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Assessment of risk factors for oral leukoplakia in West Virginia

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Abstract – Objective: To assess risk factors associated with oral leukoplakia in a US population with high use of smoked tobacco and smokeless tobacco. *Methods:* The RJ Gorlin Leukoplakia Tissue Registry was used to identify individuals with oral leukoplakia in West Virginia, USA. This case–control study consisted of 90 cases with oral leukoplakia and 78 controls with periapical cysts. Univariate–univariable (one dependent variable and one independent variable) and univariate–multivariable (one dependent variable and multiple independent variables) logistic regression modeling quantified the association between oral leukoplakia and potential explanatory variables. *Results:* Unadjusted measures of association indicate that those with oral leukoplakia were more likely to be older [odds ratio of crude: $OR_{Crude} = 2.72$; 95% confidence interval (CI): 1.45–5.11], more likely to currently use smokeless tobacco ($OR_{Crude} = 3.16$; 95% CI: 1.10–9.07), and more likely to currently use snuff ($OR_{Crude} = 8.32$; 95% CI: 1.83–37.80). Individuals currently using smokeless tobacco or currently using snuff were more likely to have oral leukoplakia [adjusted odds ratio, $OR_{Adj} = 9.21$ and 30.08; 95% CI: 1.49–57.00 and 2.67–338.48, respectively], after simultaneously adjusting for age, gender, currently using smoked tobacco, currently using alcohol daily, and dental prostheses use. *Conclusions:* Generalizability is an issue when studying risk factors associated with oral leukoplakia because of geographical variations in the composition of smokeless tobacco (i.e. betel, lime, ash, and *N*-nitrosamines) and cultural variations in the use of tobacco (i.e. reverse smoking). Snuff was the main smokeless tobacco product currently used in West Virginia, and was strongly associated with oral leukoplakia, after adjusting for potential explanatory variables.

Key words: case control; oral leukoplakia; risk assessment; smokeless tobacco; tobacco

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Oral leukoplakia is a white patch on the oral mucosa that represents approximately 85% of all oral precancers or 'potentially malignant lesions' and affects approximately 3% of adults in Western populations (1–3). Clinicopathologic and follow-up studies have reported an overall 4% malignant transformation rate, with certain clinical subtypes showing rates as high as 47% (2–5). A recent study reported oral cancer developed in 31% of the patients with oral leukoplakia during an average of 80 months of follow-up, and that only patients with the genetic instability marker of aneuploidy died of oral cancer (5).

One of the limitations of the oral leukoplakia literature is the decided lack of large US etiologic investigations using a control group. Almost all leukoplakia epidemiologic investigations are simple prevalence studies of the proportion of affected individuals from regions with a high prevalence of oral cancer, such as India and Southeast Asia where the most common cancer is oral cancer (6). Investigations of the risk factors for oral leukoplakia are not without equivocal results for heavy and chronic tobacco use (smoked tobacco and smokeless tobacco), heavy and chronic alcohol use, chronic trauma or irritation, chronic infection, and the use of certain oral hygiene products (2–21). The inconclusive results from studies of risk factor assessments may be due in part to the use of a clinical definition of oral leukoplakia, which is

based on exclusions. Thus, it is problematic when comparing results from studies with no specific inclusion criteria for the case definition. Recent studies have addressed this by using a well-defined histopathology case definition (15, 21).

Chronic smoked tobacco use, especially, has been associated with oral leukoplakia in countries with high prevalence of oral cancer and with smoking behaviors that are not so common in the US, including reverse smoking, i.e. smoke with the lit end of the cigarette in their mouths (7), and smoking bidi and cigarettes without filters (20, 22). The few epidemiologic studies of the US population, conversely, have found no association between oral leukoplakia and smoked tobacco use (19, 21), although adult US males currently using smokeless tobacco were 42 times more likely to have oral leukoplakia than non-users (23). The inclusion of smokeless tobacco keratoses in leukoplakia investigations in the United States and Scandinavia probably explains why most oral leukoplakia lesions in these studies disappeared with cessation of smokeless tobacco use (23, 24).

Smoked and smokeless tobacco habits vary around the world, with quite different risks of inducing oral cancer and precancer (6, 25). The geographical variation in oral cancer and precancer may be because of the differences in the composition of smokeless tobacco such as the inclusion of tobacco leaves with carbonate of lime, ash, betel nut, etc. and because of the differences in tobacco habits such as reverse smoking in the areas with high oral cancer rates. For example, reverse smoking resulted in substantial increases in the incidence of oral leukoplakia, with a 2.6 to 5.7-fold increase in men, and a 55.5 to 373.3-fold increase in women in India (7). As an additional example of the different chemical composition of moist snuff, the levels of tobacco specific *N*-nitrosamines was 2.8–7.5 μg/g in Sweden products, compared with 17–128 μg/g in US products (26). Hence, the results of studies on the risk factors associated with oral leukoplakia may not be applicable to all populations worldwide. This issue is known as external validity, or generalizability of the results to populations other than the study population (27).

The aim of the present study was to assess risk factors associated with oral leukoplakia in the high-risk US population of West Virginia where the use of smoked tobacco and smokeless tobacco routinely ranks extremely high compared with the other states (28). This addresses the external validity issue when attempting to apply results from other areas in the world to the US, when the composition of smokeless tobacco and tobacco habits are different from that found in the US. The objective of the investigation was to assess the association of oral leukoplakia with ever, current, former, and never use of smokeless tobacco or smoked tobacco, current daily alcohol use, and use of dental prostheses among the rural population of West Virginia, USA.

Material and methods

Study population and description of the dependent variable

This investigation was approved by the West Virginia University Institutional Review Board. We conducted a case–control study of the West Virginia population, from September 2001 to March 2002. The dichotomous dependent variable was coded as case or control. Cases diagnosed with oral leukoplakia were identified through the R.J. Gorlin Leukoplakia Tissue Registry at the Maxillofacial Center for Education and Research, Morgantown, West Virginia. The case definition of oral leukoplakia was based on the international classification of diseases, 9th revision code (ICD-9) of 528.6 with a biopsy of hyperkeratosis with or without epithelial atypia or dysplasia. Biopsies were excluded that had a clinical diagnosis of smokeless tobacco keratosis or frictional keratosis, similar to the histopathology case definition of previous studies (15, 21). Controls were also identified through the same surgical pathology biopsy service from which the leukoplakias were derived. The control definition of periapical cyst was based on the ICD-9 code of 522.8 and having no known diagnosis of oral leukoplakia.

From January 1, 1999 to July 31, 2001, 332 cases and 166 controls were diagnosed. Probability sampling was used to systematically select every other case, thus identifying 166 cases, along with all of the 166 controls (a census), except for exclusion of four non-eligible cases and nine non-eligible controls (i.e. under 18 years of age), resulting in the inclusion of 162 cases and 157 controls. Self-administered mailed questionnaires about the generally recognized potential risk factors were completed by 90 cases and 78 controls.

Description of the independent variables

The potential explanatory variables included gender, age, tobacco use, smokeless tobacco use,

chewing tobacco use, snuff use, smoked tobacco use, current daily alcohol use, and dental prosthesis use. The main exposure variable of tobacco use was defined as any tobacco product, including cigarettes, cigars, pipe, chewing tobacco or snuff. Smokeless tobacco use was defined as using chewing tobacco or snuff. Smoked tobacco use was defined as using cigarettes, cigars, or pipe. Tobacco use was defined as ever use tobacco, current tobacco use, former tobacco use, and never used tobacco. Tobacco use was further specified as smokeless tobacco or smoked tobacco; and smokeless tobacco was further specified as chewing tobacco or snuff. Smoked tobacco use was categorized as ever use smoked tobacco, current smoked tobacco use, former smoked tobacco use, and never used smoked tobacco. Smokeless tobacco use was categorized as ever use smokeless tobacco, current smokeless tobacco use, former smokeless tobacco use, and never used smokeless tobacco. Chewing tobacco use was categorized as ever use chewing tobacco, current chewing tobacco use, former chewing tobacco use, and never used chewing tobacco. Snuff use was categorized as ever use snuff, current snuff use, former snuff use, and never used snuff.

The potential explanatory variables were coded as dichotomous variables. Age was coded as less than 50 years old, or at least 50 years old, similar to a previous study that found individuals 50 years and older had significantly higher prevalence of oral leukoplakia than those less than 50 years of age (29). A dental prosthesis was defined as wearing a partial or complete denture. Current daily alcohol use was defined as currently drinking seven or more alcoholic beverages (beer, wine, or liquor) per week.

Statistical analyses

The null hypothesis was that the potential explanatory variables or etiologic factors which include age, tobacco use, smokeless tobacco use, chewing tobacco use, snuff use, smoked tobacco use, current daily alcohol use, and dental prostheses use, are similar in those with and those without oral leukoplakia.

Each individual was classified with respect to case or control status, exposure, and other potential explanatory variables. Persons for whom valid responses were not available for individual items were excluded from the analyses. This exclusion of unknowns implicitly assumes that the response distribution for the missing values is the same as for the responses that were provided. Univariate–univariable (one dependent variable and one independent variable) logistic regression modeling quantified the unadjusted association between oral leukoplakia and potential explanatory variables. The odds ratio of crude (OR_{Crude}) with 95% confidence intervals (CI) were computed to measure this association between the dependent variable which was a dichotomous outcome (presence or absence of oral leukoplakia lesion) and the independent potential explanatory variables. Univariate–multivariable (one dependent variable and multiple independent variables, henceforth referred to as multivariable) logistic regression modeling was used to evaluate potential explanatory variables, computing the adjusted odds ratio (OR_{Adj}) and 95% CI.

The questionnaire data were entered using a program that was custom designed in EPI-INFO version 6 (30). Cross-tabulations, chi-square calculations, and logistic regression analyses were conducted using SAS systems for Windows®, version 9.0 (SAS Institute, Inc., Cary, NC, USA, 2002).

Results

The descriptive summary and unadjusted measures of association reported in Table 1 indicate that those with oral leukoplakia were more likely to be older (50 years of age and older), more likely to ever, currently, or formerly use smokeless tobacco; and more likely to ever or currently use snuff. The unadjusted association between oral leukoplakia and age ($OR_{Crude} = 2.72$; 95% CI: 1.45–5.11); ever use smokeless tobacco ($OR_{Crude} = 2.91$; 95% CI: 1.42–5.96), current smokeless tobacco use ($OR_{Crude} = 3.72$; 95% CI: 1.28–10.82), former smokeless tobacco use ($OR_{Crude} = 2.46$; 95% CI: 1.03–5.87), ever use snuff ($OR_{Crude} = 3.96$; 95% CI: 1.61–9.78), and current snuff use ($OR_{Crude} = 8.32$; 95% CI: 1.83–37.80) was statistically significant at the $P < 0.05$ level, while the association with gender ($OR_{Crude} = 1.66$; 95% CI: 0.90–3.07) approached statistical significance at the $P < 0.05$ level. Thus, these data indicate that age was associated with oral leukoplakia, with individuals at least 50 years old being 2.7 times more likely to have oral leukoplakia than individuals less than 50 years old. Use of smokeless tobacco was associated with oral leukoplakia with strongest association among those currently using smokeless tobacco; individuals currently using smokeless tobacco were 3.7 times more likely to have oral

Table 1. Descriptive summary and association with oral leukoplakia

Variables	Cases ($n = 90$) [n (%)]	Controls ($n = 78$) [n (%)]	OR_{Crude} (95% CI)
Gender			
Males	54 (60.0)	37 (47.4)	1.66 (0.90–3.07)
Females	36 (40.0)	41 (52.6)	1.0
Age			
At least 50 years old	62 (68.9)	35 (44.9)	2.72 (1.45–5.11)*
Less than 50 years old	28 (31.1)	43 (55.1)	1.0
Dental prostheses use	32 (36.8)	28 (36.8)	1.00 (0.53–1.89)
Current daily alcohol use	12 (20.0)	8 (14.0)	1.53 (0.58–4.08)
Tobacco use			
Ever	68 (75.6)	55 (70.5)	1.29 (0.65–2.56)
Current	33 (36.7)	26 (33.3)	1.33 (0.61–2.89)
Former	35 (38.9)	29 (37.2)	1.26 (0.59–2.71)
Never	22 (24.4)	23 (29.5)	1.0
Smoked tobacco use			
Ever	52 (57.8)	53 (68.0)	0.65 (0.34–1.22)
Current	22 (24.4)	24 (30.8)	0.60 (0.28–1.30)
Former	30 (33.3)	29 (37.2)	0.68 (0.33–1.40)
Never	38 (42.2)	25 (32.0)	1.0
Smokeless tobacco use			
Ever	35 (38.9)	14 (18.0)	2.91 (1.42–5.96)*
Current	16 (17.8)	5 (6.4)	3.72 (1.28–10.82)*
Former	19 (21.1)	9 (11.5)	2.46 (1.03–5.87)*
Never	55 (61.1)	64 (82.1)	1.0
Chewing tobacco use			
Ever	20 (22.7)	12 (15.4)	1.62 (0.73–3.57)
Current	3 (3.4)	3 (3.9)	0.97 (0.19–4.98)
Former	17 (19.3)	9 (11.5)	1.83 (0.76–4.40)
Never	68 (77.3)	66 (84.6)	1.0
Snuff use			
Ever	25 (28.1)	7 (9.0)	3.96 (1.61–9.78)*
Current	15 (17.2)	2 (2.6)	8.32 (1.83–37.80)*
Former	8 (9.2)	5 (6.4)	1.78 (0.55–5.70)
Never	64 (73.6)	71 (91.0)	1.0

*$P < 0.05$.

leukoplakia than individuals that never used smokeless tobacco; former users and ever users of smokeless tobacco were 2.5 and 2.9 times, respectively, more likely to have oral leukoplakia than individuals that never used smokeless tobacco. The strongest unadjusted association was between oral leukoplakia and current snuff use; individuals currently using snuff were 8.3 times more likely to have oral leukoplakia, and individuals that ever used snuff were four times more likely to have oral leukoplakia.

There was no statistically significant association between oral leukoplakia and dental prostheses use, tobacco use (ever, current or former tobacco use), smoked tobacco use (ever, current or former smoked tobacco use), chewing tobacco use (ever, current or former chewing tobacco use), or current daily alcohol use in this study.

When comparing the OR_{Crude} in Table 1 to the OR_{Adj} in Table 2, the strength of the association was 2.5 times greater for current use of smokeless tobacco, with $OR_{Adj} = 9.21$; 95% CI: 1.49–57.00, after simultaneously adjusting for the potential explanatory variables of age, gender, smoked tobacco use (current and former use with never used smoked tobacco as the referent), current daily alcohol use and dental prostheses use; and former smokeless tobacco use is no longer statistically significant. After simultaneously adjusting for these same potential explanatory variables, age remained statistically significant, with those 50 years old and older over four times more likely to have oral leukoplakia than those less than 50 years old ($OR_{Adj} = 4.07$; 95% CI: 1.51–10.97).

When comparing the OR_{Crude} in Table 1 to the OR_{Adj} in Table 3, the strength of the association was 3.6 times greater for current use of snuff, with $OR_{Adj} = 30.08$; 95% CI: 2.67–338.48 after simultaneously adjusting for the potential explanatory variables of age, gender, smoked tobacco use

Table 2. Multiple logistic regression model for the association of smokeless tobacco use with oral leukoplakia

Independent variables	OR_{Adj} (95% CI)[a]
Age	4.07 (1.51–10.97)*
Gender	0.55 (0.19–1.54)
Smokeless tobacco use	
Current	9.21 (1.49–57.00)*
Former	2.73 (0.69–10.84)
Smoked tobacco use	
Current	0.48 (0.17–1.33)
Former	0.71 (0.27–1.86)
Current daily alcohol use	1.47 (0.48–4.50)
Dental prostheses use	0.41 (0.16–1.07)

[a]Odds Ratios for each independent variable adjusted for all the other independent variables listed in this table.
*$P < 0.05$.

Table 3. Multiple logistic regression model for the association of snuff use with oral leukoplakia

Independent variables	OR_{Adj} (95% CI)[a]
Age	4.68 (1.73–12.71)*
Gender	0.55 (0.20–1.50)
Snuff use	
Current	30.08 (2.67–338.48)*
Former	0.98 (0.17–5.61)
Smoked tobacco use	
Current	0.47 (0.15–1.42)
Former	0.88 (0.33–2.36)
Current daily alcohol use	1.44 (0.44–4.70)
Dental prostheses use	0.40 (0.15–1.08)

[a]Odds Ratios for each independent variable adjusted for all the other independent variables listed in this table.
*$P < 0.05$.

(current and former use with never used smoked tobacco as the referent), current daily alcohol use and dental prostheses use. After simultaneously adjusting for these same potential explanatory variables, age remained statistically significant, with those 50 years old and older being 4.7 times more likely to have oral leukoplakia than those less than 50 years old ($OR_{Adj} = 4.68$; 95% CI: 1.73–12.71).

Discussion

The results from this case–control study support a strong positive association between oral leukoplakia and current use of smokeless tobacco, and more specifically current use of snuff among rural West Virginians. These findings are scientifically relevant because the definitions of exposure and potential explanatory variables in our study were based on the current epidemiologic data relating to the prevalence and progression of oral leukoplakia (6). While many studies investigate the association of tobacco and/or smoking with oral leukoplakia using a measure of ever/never use, this may not be the most appropriate measure. According to our present understanding of oral leukoplakia in the US, using a histopathology case definition rather than a clinical definition of exclusions, a measure of current smokeless tobacco use should be assessed because most oral leukoplakia lesions resolve after cessation of smokeless tobacco use (6, 23). Unlike oral cancer which is irreversible, this histopathologically defined oral leukoplakia appears to be reversible, so the mixing of present and past smokeless tobacco use into an exposure of ever/never smokeless tobacco use, does not assess the appropriate biological exposure risk factor of current use. Hence, there is a potential for much misclassification of the biologically plausible exposure variable because individuals that used smokeless tobacco in the past would be counted the same as those currently using smokeless tobacco.

The currently available scientific data on the potential biological plausibility of excessive alcohol inducing oral cancer was incorporated into our measure of current daily alcohol use. We failed to find an association between oral leukoplakia and current daily alcohol use or current smoked tobacco use, similar to other epidemiologic US studies (19, 21). There may truly be no association of current daily alcohol use and oral leukoplakia in this study. Alternatively, we may have failed to detect an association because of a lack of power, i.e. a beta or type 2 error, because the sample size was inadequate to detect a statistically significant difference. In order to detect statistical significance at the alpha = 0.05 and beta = 0.20 level in this study with 20.0% of the cases and 14.0% of the controls currently using alcohol daily, a sample size of 1294 would have been needed (30).

We addressed the temporal association limitation of this study through the definition of the potential explanatory variables. While the temporal association can be better addressed in a longitudinal study, this case–control study used the measure of current alcohol and current tobacco use to eliminate the possibility of misclassifying potential explanatory variables that occurred in the past, and when the oral leukoplakia lesion may have also been present in the past, but would have most likely resolved at the time of the questionnaire. That is, by distinguishing between current

and past use, the current user eliminates the possibility of misclassifying the dependent variable (oral leukoplakia) that may have been present at the time of the exposure, but has subsequently resolved after cessation of the product.

The strength of this study approach is that it incorporates a control group as a comparison, and this is the only study known to the authors that assesses the risk factors for oral leukoplakia in a high-risk rural US population. An additional strength is that the cases and controls were reviewed and identified by a single oral pathologist (JEB) with extensive experience relative to the lesions under investigation. Having one oral pathologist addresses the concern about inter-observer agreement in typing and grading the histology of the oral mucosa (31).

In Scandinavia and the United States, most oral leukoplakia lesions resolve after cessation of smokeless tobacco use (23, 24), and after cessation of betel nut chewing in Taiwan (22). This indicates the importance of assessing the risk factor of current tobacco use rather than never/ever tobacco use, and the importance of distinguishing between tobacco types (smoked versus smokeless). Hence, this study provides new data regarding the risk factors for oral leukoplakia among a high-risk rural US population of older adults who may have a long-established tobacco behavior. The oral leukoplakia lesions among our study population may be different in terms of reversibility and other characteristics when compared with the previous US study which did not clearly define oral leukoplakia as being a white lesion, and whose study population was that of younger military recruits whose duration of tobacco use (and lesion occurrence) was much less (23). However, our results are consistent with the finding that the oral leukoplakia lesion resolves upon cessation of smokeless tobacco use or snuff use because former use was not associated with these lesions (Tables 2 and 3).

Our study was not designed to address the gap in knowledge regarding the potentially different risks for oral cancer associated with different types of smokeless tobacco because we studied oral leukoplakia, not oral and pharyngeal cancer. However, because of the precancerous potential of oral leukoplakia, we will provide a brief critical review of a previous report that different types of smokeless tobacco have different risks for oral and pharyngeal cancer (32). Methodological issues are likely explanations for this report. There are two concerns regarding the review of 21 studies published in the US and western Europe (32): (i) Internal validity can be called into question because the authors failed to adjust for age, cigarette smoking, and alcohol use – these are well known and accepted confounders that must be addressed in any study of cancer of the upper respiratory tract. While it appears that the authors have attempted to conduct a meta-analysis to obtain summary measures of association, it is not clear that necessary adjustments for cohort differences were made in order to yield an appropriate meta-analysis; and (ii) External validity is also a concern because of the different amounts of tobacco specific *N*-nitrosamines in moist snuff used in Sweden compared with US products (26). Thus, the conclusions from this previous review (32), that any one type of smokeless tobacco has a stronger risk for oral and pharyngeal cancer, may be explained by these internal and external validity concerns. Further well-designed studies are needed that take into account the known risk factors for oral and pharyngeal cancer when evaluating the risk of different types of smokeless tobacco for oral cancer.

In an attempt to address this gap in knowledge regarding the potentially different risk of developing oral leukoplakia for the different types of smokeless tobacco, we delineated smokeless tobacco use as chewing tobacco use or snuff use. Although it was not possible to evaluate this further because of the small number of individuals currently using chewing tobacco (only three cases and three controls), there were sufficient numbers to report on current snuff use. After simultaneously adjusting for age, gender, smoked tobacco use, current daily alcohol use and dental prostheses use, individuals currently using snuff were 30.1 times more likely to have oral leukoplakia, which is 3.3 times greater than the same adjusted measure of association between oral leukoplakia and current smokeless tobacco use. However, our findings do not support a conclusion that current snuff users have a greater risk of developing oral leukoplakia than individuals currently using other smokeless tobacco products because there were too few individuals currently using chewing tobacco in our study. Thus, in our study it is appropriate to report on the current use of smokeless tobacco, or the current use of snuff, but it is not appropriate to report on, or compare, current use of chewing tobacco.

Further US studies are needed to provide additional scientific data regarding the induction of oral

leukoplakia by both smoked and smokeless tobacco use, and regarding the association of leukoplakia with oral cancer being conditional in part on tobacco use (6). These studies are needed to translate scientific evidence into practice to prevent the development of oral leukoplakia and to decrease the occurrence of oral cancer. Furthermore, if the ultimate goal is to decrease the mortality rate of oral leukoplakia, additional studies are needed to assess the role of tobacco in the recent finding that only patients with aneuploid leukoplakia lesions died of oral cancer (5).

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