Smokeless Tobacco Use, Cigarette Smoking, and Upper Aerodigestive Tract Cancers: A Case-Control Study in the Batna Region, Algeria, 2008-2011

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Messaouda Oudjehih[1,2], Isabelle Deltour[3], Mohamed Larbi Bouhidel[1,2], Atika Bouhidel[1,2], Abdelwahab Marref[2], Véronique Luzon[3], Joachim Schüz[3], Hocine Bouneceur[1] and Maria E Leon[3]

[1]Medical Faculty, Epidemiology and Preventive Medicine Department, University of Batna, Batna, Algeria. [2]Cancer Registry of the Wilaya of Batna, University Hospital of Batna, Batna, Algeria. [3]Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France.

ABSTRACT

BACKGROUND: A significant proportion of the Algerian population uses tobacco products and is at risk of developing tobacco-associated cancers.

AIMS: This case-control study reports on the association between tobacco use and the occurrence of upper aerodigestive tract (UADT) cancers in Batna, Algeria.

METHODS: Incident primary UADT cancer cases in residents of Batna in 2008-2011 were identified using the regional tumor registry. One hospital and 1 population control were matched to each case by sex, year of birth, and residence. Information on tobacco use was collected, and odds ratios (ORs) were obtained using conditional logistic regression also after sex stratification.

RESULTS: The study included 192 cases (80%) of the 241 primary UADT cancer cases identified and 384 controls. Males represented 76.6% of cancer cases. Cancers of the nasopharynx (48%) and the larynx (26%) were the most common types. Ever use of smokeless tobacco (ST) (OR = 1.0; 95% confidence interval [CI]: 0.6-1.5) or current ST use (OR = 1.1; 95% CI: 0.6-1.7) was not associated with overall risk of UADT cancers. Associations with cancers of the nasopharynx (OR = 1.5; 95% CI: 0.5-4.6) and oral cavity/oropharynx (OR = 3.0; 95% CI: 0.8-11.8) were found when comparing use of ST only to no consumption of any tobacco. Cigarette smoking was associated with an increase in the overall risk of UADT cancers, with a 3-fold increase in the risk of laryngeal cancer when comparing smoking only to no consumption of any tobacco (OR = 3.3; 95% CI: 1.0-11.5). Associations for smokers who also consumed ST differed by cancer site.

CONCLUSION: In this study from Algeria dominated by male cases and by cancer in the nasopharynx, cigarette smoking but not ST was associated with UADT cancer. Analyses by anatomical site and using as reference never use of any type of tobacco suggested few associations with ST but of lower precision.

KEYWORDS: Smokeless tobacco, chemma, neffa, smoking, upper aerodigestive tract cancers, Batna, Algeria

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CORRESPONDING AUTHOR: Isabelle Deltour, Section of Environment and Radiation, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France. Email: DeltourI@iarc.fr

Introduction

Article 1 of the WHO Framework Convention on Tobacco Control defines tobacco products as "products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing."[1] In Algeria, *chemma* or *shammah* is the local term for moist snuff, which is placed directly on the gums or rolled in paper and then sucked in the mouth. Algerians also use dry snuff, called *neffa*,[2,3] a product described as a powdered mix containing tobacco leaf, calcium phosphate, and lime, which is sniffed or chewed.

The International Agency for Research on Cancer has classified smokeless tobacco (ST) as carcinogenic, with sufficient evidence that it causes cancers of the oral cavity, esophagus, and pancreas.[4,5] The relationship between ST use and the development of upper aerodigestive tract (UADT) cancers has been investigated in several studies, some with conflicting results for specific anatomical sites.[5-11] The evidence is limited by the low number of studies exploring cancer risk by anatomical site in the UADT, or in the head and neck, in association with ST use, a shortcoming probably explained by the large geographical variation in product composition and inherent health hazard. There are very few studies outside of India reporting on the association of ST use with cancer of the salivary glands, nasopharynx, hypopharynx, sinuses, larynx, and esophagus.[5,7,12]

According to a 2005 Algerian nationwide survey, the prevalence of ST use was 9.5% (21.4% in men and 1.1% in women).[13] The Algeria Adult Tobacco Survey of 2010, with respondents

aged 15 to 74 years, generated an overall national estimate of current ST use of 5.3%, differing markedly between men (9.8%) and women (0.8%), and an overall prevalence of current tobacco smoking of 15.3% (27.1% in men and 1.7% in women). Daily smoking was reported by 17.6% of men and 0.9% of women.[14] Thus, a significant proportion of the Algerian population uses tobacco regularly, including noncombustible forms, and is at risk of developing tobacco-associated cancers.

Objective

The objective of this study was to report on the relationship between ST use, cigarette smoking, and the occurrence of UADT cancers in the *wilaya* of Batna in 2008-2011 using a case-control design.

Methods

Study population

Cancer cases. The *wilaya* of Batna is an administrative region with an area of 12 000 km^2, located in the east of Algeria (latitude 35-36°N, longitude 4-7°E), with a population of 1 140 000 (2008 estimate) and the capital city of Batna. All patients, without age restrictions, who resided in the *wilaya* of Batna for at least 6 months and had been diagnosed with a primary UADT cancer between January 1, 2008, and December 31, 2011, were eligible to participate. The diagnosis was confirmed pathologically in cases using the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10) codes C00-C14 and C30-C32. All histological subtypes were included. Case identification was performed retrospectively for 2008-2009 and prospectively for 2010-2011. The Cancer Registry of the Wilaya of Batna was responsible for identifying incident cancers and for collecting demographic and histopathological data needed for the study. This population-based tumor registry, associated with the University Hospital of Batna, has been recording cancer cases for the population in the *wilaya* of Batna since 1995.

Information on cancer cases occurring in residents of the region of Batna who are diagnosed and treated elsewhere is obtained periodically by the registry through close collaboration with individual public and private health facilities outside of Batna. To avoid selective survival bias, deceased primary UADT cancer cases diagnosed in 2008-2011 were also included (n = 53). Patients with recurrence or metastasis and those whose primary tumor was diagnosed outside the study period were not eligible.

Controls. Two types of controls were matched to each case to assess potential selection effect that could have been associated to recruitment method. Hospital controls enrolled in the region's hospitals were matched to cases by primary care center, sex and year of birth (± 5 years) among patients with eye diseases, or trauma, or those treated in the obstetric department of the 6 hospitals (the University Hospital of Batna and the hospitals of Arris, N'Gaous, Merouana, Barika, and Aïn Touta; see hospitals' locations on Supplemental Appendix Figure 1). The first patient who met the age and sex criteria of the case was interviewed.

The second control was selected from the general population by a random draw from the electoral roll of the Batna region for subjects older than 18 years. Controls younger than 18 years were drawn from the lists of pupils of the Algerian Education and Teaching Directorate. This was necessary because 2 cases younger than 18 years were included. The population controls were matched by sex, year of birth, and municipality of residence.

A total of 192 hospital controls and 192 population controls were interviewed, equal to the number of cases. Population controls who had moved since the last update of the electoral roll, worked far away from their residential address, or refused to participate in the study were replaced. Overall, the identification of 289 population controls, including those with out-of-date addresses, working far away from their residence, and refusals, was necessary to interview 192 controls.

Data collection and consent procedure. Interviews with cases were conducted between 2010 and 2012 at the hospital or at home, and interviews with controls were conducted in 2011 and 2012 at the hospital (hospital controls) or most often at home (population controls). Information on lifestyle factors was collected during a 30- to 45-minute face-to-face interview. Proxy interviews were conducted for 80 subjects, more often in cases (n = 62) than in controls (n = 18), especially for cases who had died and for controls who were not at home when the interviewer visited (9% of controls). Respondents in the study were informed of a generic research question to avoid influencing their replies, and for the same reason, interviews in presence of the interviewee and a proxy only occurred for illiterate cases who were unable to speak after tumor resection (especially oral cavity and laryngeal cancer cases), and for interviews of minors during which a parent was present. All interviews were conducted by the same person (M.O.) after obtaining oral consent from the subject or the parents for minors. Oral consent was collected in line with norms for locally conducted research when a large proportion of the study population is illiterate, because it seemed inappropriate to ask prospective participants to sign a document that they could not read and did not know how to sign. The study was approved by the Scientific Council of the Medical Faculty of the University of Batna, including the use of oral consent, on April 17, 2008. The approval or refusal to participate was documented in the study database.

Questionnaire

The questionnaire was developed on the basis of existing and validated questionnaires from previous studies.[3,15,16] Besides demographic data, ever snuff users and ever cigarette smokers

were defined as subjects who had consumed ⩾100 g of snuff and smoked ⩾100 cigarettes, respectively, during their lifetime. Former users were those who had quit at least 1 year before the date of cancer diagnosis in cases. This date was used as a reference to assess former tobacco use status in matched controls. History of tobacco use was assessed, including age at which snuffing or smoking was initiated, type of snuffing or smoking, average number of grams of snuffing and average number of cigarettes per day, time since stopping, and duration of the habit in years. History of alcohol consumption recorded age at which drinking was initiated.

Data analysis

Exposure-effect relationships were reported on the basis of tobacco use status and duration of use, mean number of grams of ST used per day, and pack-years of cigarette smoking. The measures of association between exposure to various risk factors and cancers of the UADT overall were estimated including several subsites: nasopharynx (C11), oral cavity and oropharynx (C00-C06, C09, and C10), larynx (C32), and other UADT sites (C07, C08, C12, C13, C14, C30, and C31).

We performed conditional logistic regression analyses for matched sets to estimate odds ratios (OR) and their 95% confidence intervals (CI), combining the 2 control groups. We adjusted for potential confounders, namely ethnicity, education level, alcohol consumption, and mutually adjusted cigarette smoking status and ST use status. In subsite analyses, the reference group was never users of any form of tobacco. In sensitivity analyses, we repeated the main analyses comparing cases to hospital controls and cases to community controls separately, we conducted sex-specific subsite analyses, and analyses of nasopharyngeal cancer (NPC) with additional adjustment on consumption of rancid fat because its consumption has been associated with this cancer in Algeria.[3,17]

Results

In total, 241 primary UADT cancer cases were identified, of which 192 were interviewed (80% participation rate). Nonresponse among cases was due to unknown address (n = 46) and refusals to participate (n = 3). The overall participation rate among population controls was 66%. Table 1 shows the characteristics of the study population.

We noted that the majority of the participants were either illiterate (49%) or poorly educated (32%). Subjects with all 4 grandparents of Berber origin accounted for nearly 65% of the study sample in cases and controls. The distribution of characteristics was the same in hospital controls and in population controls, except for alcohol consumption which was significantly more commonly reported by population controls than hospital controls (Table 1). Among male controls, ever ST use was not associated with smoking (36.8 % ever ST users among never smokers and 42.4% among ever smokers, chi-square *P* value = 0.3). However, smokers who ever consumed ST had used ST for shorter durations (25 years on average) than exclusive ST users (38 years on average, *t*-test *P* value < .0005) and smokers had more often stopped ST consumption (87% former ST users among ever smokers vs 12% former ST users among never smokers, chi-square *P* value < .0005). Women consumed very little tobacco, with six women only who reported ST use and 1 who reported smoking and ST use.

A total of 139 cancer cases (72%) were alive at the time of the interview (Table 2). Cancers of the nasopharynx were the largest group (48%), followed by cancers of the larynx (26%) and of the oral cavity and oropharynx (19%). Differentiated cell carcinoma was the most common histological type (59%), followed by undifferentiated cell carcinoma (32%). Cases were interviewed from the entire study region (Supplemental Appendix Figure 1).

Ever ST use was not associated with risk of UADT cancers (OR = 1.0; CI: 0.6-1.5) (Table 3). No differences in risk were observed with increasing duration of use or consumption.

We observed indications of an increase in the risk of UADT cancers with current smoking (OR = 1.4; CI: 0.8-2.4) and with increasing duration (20-40 years: OR = 1.2; CI: 0.6-22.; > 40 years: OR = 1.7; CI: 0.9-3.2) (Table 4). We observed an increased risk of UADT cancers only with the largest smoking intensity and with exposure of >27 pack-years compared with never smokers. However, there was a reduction in risk with a duration of <20 years of smoking (OR = 0.5; CI: 0.2—1.0), with exposure of <10 pack-years (OR = 0.5; CI: 0.2-0.9), and with >15 years since stopping smoking compared with current smokers (OR = 0.4; CI: 0.2-0.9) (Table 4).

Table 5 shows ORs by cancer subsite in association with ST use and with cigarette smoking and by histology, in the nasopharynx. The associations did not appear to be the same in all UADT cancer sites; nevertheless, the OR tended to be similar for ST users who smoked compared with smokers who never consumed ST, except for laryngeal cancers. We observed an increase in the risk of NPC (Table 5) and of oral cavity cancer (Table 5) in exclusive ST users versus never consumers of tobacco, although neither estimate was statistically significant. Smoking was not associated with the risk of NPC overall (Table 5), and neither was it associated with the risk of oral cavity cancer (Table 5). For laryngeal cancer, exclusive use of ST was associated with a nonstatistically significant OR below 1, based on 1 exposed case, whereas the risk of laryngeal cancer in exclusive smokers was 3.3 (95% CI: 1.0-11.5) compared with the small group of never tobacco-consumers (6 cases had never consumed tobacco) (Table 5). While numbers were too small for the analysis of differentiated nasopharyngeal cancer (Table 5), results for undifferentiated NPC were similar to the whole group (Table 5). Sensitivity analyses comparing cases to either the hospital controls or the community controls did not show major differences from the main results (data not shown in tables). Overall results were derived from the male population (Supplemental Appendix Table 1) suggesting an association between ST use and overall UADT cancer (OR = 1.3; 95%

Table 1. Characteristics of the study population in the case-control study of upper aerodigestive tract cancers in Batna, Algeria, 2008-2011.

CHARACTERISTIC	CASES		HOSPITAL CONTROLS		COMMUNITY CONTROLS		*P* VALUE[a]
	N = 192		N = 192		N = 192		
	N	%	N	%	N	%	
Sex							matched
Male	147	76.6	147	76.6	147	76.6	
Female	45	23.4	45	23.4	45	23.4	
Age at interview (years)[b]							
Average	57.2		57.4		57.9		matched
Standard Deviation	16.8		17.0		16.8		
Range	11-94		14-97		12-95		
Education level							.95
Illiterate	96	50.0	95	49.5	92	47.9	
Primary/junior	60	31.3	63	32.8	64	33.4	
Secondary/university	36	18.7	34	17.7	36	18.7	
Marital status							.70
Married	158	82.3	152	79.2	157	81.8	
Single	23	12.0	22	11.5	17	8.9	
Divorced/widowed	11	5.7	18	9.4	18	9.4	
Ethnicity							.85
Berber	125	65.1	122	63.5	126	65.6	
Arab	54	28.1	55	28.6	50	26.0	
Mix[c]	13	6.8	15	7.8	16	8.3	
Longest occupation							.58
Worker	108	56.2	112	58.3	108	56.2	
Farmer/artisan	19	9.9	11	5.7	18	9.3	
Intellectual/professional	32	16.6	34	17.7	39	20.3	
Retired/unemployed	31	16.1	32	16.6	26	13.5	
Unknown	2		1		1		
Use of smokeless tobacco							.24
Never	134	69.7	124	64.5	139	72.3	
Former	26	13.5	32	16.6	27	14.0	
Current	32	16.6	36	18.7	26	13.5	
Smokeless tobacco types							
Industrial, sucked							.55
Never	151	78.6	143	74.5	148	77.1	
Ever	41	21.4	49	25.5	44	22.9	
Artisanal, sucked							.19
Never	170	88.5	173	90.1	180	93.8	

(Continued)

Table 1. (Continued)

CHARACTERISTIC	CASES		HOSPITAL CONTROLS		COMMUNITY CONTROLS		*P* VALUE[a]
	N = 192		N = 192		N = 192		
	N	%	N	%	N	%	
Ever	22	11.5	19	9.9	12	6.2	
Industrial, snuff							.09
Never	186	96.9	179	93.2	187	95.8	
Ever	6	3.1	13	6.8	5	2.6	
Artisanal, snuff							.25
Never	190	99.0	189	98.4	192	100.0	
Ever	2	1.0	3	1.6	0	0.0	
Smoking							.10
Never	83	43.2	84	43.8	85	44.3	
Former	58	30.2	75	39.1	59	30.7	
Current	51	26.6	33	17.2	48	25.0	
Alcohol consumption							.02
Never	162	84.4	167	87.0	149	77.6	
Ever	30	15.6	25	13.0	43	22.4	
Consumption of rancid fat							.10
Never	56	29.5	42	21.9	56	29.2	
Ever	136	70.5	150	78.1	136	70.8	
Respondents							.15
Proxy respondents	62	32.3	6	3.1	12	6.3	

[a]Chi-square or Fisher exact test comparing hospital and population controls.
[b]Information missing for 3 cases and 3 hospital controls.
[c]At least 1 Arab grandparent and 1 Berber grandparent.

CI: 0.6-3.1) of similar magnitude as that seen with smoking (OR = 1.3; 95% CI: 0.7-2.4) (Supplemental Appendix Table 1). The previously seen association between ST and oral cancer disappeared when considering males exclusively (27 of 37 cases). In women, an increased risk of UADT for ever tobacco consumption was found (OR = 3.5; 95% CI: 0.6-18.5) (Supplemental Appendix Table 2). In analyses of NPC, additional adjustment for rancid fat consumption did not modify the associations (data not shown in tables).

Discussion

Our study in Algeria is representative of all primary incident UADT cancers diagnosed in the *wilaya.* Notably, the cancer subsites included were a priori hypothesized to be most exposed to ST, and we did not only include anatomical sites known to be associated with ST use or with smoking.[18-20]

Most of the UADT cancer cases occurred in men. With the exception of 1 female case, all laryngeal cancers were diagnosed in men. For the other cancer sites, more than two thirds were male cases. This is in contrast to more developed countries, where more and more women are being diagnosed with these types of cancers, with the exception of nasopharyngeal cancer, which is rare in Europe and North America.[21,22]

In our study, ever or current use of ST was not associated with overall risk of UADT cancer. No trends of increasing risk were detected with duration or intensity of ST use. The most commonly affected UADT site was the nasopharynx. We observed a nonsignificant association between exclusive ST use and NPC, compared with never users of tobacco, based on small numbers. In a study from the Maghreb, Feng et al[3] showed that snuff sucking was associated with an increased risk of differentiated NPC but not of undifferentiated carcinoma.

This study provides some evidence of an association between ST use and oral cavity cancers after adjusting for cigarette smoking and alcohol consumption, based on small numbers. ST use has previously been linked with the risk of

Table 2. Description of cancer cases in the study of upper aerodigestive tract cancers in Batna, Algeria, 2008-2011.

CHARACTERISTIC	NASOPHARYNGEAL CANCER[a]	ORAL CAVITY CANCER[b]	LARYNGEAL CANCER[c]	OTHER UADT CANCERS[d]	TOTAL
	N = 92	N = 37	N = 50	N = 13	N = 192
	N (%)	N (%)	N (%)	N (%)	N (%)
Sex					
Male	63 (68.5)	27 (73.0)	49 (98.0)	8 (61.5)	147 (76.6)
Female	29 (31.5)	10 (27.0)	1 (2.0)	5 (38.5)	45 (23.4)
Age at diagnosis (years)					
Average (Standard Deviation)	48.7 (15.8)	65.0 (15.3)	62.3 (12.3)	49.7 (21.6)	55.4 (16.9)
Range	10-86	28-94	33-86	19-81	10-94
Distribution of age at diagnosis (years)[e]					
0-19	7 (7.9)	0 (0.0)	0 (0.0)	1 (7.7)	8 (4.3)
20-39	13 (14.6)	2 (5.6)	2 (4.2)	4 (30.8)	21 (11.3)
40-59	47 (52.8)	12 (33.3)	17 (35.4)	3 (23.1)	79 (42.5)
60-79	20 (22.5)	16 (44.4)	25 (52.1)	4 (30.8)	65 (34.9)
80+	2 (2.2)	6 (16.7)	4 (8.3)	1 (7.7)	13 (7.0)
Vital status					
Alive	69 (75.0)	29 (78.4)	34 (68.0)	7 (53.8)	139 (72.3)
Dead	23 (25.0)	8 (21.6)	16 (32.0)	6 (46.2)	53 (27.6)
Histology					
Squamous cell carcinoma, differentiated	22 (23.9)	36 (97.3)	47 (94.0)	9 (69.2)	114 (59.3)
Nonkeratinizing cell carcinoma, undifferentiated	61 (66.3)	0 (0.0)	0 (0.0)	1 (7.7)	62 (32.2)
Other histological types	3 (3.3)	0 (0.0)	0 (0.0)	3 (23.1)	6 (3.1)
Unknown[f]	6 (6.5)	1 (2.7)	3 (6.0)	0 (0.0)	10 (5.2)
Year of diagnosis					
2008	21 (22.8)	11 (29.7)	13 (26.0)	5 (38.5)	50 (26.4)
2009	29 (31.5)	5 (13.5)	11 (22.0)	1 (7.7)	46 (23.9)
2010	22 (23.9)	14 (37.8)	12 (24.0)	4 (30.8)	52 (27.0)
2011	20 (21.7)	7 (18.9)	14 (28.0)	3 (23.1)	44 (22.9)

[a]Nasopharyngeal cancer: ICD-10 code C11; any morphology code.
[b]Oral cavity cancer: ICD-10 codes C00-C06, C09, and C10; any morphology code.
[c]Laryngeal cancer: ICD-10 code C32; any morphology code.
[d]Other cancers: ICD-10 codes C07, C08, C12, C13, C30, and C31; any morphology code.
[e]Information missing for 1 oral cavity, 3 nasopharyngeal, and 2 laryngeal cancer cases.
[f]Information could not be obtained.

premalignant lesions in the oral cavity and with an excess risk of oral cancers.[5]

We unexpectedly observed a reduced risk of laryngeal cancer in exclusive ST users versus never users of tobacco, which could be associated with statistical fluctuations associated to the small sample size in the reference and the exclusive ST user group or with recall bias, especially in view of the relatively higher proportion of proxy interviews of deceased cases. However, the larynx is a site for which conflicting results have been reported in association with ST use. The study of Sapkota et al[18] did not find an association between laryngeal cancer and ST use in India, while a recent meta-analysis including studies in India reported a nonsignificant increase in risk (OR = 1.79; CI: 0.70-4.54).[7] Given the differences in the types of products

Table 3. Smokeless tobacco use and risk of upper aerodigestive tract cancers; odds ratios (ORs) and 95% confidence intervals (95% CIs) obtained using conditional logistic regression analyses, Batna, Algeria, 2008-2011.

CHARACTERISTIC	CASES		CONTROLS		CRUDE OR[a]		ADJUSTED OR[b]	
	N	%	N	%	OR	95% CI	OR	95% CI
Smokeless tobacco use								
Never	134	69.8	263	68.5	1		1	
Ever	58	30.2	121	31.5	0.9	0.6-1.4	1.0	0.6-1.5
Current status of smokeless tobacco use								
Never	134	69.8	263	68.5	1		1	
Former	26	13.5	59	15.4	0.8	0.5-1.4	0.9	0.5-1.6
Current	32	16.7	62	16.1	1.0	0.6-1.6	1.1	0.6-1.7
Duration of smokeless tobacco use (years)								
Never	134	71.2	263	68.7	1		1	
<20	23	12.3	40	10.4	1.1	0.6-1.9	1.2	0.7-2.2
20-40	14	7.5	42	11.0	0.6	0.3-1.2	0.6	0.3-1.3
>40	16	8.6	38	9.9	0.8	0.4-1.5	0.8	0.4-1.5
Unknown	5		1		—		—	
Smokeless tobacco consumption (g/day)								
Never	134	72	263	68.7	1		1	
<7	18	9.7	40	10.4	0.9	0.5-1.6	0.9	0.5-1.7
7-15	17	9.1	41	10.7	0.8	0.4-1.4	0.8	0.4-1.5
>15	17	9.2	39	10.2	0.8	0.4-1. 6	0.9	0.5-1.7
Unknown	6		1		—		—	
Types of smokeless tobacco								
Never	134	69.8	263	68.5	1		1	
Exclusively industrial	35	18.2	87	22.7	0.8	0.5-1.2	0.8	0.5-1.3
Artisanal with or without industrial	23	12.0	34	8.9	1.3	0.7-2.4	1.4	0.7-2.6

[a]Crude ORs obtained from the conditional logistic regression analyses for matched sets.
[b]Adjusted ORs were additionally adjusted for cigarette smoking, education level, alcohol consumption, and ethnicity.

available, patterns of use, and associated risks, there may be substantial differences between regions and countries in the burden of laryngeal cancer attributable to ST use.

Ever and current cigarette smoking were associated with a modest increase in the overall risk of UADT cancers in the *wilaya* of Batna, although the ORs were not statistically significant. While the ORs tended to be higher in association with the longest duration of smoking or the highest number of cigarettes smoked daily, the trend of increasing risk with increasing exposure was seen only with cumulative exposure in pack-years. In agreement with the established reduction in risk after quitting smoking,[23] former smokers with >15 years of abstinence had a reduced risk of UADT cancers. We observed a decreased risk of UADT cancers in association with exposure of <10 pack-years of cigarette smoking and with smoking duration of <20 years. These reduced risks for the lowest categories of the smoking metrics might be due to recall or reporting bias from inaccurate disclosure of smoking status of cases classified as never smokers, inaccurate reporting of duration and intensity of smoking among light smokers, a complex relationship with ST, lacking or insufficient adjustment for additional risk factors, or random fluctuation due to small numbers.

Although smoking is recognized as a cause of NPC,[5] we did not detect an association between smoking and risk of NPC, overall or for the undifferentiated carcinoma type in this

Table 4. Cigarette smoking and risk of upper aerodigestive tract cancers; odds ratios (ORs) and 95% confidence intervals (95% CIs) obtained using conditional logistic regression analyses, Batna, Algeria, 2008-2011.

CHARACTERISTIC	CASES		CONTROLS		CRUDE OR[a]		ADJUSTED OR[b]	
	N	%	N	%	OR	95% CI	OR	95% CI
Cigarette smoking status								
Never	83	43.2	169	44.0	1		1	
Ever	109	56.8	215	56.0	1.0	0.7-1.7	1.1	0.7-1.8
Current status of cigarette smoking								
Never	83	43.2	169	44.0	1		1	
Former	58	30.2	134	34.9	0.9	0.5-1.5	0.9	0.5-1.5
Current	51	26.6	81	21.1	1.3	0.8-2.2	1.4	0.8-2.4
Duration of cigarette smoking (years)								
Never	83	43.5	169	44.0	1		1	
<20	20	10.5	74	19.3	0.5	0.3-1.0	0.5	0.3-1.0
20-40	50	26.2	89	23.2	1.1	0.6-2.0	1.2	0.6-2.2
>40	38	19.9	52	13.5	1.6	0.9-3.0	1.7	0.9-3.2
Unknown	1							
Intensity of smoking (cigarettes per day)								
Never	83	45.4	169	44.1	1		1	
0-9	18	9.8	67	17.5	0.5	0.3-1.1	0.5	0.3-1.0
10-20	42	23.0	96	25.1	0.9	0.5-1.6	0.9	0.5-1.6
>20	40	21.9	51	13.3	1.6	0.8-2.6	1.8	0.9-3.3
Unknown	9		1					
Cigarette smoking exposure (pack-years)								
Never	83	45.4	169	44.1	1		1	
<10	17	9.3	66	17.2	0.5	0.2-1.0	0.5	0.2-0.9
10-27	22	12.0	71	18.5	0.6	0.3-1.2	0.6	0.3-1.2
>27	61	33.3	77	20.1	1.7	0.9-2.9	1.8	1.0-3.3
Unknown	9		1					
Age at starting cigarette smoking (years)								
Never	83	44.1	169	44.1	1		1	
<14	23	12.2	49	12.8	0.6	0.3-1.2	1.0	0.5-1.9
14-23	73	38.8	136	35.5	0.7	0.4-1.4	1.0	0.6-1.8
>23	9	4.8	29	7.6	1.3	0.7-2.2	0.5	0.2-1.4
Unknown	4		1					
Time since cigarette smoking cessation (years)								
Current smoker	51	26.6	81	21.1	1		1	
⩽15	38	19.8	58	15.1	1.0	0.5-1.8	1.1	0.6-2.1
>15	20	10.4	76	19.8	0.4	0.2-0.8	0.4	0.2-0.9

[a]Crude ORs obtained from the conditional logistic regression analyses for matched sets.
[b]Adjusted ORs were additionally adjusted for smokeless tobacco use status, education level, alcohol consumption, and ethnicity.

Table 5. Smokeless tobacco use, cigarette smoking, and risk of site-specific UADT cancers; odds ratios (ORs) and 95% confidence intervals (95% CIs) obtained using conditional logistic regression analyses, Batna, Algeria, 2008-2011: nasopharynx, oral cavity/oropharynx, larynx, differentiated nasopharynx, and undifferentiated nasopharynx cancers.

TOBACCO USE	CASES	%	CONTROLS	%	CRUDE OR[a]	95% CI		ADJUSTED OR[a]	95% CI	
Nasopharyngeal cancer (all, N = 276)										
Never	42	46	83	45	1.0			1		
Ever cigarette smoker, never smokeless tobacco user	26	28	59	32	0.8	0.4	–1.8	0.8	0.3	–1.8
Never cigarette smoker, ever smokeless tobacco user	10	11	11	6	1.8	0.6	–5.2	1.5	0.5	–4.6
Cigarette smoker and smokeless tobacco user	14	15	31	17	0.8	0.3	–2.1	0.7	0.3	–2.0
Oral cavity cancer (N = 111)										
Never	10	27	26	35	1.0			1		
Ever cigarette smoker, never smokeless tobacco user	9	24	20	27	1.2	0.3	–4.7	1.3	0.3	–5.4
Never cigarette smoker, ever smokeless tobacco user	8	22	8	11	2.9	0.8	–11.2	3.0	0.8	–11.8
Cigarette smoker and smokeless tobacco user	10	27	20	27	1.4	0.4	–5.0	1.4	0.3	–5.9
Laryngeal cancer (N = 150)										
Never	6	12	20	20	1.0			1		
Ever cigarette smoker, never smokeless tobacco user	31	62	36	36	3.6	1.1	–11.9	3.3	1.0	–11.5
Never cigarette smoker, ever smokeless tobacco user	1	2	8	8	0.4	0.0	–4.3	0.3	0.0	–3.5
Cigarette smoker and smokeless tobacco user	12	24	36	36	1.4	0.4	–4.6	1.3	0.4	–4.5
Nasopharyngeal cancer of differentiated cell carcinoma type[b] (N = 66)										
Never	7	32	15	34	1.0			—[c]		
Ever cigarette smoker, never smokeless tobacco user	8	36	16	36	1.5	0.1	–15.7	—		
Never cigarette smoker, ever smokeless tobacco user	2	9	4	9	1.4	0.1	–20.8	—		
Cigarette smoker and smokeless tobacco user	5	23	9	20	1.6	0.1	–19.1	—		
Nasopharyngeal cancer of undifferentiated cell carcinoma type[b] (N = 183)										
Never	30	49	61	50	1.0			1		
Ever cigarette smoker, never smokeless tobacco user	17	28	36	30	0.9	0.3	–2.4	0.7	0.3	–2.0
Never cigarette smoker, ever smokeless tobacco user	5	8	5	4	2.1	0.5	–8.7	1.8	0.4	–8.2
Cigarette smoker and smokeless tobacco user	9	15	20	16	0.9	0.3	–2.9	0.6	0.2	–2.0

[a]Crude ORs obtained from the conditional logistic regression analyses for matched sets, and adjusted ORs were additionally adjusted for education level, alcohol consumption, and ethnicity.
[b]Three cases of nasopharyngeal lymphoma and 6 cases with unknown histology were not included.
[c]No reliable estimate available due to small numbers.

population of mainly Berber ethnicity. Few studies have reported epidemiological findings of NPC by histology in association with smoking.[24,25] In the study of Polesel et al[25] in a low-risk population, current smoking was associated with a nonsignificant increase of overall NPC, while an increased risk was observed for differentiated NPC. In one study from the Maghreb, a region of intermediate NPC incidence,[26] Feng et al[3] reported a similar pattern in populations of predominantly Arab ethnicity. Two meta-analyses found a stronger association with smoking in low-risk populations and with differentiated NPC than with undifferentiated NPC.[20,27] However, NPC has been associated with smoking-related reactivation of Epstein-Barr virus infection in China, an area with high NPC incidence, in a study of almost exclusively undifferentiated carcinomas.[28,29] The lack of an effect of smoking on NPC risk in the current study may be due to possible different etiologies for the 2 histological types, with smoking being more strongly associated with the histology less prevalent in our NPC population. Socioeconomic differences between cases and controls not accounted for entirely by education level, such as income, may have also played a role in the results we observed. Our findings point to the importance of separating undifferentiated and differentiated NPC in analyses exploring exposure to tobacco with larger samples.

Our study detected a modest increase in the risk of oral cancer with smoking albeit nonsignificant in this population consuming very little alcohol. We found a marked increase in the risk of laryngeal cancer with ever smoking after adjusting for alcohol consumption, education level, and ethnicity. The magnitude of the association is lower than risk estimates obtained in countries on other continents.[5] Lower level of alcohol consumption and intensity and duration of smoking may account for differences in the strength of the association we report in our study.

This is the first case-control study in Algeria investigating UADT cancers and the use of ST as marketed and consumed in the *wilaya* of Batna. The use of ST is a rooted tradition in Algeria, particularly in men. This study benefited from the collection of detailed information on other risk factors, such as alcohol consumption; this made it possible to adjust for this risk factor for UADT cancers, which is also associated with ST use and tobacco smoking. Our study is based on a high response rate in both cases and controls.

Despite the strengths of this study, it has limitations: the small number of cases by UADT subsite conditioned our analysis because the statistical power to assess the effects of ST use was low when anatomical subsites were analyzed; therefore, it was not feasible to completely disentangle if ST use was a primary or secondary factor compared with smoking for the various cancers studied. Due to its retrospective nature, the possibility of recall bias and uncertainties in exposure assessment also remained. Population controls are preferable to hospital control but this study design complicates the data collection. In our study, the risk factor profile of hospital controls was in between that of cases and population controls and only small differences between the series of controls were apparent; these are unlikely to have played a major role in the findings. Interviews were conducted face to face and as far as possible in person, avoiding the presence of another person, to attempt to limit reporting biases in culturally sensitive lifestyle habits such as alcohol consumption or smoking for women. Accuracy of reporting could have been affected by interviewing proxy respondents. However, it should be noted that the study questionnaire was presented to participants as part of a general health study, and for many of the associations explored, the distribution of the factors was similar in both cases and controls.

Cancer is an increasing public health problem in the Algerian population. UADT cancers tend to be diagnosed at an advanced stage, highlighting the importance of educating the general population about the harmful effects of ST use and tobacco smoking, even in the presence of other risk factors. The effectiveness of prevention depends partially on the identification of the risk factors that may be involved locally in the occurrence of cancer. In our study, ST use was suggestive of an increased risk of oral cancer and of NPC, and an increased risk of UADT cancers was observed with the longest duration and cumulative exposure to smoking, with a 3-fold increase in the risk of laryngeal cancer. These findings deserve follow-up in locally conducted larger case-control studies. Characterization of the diversity and composition of locally available ST products would be relevant to etiological studies and also provide useful evidence to advocate for healthier, tobacco-free lifestyles.

Conclusion

While ST use was not associated with overall risk of UADT cancers, associations with cancers of the nasopharynx and the oral cavity/oropharynx were obtained. This study suggests that the association between ST use, cigarette smoking, and UADT cancers differed among the nasopharynx, larynx, and oral cavity and oropharynx anatomical sites, but numbers for subsites were small.

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Author Contributions

MO and HB designed the study in collaboration with ID and JS. MEL and MO conducted the field work in collaboration with MLB, AB. AM, MO and VL performed the data management. MO performed the statistical analyses in collaboration with ID and JS. MEL and MO wrote the first draft of the manuscript. All authors commented on the manuscript and read and approved the final version.

ORCID iDs

Isabelle Deltour https://orcid.org/0000-0002-6602-6292
Joachim Schüz https://orcid.org/0000-0001-9687-2134

Supplemental Material

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