispanic White, living in the South, and having a high school education or less.[2, 3] The U.S. National

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Survey on Drug Use and Health in 2009 showed that past month smokeless tobacco use increased from 2.0 percent in 2002 to 2.3 percent in 2009 among youths.[1]

Although several health authorities, including the U.S. Surgeon General[4], the International Agency for Research on Cancer[5], and the U.S. National Cancer Institute[6], have reported that the use of smokeless tobacco is associated with an increase risk of cancer of the oral cavity, the totality of the evidence from epidemiologic studies has been hampered by small, inconsistent studies. Early studies, conducted in the US and Europe (before 1990), showed an elevated risk of oral or pharyngeal cancer with the use of smokeless tobacco;[7–9] however, studies after 1990 no longer provided support for a positive association between smokeless tobacco use and head and neck cancer risk.[10–16]

To further elucidate the nature of the association between the use of smokeless tobacco products and the risk of head and neck squamous cell carcinoma (HNSCC), we examined this association in a large, population-based case-control study.

Materials and methods

Study subjects

Incident cases of HNSCC were identified and recruited from head and neck clinics and departments of otolaryngology or radiation oncology at 9 medical facilities in the Greater Boston Metropolitan Area. Patients with a confirmed diagnosis of primary HNSCC were included if they were 18 years or older and residents of the Greater Boston. Recurrent cases or incident cases diagnosed more than 6 months prior to contact were excluded. HNSCC cases consisted of those with a diagnosis code of 141–146, 148, 149, or 161 based on the International Classification of Disease, Ninth Revision (ICD-9). Control subjects were frequency-matched to cases by age (± 3 yrs), gender, and town of residence using the Massachusetts town books, which are required by state law to list all residents 17 years and older[17]. Participation rates for cases and controls were 78% and 47%, respectively. A total of 1,056 cases and 1,252 controls were available for this study.

Study protocols and materials for recruitment of both cases and controls were approved by the Institutional Review Board at all the 9 medical facilities and Brown University. Written informed consent was obtained from all enrolled cases and controls.

Data collection

An interviewer-reviewed, self-administered questionnaire was developed to gather information about demographic characteristics, medical history, family history of cancer, detailed smoking and drinking habits, detailed history of smokeless tobacco use, occupational history, and residential history. Questionnaires were given to cases during the initial clinic visit and to controls by mail, which were returned during the second in-person visit for cases and first in-person visit for controls. All subject responses were reviewed by study personnel during the in-person visits.

To obtain the history of smokeless tobacco use, all subjects were first asked to report whether or not they had ever used smokeless tobacco. Subjects who reported having ever used smokeless tobacco were asked to report whether they were current users, whether they had used smokeless tobacco at least 20 times in their lifetime, their ages at starting and stopping using smokeless tobacco, and average number of times per week they used smokeless tobacco.

Statistical analysis

To describe the distribution of demographic variables and explore the potential confounders, t-tests were used for the continuous variables and X^2 tests were used for categorical variables. Unconditional multivariate logistic regression was used to estimate the association between smokeless tobacco use and the risk of HNSCC.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated with and without adjustment for potential confounders. To examine the effect of ever use of smokeless tobacco, ever users were defined as those who had used smokeless tobacco at least 20 times and those who had never used smokeless tobacco were used as the reference group. The lifetime duration of smokeless tobacco use for current users was determined as the difference between the age at diagnosis and the age at starting smokeless tobacco use. For non-current users, the lifetime duration was estimated as the difference between the age at stopping smokeless tobacco use and the age at starting smokeless tobacco use. To estimate the overall lifetime numbers of smokeless tobacco use, the number of times per week of use was multiplied by the duration of lifetime use (time/week*year). Never users served as the reference group for the estimates of duration, times per week, and total numbers of use in lifetime. Crude and adjusted logistic regression models controlled for the frequency-matching variables (age and gender); adjusted models additionally controlled for race (*White* versus *other*), smoking status (*ever* versus *never*), cigarette smoking dose (pack-years as a continuous variable), average alcoholic drinks per week (continuous), and education level (*less than high school*, *high school or equivalence*, *more than high school*). One alcoholic drink was defined as one bottle, can or glass of beer, or one glass of wine, or one shot, cocktail, or mixed drink of liquor. We performed tests of trend by assigning the median value for each category and modeling this variable as a continuous variable using logistic regression models. Multinomial logistic regression was used to investigate the association between smokeless tobacco use and HNSCC risk by tumor site, classified as oral cavity, pharynx, and larynx, as defined by the American Joint Committee on Cancer Staging Manual.[18] Oral cavity tumors corresponded to ICD-9 codes 143, 144, 145, and, if located at the anterior of the tongue, 141; pharyngeal tumors corresponded to ICD-9 codes 146, 148, 149, and if at the base of the tongue, 141; and laryngeal tumors corresponded to ICD-9 code 161. All statistical tests were performed using Stata version 11.1 (StataCorp, College Station, TX), and all reported p-values were based on two-sided tests with significance considered where $p < 0.05$.

Results

After excluding 23 subjects (10 cases and 13 controls) with missing data on ever use of smokeless tobacco, a total of 1,239 controls and 1,046 cases were available for analysis. A description of subject characteristics by case-control status is presented in Table 1. An additional 32 subjects were excluded from the regression models due to missing values for race (n = 16), education level (n = 10), or alcohol consumption (n = 6). The mean age of the participants in both groups was about 60. The majority of the study population was male (72.6%) and White (91.1%). Relative to control subjects, cases attained a lower level of education ($p < 0.001$), smoked more pack-years of cigarettes ($p < 0.001$), and consumed more alcoholic beverages per week ($p < 0.001$).

Among the 1,239 participants in the control group, 39 (3.15%) participants reported having ever used smokeless tobacco, with 22 (1.78%) reporting having used it at least 20 times. Table 2 shows the association of smokeless tobacco use with HNSCC among the entire study population. After controlling for potential confounders, we observed an elevated, but statistically non-significant, risk for HNSCC among individuals reporting having ever used smokeless tobacco (at least 20 times) (OR = 1.20, 95% CI: 0.67, 2.16), compared to never

users. Subjects who reported 10 or more years of smokeless tobacco use had a statistically significant increased HNSCC risk (OR = 4.06, 95% CI: 1.31, 12.6), compared to never users. We also observed a significant trend with duration of smokeless tobacco use (p=0.02). Subjects who had used smokeless tobacco for 14 or more times per week had a statistically non-significant elevated risk of HNSCC (OR = 1.39, 95% CI: 0.39, 4.89), as did those whose lifetime numbers of smokeless tobacco use (times/week*year) equal to or more than 20 (OR = 1.72, 95% CI: 0.81, 3.68). In addition, we evaluated whether the relationships were altered if dose (average cigarettes per day) and total duration (years) of cigarette smoking were controlled as separate variables in the adjusted models, instead of pack-years as one continuous variable; only very small changes were observed ($OR_{\geq 20 \text{ times vs never users}}$ = 1.23, 95% CI: 0.68, 2.21; $OR_{\geq 10 \text{ years vs never users}}$ = 4.08, 95% CI: 1.31, 12.67).

We further investigated the tumor site-specific association between smokeless tobacco use and HNSCC, using multinomial logistic regression; no substantial difference was observed across the tumor sites (Table 3). Ten or more years of smokeless tobacco use was associated with an elevated risk at all three HNSCC sites; this was significant for cancers of the larynx (OR = 5.35, 95% CI: 1.11, 25.7) and pharynx (OR = 4.46, 95% CI: 1.33, 14.9). A significant trend for an increased risk associated with the duration of smokeless tobacco use was observed for pharyngeal cancer (p=0.02).

To further examine the association of smokeless tobacco use independent of tobacco smoking, we restricted the analysis to never cigarette smokers only (Table 4). Among never cigarette smokers, there was a statistically significant association between having used smokeless tobacco 20 or more times and HNSCC (OR = 4.21, 95% CI: 1.01, 17.6), relative to never smokeless tobacco users. Additionally, a significant trend with the duration of smokeless tobacco use was observed (p=0.02).

Discussion

In this large, population-based case-control study, long term use of smokeless tobacco was associated with a significantly elevated risk of HNSCC. The risk of HNSCC associated with smokeless tobacco use was also evident when the analysis was restricted to never cigarette smokers.

Thus far, seven studies have examined the relation of smokeless tobacco use and risk of oral cancer or oral and pharyngeal cancer in the US [7–9, 13, 15, 16]; the number of cases included in these studies ranges from 13 [13] to 755 [8]. In a recent meta-analysis summarizing findings from Europe and North America, a summary relative risk of 1.8 (95% CI: 1.1–2.9) was obtained for oral cancer in users of smokeless tobacco products.[19] Our study is among the largest to date to evaluate this association and our estimate of relative risk is similar to that reported by Winn et al in 1981.[7]

Tobacco-specific nitrosamines have been shown in rats to induce oral cavity tumors after direct swab application.[20] More than 30 types of carcinogens have been found in smokeless tobacco, including tobacco-specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, and various types of metals.[19, 21] One gram of smokeless tobacco product typically contains 1–5 μg of the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and NL′-nitrosonornicotime, two of the most carcinogenetic compounds in the tobacco-specific nitrosamine family.[22] Other tobacco-specific nitrosamines have also been detected in smokeless tobacco products.[22] The metabolites of these tobacco-specific nitrosamines have been found in urine of smokeless

tobacco users, demonstrating that these carcinogens are absorbed locally, metabolized and excreted.[19]

The 2009 National Survey on Drug Use and Health estimated that 8.6 million Americans (3.4 percent) were current smokeless tobacco users.[23] Substantial geographic variation of smokeless tobacco use among adult men was also reported by the 2009 Behavioral Risk Factor Surveillance System, a state-based, landline telephone survey of non-institutionalized adults living in the United States; the highest prevalences were observed in Wyoming (9.1 percent), West Virginia (8.5 percent), and Mississippi (7.5 percent), and the lowest was observed in California (1.3 percent).[2] It has been suggested that smokeless tobacco is a means of "harm reduction" and the use of smokeless tobacco products has been promoted as a healthy alternative to smoking tobacco.[24–26] In particular, Coral Gartner and colleagues concluded that Swedish snus, a smokeless tobacco product, could produce a net health benefit at the population level, with the size of the benefit dependent on how many inveterate smokers switch to snus.[24] Our findings argue that use of today's smokeless tobacco products still carries a quite significant risk of head and neck cancer. The magnitude of the overall risk is comparable to that of tobacco smoking[27, 28], indicating that it should not be considered as a viable alternative.

One of the main strengths of this study is that cigarette smoking and alcohol consumption were measured based on decade-specific exposures, providing more precise control for these known risk factors. Other strengths of this study include a large number of incident cases of HNSCC, and the collection of start and end ages of smokeless tobacco to determine lifetime duration of use. A limitation includes the retrospective study design. However, to minimize the influence of recall bias, we defined ever smokeless tobacco use as having ever used smokeless tobacco for 20 or more times, as moderate or heavy users are less likely to fail in reporting use.

In conclusion, the use of smokeless tobacco results in exposure to potent carcinogens. We report a positive association between ever use of smokeless tobacco and risk of HNSCC among never cigarette smokers. Additionally, long term use (≥ 10 years) of smokeless tobacco was associated with an elevated risk of HNSCC. These findings refute the notion that smokeless tobacco is a viable alternative to cigarette smoking, underscoring the serious health risk associated with this harmful habit.

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Abbreviations

HNSCC	head and neck squamous cell carcinoma
OR	odds ratio
CI	confidence interval

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Novelty and Impact

This study is among the largest to date to investigate the association between smokeless tobacco use and head and neck squamous cell carcinoma. We report a positive association between use of smokeless tobacco and risk of head and neck squamous cell carcinoma among never cigarette smokers. The findings refute the notion that smokeless tobacco could be a viable alternative to cigarette smoking, underscoring the serious health risk associated with this harmful habit.

Table 1

Distribution of descriptive characteristics for the study population.

Characteristic	Cases (n = 1,046)	Controls (n = 1,239)	*p*-value
Age, mean (± SD)	59.74 ± 11.30	60.88 ± 11.10	0.02
Gender, n (%)			0.82
Female	289 (27.63)	337 (27.20)	
Male	757 (72.37)	902 (72.80)	
Race, n (%)			0.72
White	948 (91.33)	1,119 (90.90)	
Other	90 (8.67)	112 (9.10)	
Education, n (%)			<0.001
Lower than high school	131 (12.55)	84 (6.82)	
High school or equivalence	405 (38.79)	413 (33.55)	
College or higher	508 (48.66)	734 (59.63)	
Family history of cancer, n (%)			0.27
No	587 (56.12)	724 (58.43)	
Yes	459 (43.88)	515 (41.57)	
Ever cigarette smoker, n (%)			<0.001
No	250 (23.90)	496 (40.03)	
Yes	796 (76.10)	743 (59.97)	
Average pack-years of cigarette smoking, mean (± SD)	29.93 ± 31.88	18.74 ± 26.46	<0.001
Average alcohol drinks per week, mean (± SD)	24.03 ± 35.82	12.18 ± 20.23	<0.001
Tumor sites, n (%)			
Oral	392 (37.98)		
Pharynx	471 (45.64)		
Larynx	169 (16.38)		

Abbreviation: SD, standard deviation

Table 2

Association of HNSCC with smokeless tobacco use.

Variables	Case (%)	Control (%)	OR[1]	95% CI[1]	OR[2]	95% CI[2]
Smokeless tobacco use history						
Never	1,003 (96.91)	1,200 (98.20)	1.00	---	1.00	---
≥ 20 times	32 (3.09)	22 (1.80)	1.63	0.94, 2.85	1.20	0.67, 2.16
Duration of smokeless tobacco use in lifetime (y)						
Never	1,003 (96.16)	1,200 (97.32)	1.00	---	1.00	---
> 0 to < 2	6 (0.58)	10 (0.81)	0.71	0.26, 1.97	0.63	0.22, 1.77
≥ 2 to <10	18 (1.73)	19 (1.54)	1.09	0.56, 2.09	0.83	0.41, 1.66
≥ 10	16 (1.53)	4 (0.32)	4.43	1.47, 13.36	4.06	1.31, 12.64
p for trend			0.008		0.021	
Average frequency of smokeless tobacco use per week (times)						
Never	1,003 (96.44)	1,200 (97.48)	1.00	---	1.00	---
> 0 to < 7	16 (1.54)	19 (1.54)	0.97	0.50, 1.91	1.00	0.50, 2.00
≥ 7 to < 14	12 (1.15)	8 (0.65)	1.66	0.67, 4.11	1.23	0.48, 3.14
≥ 14	9 (0.87)	4 (0.32)	2.51	0.77, 8.21	1.39	0.39, 4.89
p for trend			0.100		0.572	
Lifetime numbers of smokeless tobacco use (times/wk*y)						
Never	1,003 (96.54)	1,200 (97.80)	1.00	---	1.00	---
> 0 to < 20	12 (1.15)	16 (1.30)	0.87	0.41, 1.85	0.93	0.43, 2.01
≥ 20	24 (2.31)	11 (0.90)	2.43	1.18, 5.02	1.72	0.81, 3.68
p for trend			0.016		0.159	

[1]OR adjusted for age and gender.

[2]OR adjusted for age, gender, race (White, non-White), education (3 categories), smoking (continuous), ever smoker, alcohol drinking (continuous).

Table 3

Association of HNSCC with smokeless tobacco by cancer site.

Variables	Control	Larynx					Oral cavity					Pharynx				
		Case	OR[1]	95%CI[1]	OR[2]	95%CI[2]	Case	OR[1]	95%CI[1]	OR[2]	95%CI[2]	Case	OR[1]	95%CI[1]	OR[2]	95%CI[2]
Smokeless tobacco use history																
Never	1,200	166	1.00	---	1.00	---	378	1.00	---	1.00	---	445	1.00	---	1.00	---
≥ 20 times	22	3	0.98	0.29, 3.35	0.67	0.19, 2.36	8	1.26	0.55, 2.88	0.90	0.38, 2.12	21	2.09	1.13, 3.88	1.59	0.84, 3.01
Duration of smokeless tobacco use in lifetime (y)																
Never	1,200	166	1.00	---	1.00	---	378	1.00	---	1.00	---	445	1.00	---	1.00	---
> 0 to < 2	10	0	---	---	---	---	2	0.75	0.16, 3.43	0.68	0.15, 3.19	4	0.95	0.29, 3.05	0.84	0.26, 2.74
≥ 2 to <10	19	0	---	---	---	---	6	1.15	0.45, 2.91	0.90	0.34, 2.35	12	1.41	0.67, 2.95	1.07	0.49, 2.32
≥ 10	4	3	5.48	1.20, 24.97	5.35	1.11, 25.68	4	3.41	0.84, 13.83	2.88	0.68, 12.25	9	4.81	1.46, 15.81	4.46	1.33, 14.93
p for trend			0.056		0.09			0.086		0.19		0.008			0.017	
Average frequency of smokeless tobacco use per week (times)																
Never	1,200	166	1.00	---	1.00	---	378	1.00	---	1.00	---	445	1.00	---	1.00	---
> 0 to < 7	19	1	0.38	0.05, 2.84	0.40	0.05, 3.07	4	0.75	0.25, 2.23	0.78	0.26, 2.36	11	1.33	0.62, 2.83	1.32	0.62, 2.84
≥ 7	12	2	1.20	0.26, 5.47	0.74	0.16, 3.47	4	1.17	0.37, 3.68	0.74	0.23, 2.42	15	2.66	1.23, 5.79	1.84	0.82, 4.13
p for trend			0.887		0.652			0.827		0.601			0.013		0.132	
Lifetime numbers of smokeless tobacco use (times/wk*y)																
Never	1,200	166	1.00	---	1.00	---	378	1.00	---	1.00	---	445	1.00	---	1.00	---
> 0 to < 20	16	1	0.45	0.06, 3.41	0.46	0.06, 3.65	1	0.23	0.03, 1.73	0.25	0.03, 1.90	10	1.42	0.64, 3.17	1.45	0.64, 3.26
≥ 20	11	2	1.32	0.29, 6.05	0.92	0.20, 4.33	7	2.25	0.86, 5.89	1.55	0.57, 4.21	15	2.91	1.31, 6.44	2.12	0.93, 4.84
p for trend			0.726		0.913			0.098		0.384			0.009		0.076	

[1]OR adjusted for age and gender.

[2]OR adjusted for age, gender, race (White, non-White), education (3 categories), smoking (continuous), ever smoker, alcohol drinking (continuous).

Table 4

Association of HNSCC with smokeless tobacco among never cigarette smokers.

Variables	Control	Case	OR[1]	95% CI[1]	OR[2]	95% CI[2]
Smokeless tobacco use status						
Never	490	241	1.00	---	1.00	---
≥ 20 times	3	7	5.05	1.27, 20.05	4.21	1.01, 17.57
Duration of smokeless tobacco use in lifetime (y)						
Never	490	241	1.00	---	1.00	---
> 0 to < 10	5	2	0.87	0.17, 4.58	0.78	0.15, 4.13
≥ 10	1	7	15.21	1.84, 125.81	13.21	1.53, 114.46
p for trend			0.011		0.018	
Average frequency of smokeless tobacco use per week (times)						
Never	490	241	1.00	---	1.00	---
> 0 to < 7	5	5	2.17	0.61, 7.70	1.94	0.54, 7.03
≥ 7	1	3	6.50	0.67, 63.50	5.11	0.47, 55.94
p for trend			0.083		0.142	
Lifetime numbers of smokeless tobacco use (times/wk*y)						
Never	490	241	1.00	---	1.00	---
> 0 to < 20	5	3	1.30	0.30, 5.58	1.22	0.29, 5.26
≥ 20	1	5	10.85	1.25, 94.32	9.15	0.97, 86.59
p for trend			0.031		0.053	

[1]OR adjusted for age and gender

[2]OR adjusted for age, gender, race (White, non-White), education (3 categories), smoking (continuous), ever smoker, alcohol drinking (continuous)