EXPLANATORY VARIABLES OF TOBACCO AND ALCOHOL CESSATION IN PATIENTS UNDERGOING ORAL BIOPSY

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ABSTRACT

Tiffany Marie Peters: Explanatory Variables of Tobacco and Alcohol Cessation in Patients Undergoing Oral Biopsy
(Under the direction of Valerie A. Murrah)

Tobacco and alcohol are the predominant etiologic factors for oral cancer. Studies show an association between disease severity and tobacco cessation. Relationship between oral biopsy diagnosis and risk factor cessation is unknown.

Patients diagnosed with hyperkeratosis, dysplasia or carcinoma were sent questionnaires addressing demographics and risk factor use. Statistical analyses assessed whether behavior change was associated with the biopsy procedure and whether that change was related to diagnostic or demographic categories.

Response rate was 37.4% (605/1619). Higher percentages of subjects with more severe diagnoses quit cigarettes and alcohol following biopsy. Younger respondents were less likely to quit smoking prior to biopsy and more likely to be still smoking ($p<0.01$).

For patients with suspicious oral lesions, clinicians should be aware that oral biopsy diagnosis is an important tool against risk factor addiction. Younger patients are more likely to continue to be cigarette users even after controlling for severity of diagnosis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS

CAD	Coronary artery disease
CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
HPV	Human papillomavirus
FDA	United States Food and Drug Administration
MI	Myocardial infarction
NHIS	National Health Interview Surveys
UNC	University of North Carolina

CHAPTER 1: TOBACCO, ALCOHOL AND THE DENTAL PATIENT

Introduction

Approximately fifty percent of current smokers will die from a tobacco related disease.[1] Nearly one third of these current smokers will visit a dentist each year.[1, 2] This places oral healthcare providers in a unique position to advance public health in the crusade against tobacco use. This is especially relevant as tobacco, along with alcohol, are recognized as the predominant etiologic factors for squamous cell carcinoma of the oral cavity.[3-9] It is recognized that oral cancer has an especially poor prognosis; regardless of scientific progress in treatment, there have been only minor improvements in survival rates of human papillomavirus (HPV)-negative oral carcinomas over the past several decades.[4, 8, 10-14] In addition, the risk of developing a second primary tumor is increased in tobacco and alcohol consumers according to the theory of "field cancerization."[15] Thus, strategies to decrease etiologic factors are critically needed.

There are many elements that may play a role in risk factor cessation. For instance, gender is implicated as a factor; one literature review found that men are more likely to stop smoking compared to women.[16] In addition, it is noted that the severity of smoking-related disease, including head and neck cancer, has a positive association with cessation.[16, 17] The experience of receiving a diagnosis for a serious illness is recognized as a "teachable moment" during which the patient is compelled to adhere to clinician advice.[18, 19]

This knowledge can lead to more effectively targeted cessation strategies for health care providers seeking to aid in the cessation process. Historically, strategies that have been used for

cessation include behavioral therapy, such as counseling, and pharmacotherapy, including nicotine replacement products as well as bupropion hydrochloride (Wellbutrin®, Zyban®) and varenicline (Chantix®). However, according to the American Cancer Society, cessation attempts with pharmacotherapy yield only about a 25% quit rate.[20]

In this study, we hypothesized that a malignant or premalignant oral biopsy diagnosis, in addition to providing objective data on which to base patient management, may also serve as a behavioral change agent to aid in risk factor cessation. While cigarette use following malignant diagnosis has been assessed in previous studies, to our knowledge, the impact of a premalignant diagnosis on behavioral change has not been evaluated. Also, our study addressed whether gender differences are present following specific oral biopsy results. Knowledge of any relationship between oral biopsy diagnosis and risk factor cessation would be relevant for clinicians who deliver diagnoses and arrange for disease treatment. These providers are in a unique position to influence at risk patients and reduce the overall use of the chief etiologic agents responsible for oral cancer.

Review of the Literature

Tobacco and alcohol are recognized as the predominant etiologic factors for squamous cell carcinoma of the oral cavity, responsible for nearly three-quarters of all cases.[3-9] Regardless of scientific progress in treatment, there have been only minor improvements in survival rates of human papillomavirus (HPV)-negative carcinomas over the past several decades; the two-year survival rate for patients treated with radiotherapy is still only about 50% when diagnosed at the regional stage.[4, 8, 10-14] Moreover, the risk for developing a second primary tumor is increased in tobacco and alcohol consumers according to the theory of "field cancerization."[15] According to this theory, carcinogenic exposure occurs across a "field" of epithelium, leading to multiple discrete sites of dysplasia that progress toward cancer at differing rates depending on several factors, such carcinogen concentration. Thus, a patient with a history of oral cancer likely harbors multiple other sites of precancerous changes throughout his oral cavity, even in areas where mucosa still appears clinically normal.[15]

Overall, about 45-75% of all cancer patients are smokers at diagnosis,[19, 21] and a study specific for head and neck cancer found that over 50% of patients used tobacco in the year preceding diagnosis.[17] For patients who already have a malignant diagnosis, continued smoking is associated with a worse prognosis. For example, persistent cigarette smoking has been linked with greater risk for initial tumor recurrence and lower overall survival.[22] In addition, there is a higher risk for the development of a second primary tumor;[10] continued use of tobacco as well as alcohol have been shown to significantly increase this risk.[23] In terms of cancer therapy, smokers have reduced rates of radiation treatment response and survival as compared to those who quit prior to treatment.[24] In addition, there are other negative side effects associated with radiation treatment and concurrent cigarette smoking, such as longer periods of mucositis.[25, 26]

Correspondingly, quitting smoking prior to accelerated radiation therapy results in decreased side effects.[25] Furthermore, a decrease or discontinuation in cigarette use is associated with an overall decrease in mortality in head and neck cancer patients; the same is true for reducing or discontinuing alcohol consumption.[27]

Study findings are inconsistent regarding the percentage of cancer patients who continue to use tobacco products following diagnosis. For example, a literature review of smoking behavior in all cancer patients noted that 14-58% of those smoking at diagnosis failed to stop using cigarettes following treatment for cancer.[19] Two studies specific for head and neck cancer found that about 65% of smokers stopped following diagnosis and treatment.[17, 18] However, other studies indicate that only about 30% of current smokers with head and neck cancer quit after diagnosis and treatment.[25, 27] Additional sources report that about 15% of those who survive cancer indicate current use of cigarettes.[21, 28] Reported cessation rates may vary among studies due to differences in study design, such as length of follow-up, self-reported versus biochemically validated tobacco abstinence, cancer location, stage of cancer and type of treatment. In addition, the Centers for Disease Control and Prevention (CDC) also found variation between different regions of the United States, with the greatest prevalence of cigarette use in cancer survivors in the South.[28]

There are many factors that may influence a patient to stop smoking. One variable that has been elucidated through research is the severity of clinical disease; indeed, a review of the literature found that patients with more serious tobacco-related illnesses were more likely to comply with the recommendation for tobacco cessation.[16] An association between severity of illness and tobacco cessation has been elucidated in both cardiovascular disease and head and neck cancer patients. For example, smokers with lower serum creatine phosphokinase (CPK)

levels and briefer stays in an intensive care unit following myocardial infarction (MI) were more likely to resume smoking as compared to patients who suffered a more serious MI.[29] Likewise, a smoking intervention study involving patients with coronary artery disease (CAD) found that those with more serious disease were more likely to be nonsmokers following intervention.[30] In addition, a study investigating the impact of various psychosocial, demographic and smoking history variables on cigarette cessation in chronic obstructive pulmonary disease (COPD) patients found that COPD itself was the variable that most strongly affected cessation rates.[31] Similarly, a study found that patients with cases of head and neck cancer associated with a poorer prognosis were more likely to quit smoking as compared to those with a less severe prognosis; patients with a more advanced stage (II-IV) of cancer were significantly more likely to quit. Interestingly, cancer site was also significantly associated with cessation as those with pharyngeal or laryngeal cancers were more likely to have quit (80%) compared to those with oral cancer (20%); however, it was also noted that those with oral cancer were less likely to have advanced disease.[17]

In addition to differences in tobacco cessation related to clinical disease severity, available literature also indicates a difference in tobacco cessation rates between males and females. One literature review noted gender as the most commonly reported variable associated with cessation; multiple studies found that men are more likely to stop smoking compared to women.[16] An analysis of the National Health Interview Surveys data found that smoking cessation prevalence was lower in Caucasian women as compared to Caucasian men in adults 65 years or older.[32] Similarly, a smoking intervention study in patients with CAD found that males in the intervention group were more likely to be non-smokers at the six month follow-up time.[30] Finally, while the incidence of oral cancer is higher in males, the difference in rates between

males and females is becoming smaller over time; this is partially attributed to both a rise in use as well as longer duration of use in females.[10]

Current research findings regarding elements associated with risk factor cessation can lead to more effectively targeted cessation strategies for health care providers seeking to aid in the cessation process. Historically, strategies that have been used for cessation include behavioral therapy, such as counseling, and pharmacotherapy, including nicotine replacement products as well as bupropion hydrochloride (Wellbutrin®, Zyban®) and varenicline (Chantix®). However, according to the American Cancer Society, cessation attempts with pharmacotherapy yield only about a 25% quit rate.[20] Furthermore, while it is clear that risk factor cessation is critical for both preventing oral cancer, as well as lowering the morbidity and mortality associated with treatment, the healthcare provider's role in how to best aid cessation efforts is much less clear. For instance, considerable emphasis is placed on promoting health knowledge and enhancing clinical outcome measures; however, studies have verified that improved knowledge in and of itself does not necessarily translate to a change in behavior or health.[33-35] It has been postulated that patients are not likely to adopt new behaviors unless there is a perceptible benefit associated with this behavior; thus, reduced pain, better function or increased quality of life may serve as motivational factors, whereas a clinical measurement of disease may not be meaningful from a patient perspective.[36] For this reason, it is critical to address risk factor cessation from a patient's viewpoint of how the associated benefits may particularly impact his or her daily life.

For some patients, one element that can render the discussion of risk factor cessation more personalized, and thus subsequent behavior change more likely, is the timing of the discussion. For instance, it has been noted that patients who continue to smoke have a lower

perception of the risks associated with cigarettes and a reduced motivation to quit.[37-39] However, the time period surrounding receipt of a malignant diagnosis and subsequent treatment may serve as a "teachable moment" during which the patient is compelled to adhere to clinician advice.[18, 19] Several studies note that health crises intensify awareness and may enhance the prospect of cessation.[16, 30, 40] For example, one study found greater motivation to quit smoking as well as higher six-month abstinence rates in lung cancer patients as compared to controls, and thus suggested that clinicians "capitalize" on the time near initial diagnosis by providing valuable cessation support.[41]

While it is important to convey the seriousness of an oral lesion and the etiologic role of tobacco or alcohol, it is equally important to remember that discussion of biopsy results should not be approached as a "scare tactic." It is thought that some patients with persistent tobacco use after a diagnosis of cancer may paradoxically reach for a pack of cigarettes because of the psychosocial stress that accompanies such a situation. Fear, hopelessness or resignation may diminish the prospects of cessation. Some studies have noted that cancer patients, while expressing interest in quitting, also convey low confidence in being able to do so and are only about half as likely to have attempted to quit in the past year as compared to all smokers.[21]

While these findings are somewhat negative, healthcare providers should be inspired to approach cessation in a constructive manner as studies have also shown that patients with cancer have both the desire and the ability to overcome addictions.[19] Patients who quit smoking after a cancer diagnosis attested to the value of support from family and friends. For those surrounded by other tobacco users, having close contacts also engaged in quitting helped to reduce the appeal of cigarettes.[21] Indeed, several studies report that tobacco abstinence in families helps maintain abstinence in the patient who is attempting to quit.[19, 42, 43] In addition, for those cancer

survivors who have not stopped smoking, the majority express interest in both behavioral and pharmacotherapy cessation aids. A wide variation was reported in the preferred type of desired behavioral intervention or pharmacotherapy; thus, it is recommended that cessation aids be personalized on a case by case basis.[21]

Smoking cessation aids include both pharmacotherapy and behavioral approaches such as counseling. Table 1 outlines the first line pharmacotherapy agents that have been approved by the United States Food and Drug Administration (FDA). The U.S. Public Health Service has outlined evidence-based recommendations for cessation therapy. The sequence of treatment starts with evaluating all patients for tobacco use, followed by recommending cessation for all current users. The advice to quit should be unambiguous, urgent and individualized. In terms of treatment, meta-analyses reveal that cessation therapy is most effective when counseling and pharmacotherapy are used in combination. Nonetheless, combined therapy may not be appropriate for all patients, and it is important to note that counseling and pharmacotherapy are also beneficial when used individually. Situations that may necessitate a single therapy include those in which a patient is unwilling to use both forms of therapy or in patient populations for which medications may be contraindicated or have not been proven to be effective. These include adolescents, pregnant smokers, users of smokeless tobacco and light smokers. Finally, it is important to be cognizant of the chronic nature of tobacco dependence; patients should receive follow up assessment and additional intervention as needed.[1]

While there is clearly a need for involvement of healthcare providers in the fight against tobacco addiction, evidence suggests that actual engagement by clinicians is lacking. For instance, a CDC study of current smokers found that approximately 50% of those who visited a physician within a twelve month period received cessation advice, and only about 10% who

visited a dental professional received cessation advice.[44] Potential barriers to risk factor cessation discussion in a dental or oral surgery office may include the perception that the discussion must be extensive, or that such a discussion is not in the purview of oral healthcare providers. However, for busy clinicians, it is noted that interventions of merely three minutes can significantly affect tobacco abstinence.[19, 45] Also, presenting information prior to surgery regarding the adverse effect of smoking on surgical outcomes may provide further incentive for tobacco cessation.[19] Further evidence for the role of oral healthcare providers in the fight against tobacco related diseases comes from studies that highlight the importance of early intervention for tobacco cessation in patients at risk for cancer. For instance, a study focusing on patients with lung carcinoma found that those treated for nicotine dependence within three months of initial diagnosis had a greater likelihood of being tobacco free at the 6 month follow-up appointment as compared to those who received nicotine dependence treatment greater than three months after diagnosis.[19, 41] For some oral cancer patients, dental providers are best situated to provide early intervention as they are the initial clinicians in a long journey of treatment that later proceeds to otolaryngology and oncology. Finally, the role of oral healthcare personnel as related to tobacco cessation is highlighted in studies that found higher tobacco abstinence rates associated with cessation interventions performed in conjunction with diagnostic work-ups or cancer screenings.[19, 46, 47] This data suggests that risk factor cessation intervention may be particularly helpful at diagnosis and treatment planning appointments and recall examinations during which patients already undergo oral cancer screening exams.

In summary, squamous cell carcinoma of the oral cavity is a largely preventable disease, predominantly due to tobacco and alcohol abuse. Existing literature points to a positive association between severity of clinical disease and rates of tobacco cessation and also indicates

differences in cessation rates according to gender. In addition, while many patients diagnosed with cancer continue to smoke or consume alcohol, it is also known that a number of these patients will overcome addictions, whereas many others have an interest and desire to do so. For this latter group, there are many things that clinicians can do to help patients in this arduous journey, and several of these factors are relevant to oral healthcare providers. Firstly, the risk factor cessation discussion should be personalized for each patient and discussed in such a way as to elucidate the tangible benefits of quitting. Furthermore, while patients should be accurately informed of current health findings and the realistic dangers of continued risk factor use, this discussion should not be approached as a "scare tactic." Instead, encouragement for cessation should be emphasized. Cessation aids should be personalized for each patient, and may include various approaches to counseling as well as pharmacotherapy. Despite perceived barriers, oral healthcare providers have the opportunity and the means to serve as valuable team members in the struggle for tobacco cessation.

Table 1. Summary of pharmacotherapy options for smoking cessation, as adapted from "A Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update." Package inserts should be consulted for further safety and dosing information. OTC, over the counter; cig, cigarette.

Drug	Contraindications & Precautions	Possible Side Effects	Dosage	Length of Treatment	Accessibility
Nicotine Replacement Therapy					
Nicotine gum		Oral irritation, nausea	≤ 24 cig/ day: 2 mg gum ≥ 25 cig/ day: 4 mg gum (up to 24 pieces/day)	≤ 12 wks	OTC
Nicotine lozenge		Nausea, acid reflux	Time to 1st cig >30 min: 2mg lozenge Time to 1st cig ≤ 30 min: 4mg lozenge Use 4-20 lozenges/ day	≤ 12 wks	OTC
Nicotine patch		Local irritation, insomnia	Available in 21 mg, 14 mg and 7 mg patches to be tapered over time	Varies	OTC, prescription
Nicotine nasal spray		Nasal irritation	8-40 doses/day	3-6 months	prescription
Nicotine inhaler		Local oropharyngeal irritation	6-16 cartridges/day	≤ 6 months	prescription
Other					
Bupropion	History of seizures or eating disorder	Xerostomia, insomnia, seizures	Start 1-2 wks prior to quit date: 150 mg q morning for 3 days, then 150 mg bid	7-12 wks, maintenance up to 6 months	prescription

Varenicline	Kidney disease	Nausea, insomnia, depression & other psychiatric symptoms	Start 1 wk prior to quit date: 0.5 mg/ day for 3 days, 0.5 mg bid for 4 days, then 1 mg bid	3-6 months	prescription

CHAPTER 2: CANCER RISK FACTOR CESSATION AND ORAL BIOPSY

Introduction

Tobacco and alcohol are recognized as the predominant etiologic factors for squamous cell carcinoma of the oral cavity, responsible for nearly three-quarters of all cases.[3-9] Regardless of scientific progress in treatment, there have been only minor improvements in survival rates of human papillomavirus (HPV)-negative carcinomas over the past several decades; the two-year survival rate for patients treated with radiotherapy is still only about 50% when diagnosed at the regional stage.[4, 8, 10-14] Moreover, the risk for developing a second primary tumor is increased in tobacco and alcohol consumers according to the theory of "field cancerization."[15] Thus, strategies to decrease etiologic factors are critically needed. It was hypothesized that oral biopsy diagnosis, in addition to providing objective data on which to base patient management, may serve as a behavioral change agent to aid in risk factor cessation.

Overall, about 45-75% of all cancer patients are smokers at diagnosis,[19, 21] and a study specific for head and neck cancer found that over 50% of patients used tobacco in the year preceding diagnosis.[17] For patients who already have a malignant diagnosis, continued smoking is associated with a worse prognosis. For example, persistent cigarette smoking has been linked with greater risk for initial tumor recurrence and lower overall survival.[22] In addition, there is a higher risk for the development of a second primary tumor;[10] continued use of tobacco as well as alcohol have been shown to significantly increase this risk.[23] In terms of therapy, smokers have reduced rates of radiation treatment response and survival, as compared to those who quit prior to treatment.[24] In addition, there are other negative side effects associated with radiation

treatment and concurrent cigarette smoking, such as longer periods of mucositis.[25, 26] Correspondingly, quitting smoking prior to accelerated radiation therapy results in decreased side effects.[25] Furthermore, a decrease or discontinuation in cigarette use is associated with an overall decrease in mortality in head and neck cancer patients; the same is true for reducing or discontinuing alcohol consumption.[27]

Study findings are inconsistent regarding the percentage of cancer patients who continue to use tobacco products following diagnosis. For example, a literature review of smoking behavior in all cancer patients noted that 14-58% of those smoking at diagnosis failed to stop using cigarettes following treatment for cancer.[19] Two studies specific for head and neck cancer found that about 65% of smokers stopped following diagnosis and treatment.[17, 18] However, other studies indicate that only about 30% of current smokers with head and neck cancer quit after diagnosis and treatment.[25, 27] Reported cessation rates may vary among studies due to differences in study design, such as length of follow-up, self-reported versus biochemically validated tobacco abstinence, cancer location, stage of cancer and type of treatment.

There are many factors that may influence a patient to stop smoking. One variable that has been elucidated through research is the severity of clinical disease; indeed, a review of the literature found that patients with more serious tobacco-related illnesses were more likely to comply with the recommendation for tobacco cessation.[16] An association between severity of illness and tobacco cessation has been elucidated in both cardiovascular disease and head and neck cancer patients. For example, smokers with lower serum creatine phosphokinase (CPK) levels and briefer stays in an intensive care unit following myocardial infarction (MI) were more likely to resume smoking as compared to patients who suffered a more serious MI.[29] Likewise, a smoking intervention study involving patients with coronary artery disease (CAD) found that

those with more serious disease were more likely to be nonsmokers following intervention.[30] In addition, a study investigating the impact of various psychosocial, demographic and smoking history variables on cigarette cessation in chronic obstructive pulmonary disease (COPD) patients found that COPD itself was the variable that most strongly affected cessation rates.[31] Similarly, a study found that patients with cases of head and neck cancer associated with a poorer prognosis were more likely to quit smoking as compared to those with a less severe prognosis; patients with a more advanced stage (II-IV) of cancer were significantly more likely to quit. Interestingly, cancer site was also significantly associated with cessation as those with pharyngeal or laryngeal cancers were more likely to have quit (80%) compared to those with oral cancer (20%); however, it was also noted that those with oral cancer were less likely to have advanced disease.[17]

Given the high morbidity and mortality of head and neck cancer, clinicians should maximize opportune occasions in which to address risk factor cessation with patients. The time period surrounding receipt of a malignant diagnosis and subsequent treatment may serve as a "teachable moment" during which the patient is compelled to adhere to clinician advice.[18, 19] Several studies note that health crises intensify awareness and may enhance the prospect of cessation.[16, 30, 40] For example, one study found greater motivation to quit smoking as well as higher six-month abstinence rates in lung cancer patients as compared to controls, and thus suggested that clinicians "capitalize" on the time near initial diagnosis by providing valuable cessation support.[41]

In addition to differences in tobacco cessation related to clinical disease severity, available literature also indicates a potential difference in tobacco cessation rates between males and females. One literature review noted gender as the most commonly reported variable

associated with cessation; multiple studies found that men are more likely to stop smoking compared to women.[16] An analysis of the National Health Interview Surveys data found that smoking cessation prevalence was lower in Caucasian women as compared to Caucasian men in adults 65 years or older.[32] Similarly, a smoking intervention study in patients with CAD found that males in the intervention group were more likely to be non-smokers at the six month follow-up time.[30] Finally, while the incidence of oral cancer is higher in males, the difference in rates between males and females is becoming smaller over time; this is partially attributed to both a rise in use as well as longer duration of use in females. [10]

In summary, existing literature points to an association between severity of clinical disease and rates of tobacco cessation and also indicates differences in cessation rates according to gender. This knowledge can lead to more effectively targeted cessation strategies for health care providers seeking to aid in the cessation process. Historically, strategies that have been used for cessation include behavioral therapy, such as counseling, and pharmacotherapy, including nicotine replacement therapy as well as bupropion hydrochloride (Wellbutrin®, Zyban®) and varenicline (Chantix®). However, according to the American Cancer Society, cessation attempts with pharmacotherapy yield only about a 25% quit rate.[20] In this study, we hypothesized that a malignant or premalignant oral biopsy diagnosis may also serve as a behavioral change agent to aid in risk factor cessation. To our knowledge, the impact of a premalignant diagnosis on behavioral change has not been evaluated. Also, our study addressed whether the gender differences observed previously in association with risk factor cessation would also be present following specific oral biopsy results. Knowledge of the relationship between oral biopsy diagnosis and risk factor cessation can be highly significant for clinicians who deliver diagnoses and arrange for disease treatment. These providers are in a unique

position to influence at risk patients and reduce the overall use of the chief etiologic agents responsible for oral cancer.

Materials and Methods

This was an observational study that utilized a survey design. A consecutive sample of potential subjects was identified through the University of North Carolina (UNC) oral pathology laboratory database after obtaining UNC Institutional Review Board and School of Dentistry approval (see Appendix 1 for additional information). Potential subjects included any patients within a designated two-year period (August 1, 2007-July 31, 2009) who had an oral tissue specimen sent to the UNC oral pathology laboratory and received a diagnosis of hyperkeratosis, dysplasia (mild, moderate or severe) or carcinoma (in situ, verrucous or squamous cell). Subjects with a diagnosis of hyperkeratosis were considered as a control group. Subjects with lip carcinoma of the vermillion border or those with actinic damage, as well as subjects under eighteen years of age, were excluded.

A questionnaire created using Teleform was sent in the mail to potential subjects (see Appendix 2). A second questionnaire was sent to non-responders. Returned questionnaires were scanned and verified, and data was stored in an ACCESS database. Subjects were asked to record demographic information as well as information about previous or current tobacco use and alcohol use. Cigarettes and smokeless tobacco were considered separately with a combined section for pipes and cigars. For each product, subjects were asked, "Have you ever used this product?" For those who responded "yes," additional questions followed pertaining to product usage. Subjects were asked if they had changed their usage. Possible answers included no change in usage, reduced usage, quit after biopsy and quit prior to biopsy.

Demographic characteristics and percentages of subjects in product use categories were summarized using descriptive statistics. For race, respondents were categorized as Caucasian or non-Caucasian due to the small number of non-Caucasian respondents. For age, a highly skewed

distribution led to categorization based on quartiles of the entire sample. Age quartiles were defined as age 21-52 years, 53-61 years, 62-68 years and 69-98 years. Statistical analysis was focused on results associated with use of cigarettes and alcohol as relatively few subjects reported use of smokeless tobacco or pipes or cigars. The data from five subjects was eliminated from analysis due to inconsistency between responses (i.e. reporting never use of a product, then subsequently reporting amount of use). Behavior change categories were collapsed and defined as "quit prior to biopsy," "quit after biopsy" and "still using" for those subjects with no change in usage and those with reduced usage. Behavior change responses were considered ordinal data with "still using" as worst, "quit after biopsy" as satisfactory and "quit before biopsy" as the best outcome.

Bivariate analysis was performed using a chi-square test of independence, or Fisher's exact test when appropriate, to compare diagnostic categories for differences in gender, race and age, and also to compare those who never used cigarettes or alcohol versus those who did to identify differences in diagnostic category, gender, race or age among these groups. Bivariate analysis with a Cochran-Mantel-Haenzel row mean score test with modified ridits for ordinal data was used to determine if behavior change was related to diagnostic category, gender, race or age. In addition, multivariate analysis using the proportional odds model was also used to assess if behavior change was related to diagnostic category, gender, race or age. The level of significance was set at 0.05.

Results

605 out of 1619 potential subjects returned a questionnaire for a response rate of 37.4%. Demographic characteristics of respondents are summarized in Table 2. Some categories combine to less than the total number of respondents as not all respondents answered all questions. Caucasians comprised 85% of those who responded, and females comprised 49.5%. There was no statistically significant difference among diagnostic categories with respect to the proportion of Caucasians or the proportion of females who responded.

The carcinoma group had the highest response rate with 42.6% of potential subjects returning a survey. Overall, subjects with dysplasia comprised 53.7% of the total respondents. Table 3 summarizes reported changes in carcinogenic product usage. The product with the highest reported frequency of ever use was alcohol, followed in decreasing frequency by cigarettes, pipes and cigars, and smokeless tobacco (Figure 1).

Bivariate analysis indicated a statistically significant difference among diagnostic categories with respect to distribution of age ($p= 0.04$); respondents with a diagnosis of carcinoma were older than those in the other diagnostic categories. There were also differences with respect to ever use of carcinogenic products. Across diagnostic categories, there was a significant difference in the proportion of those who reported never using cigarettes, with fewer carcinoma subjects indicating this response ($p<0.01$). There was no significant difference among diagnostic categories in the proportion of those who never used alcohol. Comparison by race indicated no significant difference in the proportion of Caucasians versus non-Caucasians who never used cigarettes, but a higher proportion of Caucasians reported using alcohol ($p<0.01$). For age, there was no significant difference in the proportion of those who never used cigarettes among the age groups, but older respondents were significantly more likely to report never using

alcohol ($p<0.01$). Comparison of males and females indicated no significant difference in the proportion of males versus females who never used cigarettes, but females were more likely to report never using alcohol ($p<0.01$).

With respect to the effect of explanatory variables on change in cigarette use (Table 3), bivariate analysis indicated no significant difference among diagnostic categories. Race and gender were also not significantly associated with change in cigarette usage. There was a significant difference among age groups in behavior change, with respondents in the first and second quartiles being less likely to quit using cigarettes prior to biopsy ($p<0.01$).

With respect to the effect of explanatory variables on change in alcohol use (Table 4), bivariate analysis indicated no significant difference among diagnostic categories. Gender and age were also not significantly associated with change in alcohol use. Race was significantly associated with change in alcohol use, with Caucasians being less likely to quit using alcohol prior to biopsy than non-Caucasians ($p<0.01$).

Analysis using the proportional odds model for change in cigarette use showed similar findings as the bivariate analysis (Table 5). The score test for the proportional odds assumption was not statistically significant ($p=0.28$), indicating the odds ratios were consistent for all logits. The global test for behavioral change in cigarette usage was statistically significant ($p<0.01$), with age ($p<0.01$) contributing significantly to the variability in the respondents' change in cigarette use after controlling for all other explanatory variables. Respondents in the first and second quartiles were less likely to quit prior to biopsy and more likely to be still using cigarettes. Compared to those in the fourth quartile of age, respondents in the first quartile are approximately 3.7 times more likely to not quit using cigarettes prior to biopsy or to still be smoking (95% CI: 1.98-6.91). Respondents in the 2nd quartile of age are approximately 2.4

times less likely to quit before a biopsy and are more likely to still be smoking than those in the 4^{th} quartile (95% CI: 1.4-4.4). Race was a marginally statistically significant contributor to the respondent's change in cigarette use after controlling for all other explanatory variables. Caucasians were more likely to quit smoking prior to biopsy than non-Caucasians (OR=0.54; 95% CI= 0.3-0.99).

Analysis using the proportional odds model for change in alcohol use indicated similar findings as the bivariate analysis (Table 6). The score test for the proportional odds assumption was not statistically significant ($p=0.74$), indicating the odds ratios were consistent for all logits. The global test for behavioral change in alcohol usage was statistically significant ($p<0.05$), with race ($p<0.01$) contributing significantly to the variability in the respondents' change in alcohol usage after controlling for the other explanatory variables.

Tables 7 and 8 summarize the behavioral response for subjects who were users of carcinogenic products at the time of biopsy. Higher percentages of subjects with clinically more severe diagnoses quit following biopsy. This was true for both cigarettes and alcohol, with higher quitting percentages for cigarettes.

Table 2. Demographic characteristics and diagnostic categories of respondents (N=605). Percentages in "Total" column are representative of number of respondents within each demographic category. Percentages in other columns are representative of number or respondents in each diagnostic category.

	N (%)				
Variable	**Total**	**Carcinoma**	**Dysplasia**	**Hyperkeratosis**	**P-value**
Gender					
Male	300 (50.5%)	22 (7.3%)	158 (52.7%)	120 (40.0%)	
Female	294 (49.5%)	17 (5.8%)	158 (53.7%)	119 (40.5%)	0.75
Age					
Q_1 (21-52 years)	134 (22.6%)	4 (10.3%)	67 (21.1%)	63 (26.7%)	
Q_2 (53-61 years)	150 (25.3%)	7 (18.0%)	79 (24.9%)	64 (27.1%)	
Q_3 (62-68 years)	145 (24.5%)	10 (25.6%)	85 (26.8%)	50 (21.2%)	
Q_4 (69-98 years)	163 (27.5%)	18 (46.2%)	86 (27.1%)	59 (25.0%)	0.04
Race					
Caucasian	503 (85.8%)	33 (6.6%)	275 (54.7%)	195 (38.8%)	0.32
Non-Caucasian	83 (14.2%)	7 (8.4%)	38 (45.8%)	38 (45.8%)	

Table 3. Changes in Carcinogenic Product Usage. N= 605.

	Alcohol N (%)	Cigarettes N (%)	Pipes/ Cigars N (%)	Smokeless Tobacco N (%)
Never Used	125 (21.1%)	278 (46.2%)	479 (84.2%)	496 (85.5%)
Quit Prior to Biopsy	48 (8.1%)	130 (21.6%)	25 (4.4%)	11 (1.9%)
Quit After Biopsy	37 (6.2%)	69 (11.5%)	22 (3.9%)	32 (5.5%)
Reduced Use Since Biopsy	54 (9.1%)	47 (7.8%)	8 (1.4%)	20 (3.5%)
No change since biopsy	329 (55.5%)	78 (13.0%)	35 (6.2%)	21 (3.6%)

Figure1. Carcinogenic product usage prior to and after oral biopsy.

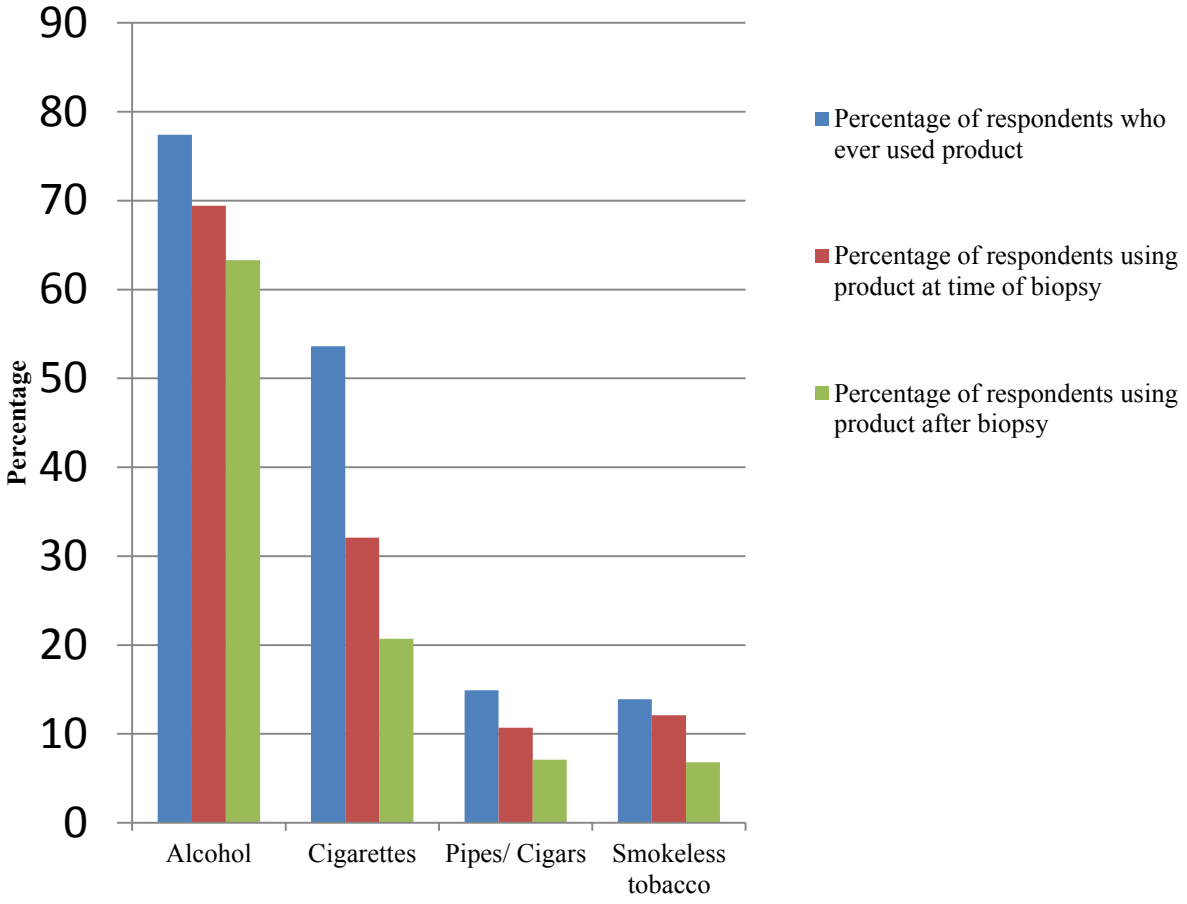

Table 4. Bivariate analysis for cigarette usage, according to gender, race, age quartiles and diagnosis. N=324 ever cigarette users.

	Still using N (%)	Quit after biopsy N (%)	Quit prior to biopsy N (%)	P-value
All	125 (38.6%)	69 (21.3%)	130 (40.1%)	
Male	63 (36.8%)	40 (23.9%)	68 (39.8%)	0.72
Female	61 (40.9%)	28 (18.8%)	60 (40.3%)	
Caucasian	101 (37.4%)	54 (20.0%)	115 (42.6%)	0.15
Non-Caucasian	21 (42.9%)	14 (28.6%)	14 (28.6%)	
Q1	39 (57.4%)	12 (17.6%)	17 (25.0%)	<0.01
Q2	37 (46.8%)	16 (20.3%)	26 (32.9%)	
Q3	23 (27.7%)	17 (20.5%)	43 (51.8%)	
Q4	23 (25.6%)	23 (25.6%)	44 (48.9%)	
Hyperkeratosis	48 (43.6%)	16 (14.6%)	46 (41.8%)	0.66
Dysplasia	70 (36.8%)	47 (24.7%)	73 (38.4%)	
Carcinoma	7 (29.2%)	6 (25.0%)	11 (45.8%)	

Table 5. Bivariate analysis for alcohol usage, according to gender, race, age quartiles and diagnosis. N= 468 ever alcohol users.

	Still using N (%)	Quit after biopsy N (%)	Quit prior to biopsy N (%)	P-value
All	383	37	48	
Male	217 (80.4%)	23 (8.5%)	30 (11.1%)	0.30
Female	161 (84.3%)	12 (6.3%)	18 (9.4%)	
Caucasian	345 (84.4%)	26 (6.4%)	38 (9.3%)	<0.01
Non-Caucasian	31 (63.3%)	9 (18.4%)	9 (18.4%)	
Q1	96 (86.5%)	8 (7.2%)	7 (6.3%)	0.09
Q2	111 (85.4%)	8 (6.2%)	11 (8.5%)	
Q3	85 (75.2%)	12 (10.6%)	16 (14.2%)	
Q4	87 (79.8%)	8 (7.3%)	14 (12.8%)	
Hyperkeratosis	153 (83.2%)	12 (6.5%)	19 (10.3%)	0.10
Dysplasia	208 (82.9%)	18 (7.2%)	25 (10.0%)	
Carcinoma	22 (66.7%)	7 (21.2%)	4 (12.1%)	

Table 6. Multivariate analysis for cigarette usage, according to gender, race, age quartiles and diagnosis. Probabilities modeled are those for the worst category. N=324 ever cigarette users. [a]OR: odds ratio. [b]CI: confidence interval of odds ratio.

	Still using N (%)	Quit after biopsy N (%)	Quit prior to biopsy N (%)	OR[a]	95% CI[b]	P-value
All	125 (38.6%)	69 (21.3%)	130 (40.1%)			
Male	63 (36.8%)	40 (23.9%)	68 (39.8%)	0.97	0.63-1.49	0.88
Female	61 (40.9%)	28 (18.8%)	60 (40.3%)	1		
Caucasian	101 (37.4%)	54 (20.0%)	115 (42.6%)	0.54	0.30-1.00	0.049
Non-Caucasian	21 (42.9%)	14 (28.6%)	14 (28.6%)	1		
Q1	39 (57.4%)	12 (17.6%)	17 (25.0%)	3.70	1.98- 6.91	<0.01
Q2	37 (46.8%)	16 (20.3%)	26 (32.9%)	2.44	1.36- 4.37	
Q3	23 (27.7%)	17 (20.5%)	43 (51.8%)	1.11	0.62- 1.97	
Q4	23 (25.6%)	23 (25.6%)	44 (48.9%)	1		
Hyperkeratosis	48 (43.6%)	16 (14.6%)	46 (41.8%)	1.07	0.48-2.58	0.91
Dysplasia	70 (36.8%)	47 (24.7%)	73 (38.4%)	1.16	0.50-2.69	
Carcinoma	7 (29.2%)	6 (25.0%)	11 (45.8%)	1		

Table 7. Multivariate analysis for alcohol usage, according to gender, race, age quartiles and diagnosis. Probabilities modeled are those for the worst category. N= 468 ever alcohol users. [a]OR: odds ratio. [b]CI: confidence interval of odds ratio.

	Still using N (%)	Quit after biopsy N (%)	Quit prior to biopsy N (%)	OR[a]	95% CI[b]	P-value
All	383	37	48			
Male	217 (80.4%)	23 (8.5%)	30 (11.1%)	0.73	0.44-1.22	0.23
Female	161 (84.3%)	12 (6.3%)	18 (9.4%)	1		
Caucasian	345 (84.4%)	26 (6.4%)	38 (9.3%)	3.17	1.63-6.15	<0.01
Non-Caucasian	31 (63.3%)	9 (18.4%)	9 (18.4%)	1		
Q1	96 (86.5%)	8 (7.2%)	7 (6.3%)	1.71	0.79-3.69	0.05
Q2	111 (85.4%)	8 (6.2%)	11 (8.5%)	1.48	0.73-3.00	
Q3	85 (75.2%)	12 (10.6%)	16 (14.2%)	0.69	0.36-1.32	
Q4	87 (79.8%)	8 (7.3%)	14 (12.8%)	1		
Hyperkeratosis	153 (83.2%)	12 (6.5%)	19 (10.3%)	2.09	0.86-5.04	0.26
Dysplasia	208 (82.9%)	18 (7.2%)	25 (10.0%)	1.82	0.78-4.22	
Carcinoma	22 (66.7%)	7 (21.2%)	4 (12.1%)	1		

Table 8. Behavioral change in subjects who were smokers at time of biopsy.
Percentage of subjects per diagnostic category who quit smoking following biopsy. N= 194 smokers at time of biopsy

	Still Using After Bx. N (%)	Quit After Bx. N (%)
All	125 (64.4%)	69 (35.6%)
Hyperkeratosis	48 (75%)	16 (25%)
Dysplasia	70 (59.8%)	47 (40.2%)
Carcinoma	7 (53.8%)	6 (46.2%)

Table 9. Behavioral change in subjects who were alcohol consumers at time of biopsy. Percentage of subjects per diagnostic category who quit drinking alcoholic beverages following biopsy. N= 420 alcohol consumers at time of biopsy.

	Still Drinking After Bx. N (%)	Quit After Bx. N (%)
All	383 (91.2%)	37 (8.8%)
Hyperkeratosis	153 (92.7%)	12 (7.3%)
Dysplasia	208 (92%)	18 (8.0%)
Carcinoma	22 (75.9%)	7 (24.1%)

Discussion

To our knowledge, this is the first study to address the effect of a premalignant diagnosis on oral cancer risk factor cessation. For those subjects using cigarettes or alcohol at the time of biopsy, higher percentages of subjects with clinically more severe diagnoses quit following biopsy, including higher percentages of subjects with dysplasia quitting as compared to those with hyperkeratosis (Tables 8 and 9). This is an encouraging finding given that dysplasia has been shown to be a potentially reversible process. [48, 49]

When all subjects who reported ever using cigarettes were combined, age was the explanatory variable found to be significantly associated with cessation (Table 4). The finding of younger subjects being both less likely to quit prior to biopsy as well as more likely to be still smoking appears to conflict with data from the most recent National Health Interview Surveys (NHIS), which found that adults ≥ 65 years had a lower interest in smoking cessation and made fewer attempts at quitting.[50] It is postulated that differences may be attributable to sampling, as this study focused on patients with a history of a suspicious oral lesion as opposed to smokers in the general population. It is possible that suspicious oral lesions may be less alarming to younger patients, who may consider cancer to be a phenomenon associated with older age.

When combining all subjects who reported ever using alcohol, race was significantly associated with cessation after controlling for other variables, with Caucasians being less likely to quit consuming alcohol prior to biopsy (Table 5). In addition, a higher proportion of Caucasians reported ever use of alcohol. This is consistent with findings from other studies that noted Caucasians to have the highest rates of current alcohol consumption[51] and high rates of binge drinking, although the highest prevalence of alcohol dependence was observed in American Indians or Alaskan Natives.[52] However, findings in this study associated with race

should be interpreted cautiously as non-Caucasians comprised less than 15% of respondents. The small number of non-Caucasian respondents may be attributable to several possible factors, including a potentially smaller pool of non-Caucasian subjects undergoing oral biopsy, or possibly because non-Caucasians were less likely to return a questionnaire. A previous epidemiological study noted that African Americans were more reluctant to take part in medical studies as compared to Caucasians, which was chiefly attributable to reduced trust in medical research.[53]

Carcinoma subjects were significantly more likely to be older than subjects with hyperkeratosis or dysplasia (Table 2). This may be related to the fact that older patients theoretically have longer periods of exposure to risk factors; however, it may also be due to the fact that the likelihood of developing cancer increases with age.[54] Significantly fewer carcinoma subjects reported never using cigarettes as compared to those in other diagnostic categories, which is compatible with current models of tobacco use as a risk factor for oral cancer.

Data from this and other studies highlights the fact that a large percentage of patients at risk for oral cancer continue to use carcinogenic products. Smoking cessation advice from healthcare personnel results in more attempts at quitting and improved utilization of pharmacotherapy agents shown to improve the rates of smoking cessation by two to three times.[1, 50] However, while there is clearly a need for involvement of healthcare providers in the fight against tobacco addiction, evidence suggests that actual engagement by clinicians is lacking. For instance, a CDC study of current smokers found that approximately 50% of those who visited a physician within a twelve month period received cessation advice, whereas only about 10% who visited a dental professional received cessation advice.[44]

It is imperative that oral care providers increase efforts to aid patients in risk factor

cessation. Nevertheless, the role of the healthcare provider in cessation efforts is not always readily evident. For instance, considerable emphasis is placed on promoting health knowledge and enhancing clinical outcome measures; however, studies have verified that improved knowledge in and of itself does not necessarily translate to a change in behavior or health.[33-35] It has been postulated that patients are not likely to adopt new behaviors unless there is a perceptible benefit associated with this behavior; thus, reduced pain, better function or increased quality of life may serve as motivational factors, whereas a clinical measurement of disease may not be meaningful from a patient perspective.[36] For this reason, it is critical to address risk factor cessation from a patient's viewpoint of how the associated benefits may particularly impact his or her daily life. For instance, it has been noted that patients who continue to smoke have a lower perception of the risks associated with cigarettes and a reduced motivation to quit.[37-39] According to this study, oral biopsy is an important initial step in risk factor cessation for those patients with oral lesions. Informing a patient that surgical removal of a suspicious lesion is recommended enlightens the patient to the fact that his health may be in jeopardy and that a painful procedure is recommended in order to determine this. Also, delivery of the biopsy diagnosis also serves as an opportunity to highlight unequivocally how the patient's tissues are being affected by risk factor use as well as how cessation will be directly beneficial. For those diagnosed with hyperkeratosis, patients should be informed that although these lesions are not considered precancerous, hyperkeratosis is a change that tissues undergo as a means of protection to an irritant. Chronic exposure to products that cause tissue injury leads to increased cell division as a means of replacing damaged cells, and this subsequently leads to increased risk for neoplasia due to the additional opportunity for errors in genetic replication.[55] This concept coincides with the finding that, when followed over time, some lesions initially diagnosed as

benign hyperkeratosis later progress to squamous cell carcinoma.[56, 57] In this study, lower percentages of risk factor cessation were found in subjects with hyperkeratosis, perhaps indicating that these patients have a misguided sense of wellness.

As previously mentioned, relatively few oral care providers currently address smoking cessation with patients.[44] Clinicians may have several perceived barriers to discussing risk factor cessation with patients, including the potential time-consuming nature of such a conversation, especially if the discussion is to be personalized for each patient. However, for busy clinicians, it is noted that interventions of merely three minutes can significantly affect tobacco abstinence.[19, 45] Another possible concern is that a patient will be encumbered with too much information at once or unable to process additional information after an alarming diagnosis. However, the vast majority of patients who undergo an oral biopsy have several possible appointments in relation to the biopsy, including an exam at a referring provider's office, a consult with a specialist, a surgery appointment and post-operative appointment(s) for follow-up and delivery of the diagnosis. Each of these can serve as a "touch point" for communication. Discussion of risk factor cessation can be incremental with introduction prior to surgery and follow-up dialogue at subsequent appointments. Also, presenting information prior to surgery regarding the adverse effect of smoking on surgical outcomes may provide further incentive for tobacco cessation.[19] Thus, both referring providers and specialists have the opportunity to assist patients in the challenging endeavor of overcoming an addiction.

Further evidence for the role of oral healthcare providers in the fight against tobacco related diseases comes from studies that highlight the importance of early intervention for tobacco cessation in patients at risk for cancer. For instance, a study focusing on lung carcinoma patients found that those treated for nicotine dependence within three months of initial diagnosis

had a greater likelihood of being tobacco free at the 6 month follow-up appointment as compared to those who received nicotine dependence treatment greater than three months after diagnosis.[19, 41] As oral biopsies often occur in a dental office, these providers may see oral cancer patients prior to the patient being referred to otolaryngology or oncology, and the initial tobacco cessation intervention should not be postponed for these other doctors. Finally, the role of oral healthcare personnel as related to tobacco cessation is highlighted in studies that found higher tobacco abstinence rates associated with cessation interventions performed in conjunction with diagnostic work-ups or cancer screenings.[19, 46, 47] Thus, research suggests that risk factor cessation intervention may be particularly helpful when performed at diagnosis and treatment planning appointments, in addition to recall examination appointments, as the patient is already undergoing an oral cancer screening exam. Furthermore, implementing a protocol for the discussion of risk factor cessation at these appointments ensures that this important aspect of patient care will not be overlooked, even for patients that do not yet have a clinically visible lesion.

This study utilized self-reporting of risk factor use, which replicates a real-world clinic setting in terms of determining a patient's history of tobacco and alcohol use. Nevertheless, this introduces a potential limitation of the study as this method may be prone to recall bias or misreporting. Some studies using biochemical analysis have documented inaccuracies in the self-reporting of tobacco use.[58-60] The likelihood of inaccuracy appears to be increased in patients who claim to be recent quitters.[58, 61] In addition, pregnant patients or patients with tobacco-related diseases may also be more likely to underreport tobacco use, perhaps because these patients feel more social obligation to quit smoking.[58-60] Conversely, other studies document good correlation between self-reported cigarette use and biochemical analysis of

nicotine metabolite levels; this was found in both studies of selected populations, such as pregnant patients and head and neck cancer patients, as well as in a meta-analysis of studies involving the general population.[61-63] In addition, it is noted that self-reported data obtained in a research setting is frequently more accurate than that obtained in a clinical setting, as the research setting is deemed to be more neutral.[60]

Due to the controversy associated with self-reporting of tobacco use, a future study of this nature that utilizes biochemical validation of nicotine exposure may prove useful. In addition, this study was limited by a cross-sectional design; a longitudinal study would be useful as risk factor usage may vary over time following diagnosis and treatment. For patients that quit prior to biopsy, it would be beneficial to know if the patient quit several years prior to the biopsy procedure, or if cessation occurred closer to the time of surgery as the latter cases could be potentially attributable to the seriousness of the need for biopsy. Furthermore, carcinogenic product usage at the time of biopsy should be used as an inclusion criterion in order to focus on oral biopsy diagnosis as associated with risk factor cessation. Finally, future studies may want to address intervention measures designed to improve patients' sense of coherence in order to enrich quality of life as associated with oral health, specifically the prevention of oral cancer. Sense of coherence is broadly defined as the extent to which a person perceives life rationally and is able to manage stressors with available resources and considers challenges as worthwhile endeavors.[33, 64] It is important for the oral health care provider to be aware that a patient must be personally empowered and motivated to overcome an addiction, and that sheer awareness of objective statistics or even personal clinical parameters may not be helpful in the cessation journey. The risk factor cessation discussion should be personalized for each patient and discussed in such a way as to elucidate the tangible benefits of quitting.

In conclusion, the current study demonstrates that undergoing an oral biopsy procedure, as well as receiving the subsequent diagnosis, is important in the arsenal against risk factor addiction. Indeed, an oral biopsy is not simply a means to determine the diagnosis of a lesion—it is a substantial opportunity to engage patients in risk factor cessation; acquiring a diagnosis is more definitive in delineating risk to the patient as it provides objective, personal and tangible evidence of physical harm resulting from risk factor use. The appointments proximate to oral biopsy are an ideal time to emphasize the implications of premalignant or malignant diagnoses. Moreover, and perhaps even more importantly, it follows that clinicians who are aware of this important relationship should be inspired to change their own behavior in a proactive way, both by performing more biopsies of suspicious lesions and by enhancing their patient education efforts to provide convincing biologic reasons why patients should quit based on the objective evidence of the biopsies. In addition, differences in risk factor cessation associated with age and race underscore the need for clinicians to address cessation with all patients. Armed with the evidence from this study, clinicians should be even more compelled not to "watch" suspicious lesions over time or to neglect cessation counseling for current risk factor users. Biopsy is indicated for non-pathognomonic lesions that do not resolve after a reasonable period of time during which all sources of physical and chemical irritation are removed. Enhanced clinical behavior should result in improved cessation results.

APPENDIX 1: ADDITIONAL MATERIALS AND METHODS

In the UNC oral pathology data base, all biopsy specimens are coded according to diagnosis and can be found by searching for the respective code(s). As some diagnoses are more common than others, it was expected that the diagnosis categories would not contain equal numbers of potential subjects. Once potential subjects were identified, a list was generated with the diagnosis, name and address of each potential subject, and each potential subject was assigned a study number. Gender, ethnicity and race were not part of the defining criteria for identifying a study population.

The questionnaire was partially modeled off the Alaskan Native Medical Center Tobacco Use Questionnaire.[65] A cover letter gave a brief description of the study and its purpose, and the subject was asked to complete and return the questionnaire if they consented to participate in the study. A postage-paid envelope was included with the questionnaire. The questionnaire was created using Teleform so that returned questionnaires could be electronically scanned to record answers. When a completed questionnaire was returned, it was matched with its corresponding study number to keep track of which potential subjects had responded. Questionnaires were scanned and answers electronically recorded within a secure database in the School of Dentistry. Data recorded included: study number, diagnosis, subject gender, subject age, subject race, tobacco use (type, duration, frequency), alcohol use (duration, frequency), use change since biopsy (quit before biopsy, no, reduced use or quit) and any knowledge of previous diagnosis of oral human papillomavirus. Subject name and address were not recorded. The original list with subject names and addresses was destroyed at the completion of the study. A biostatistician (Dr. Ceib Phillips) was consulted in study design and data analysis.

Some subjects had multiple diagnoses; only the most severe diagnosis was counted and

used to categorize the subject. For statistical analysis, all subjects diagnosed with carcinoma were grouped together. Similarly, all subjects diagnosed with dysplasia (mild, moderate or severe) were grouped together.

APPENDIX 2: QUESTIONNAIRE

UNC SCHOOL OF DENTISTRY
DEPARTMENT OF DIAGNOSTIC SCIENCES AND GENERAL DENTISTRY
Latency of Oral Carcinogenesis in Tobacco Users

ID: ☐☐☐☐

INSTRUCTIONS: **If you consent to participate in this study, please use pen to complete forms. Fill in circles completely for the most appropriate option or fill in the blanks as needed. Please fill in only ONE option for each question.**

Please shade circles like this: ●

Gender: ○ Male ○ Female

Age: ☐☐

Race: ○ African-American ○ Asian ○ Native American ○ Caucasian ○ Other

Have you ever been diagnosed with human papillomavirus (HPV)? ○ Yes ○ No ○ Don't know

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Cigarettes

Have you ever used this product? ○ Yes ○ No (SKIP TO NEXT SECTION - Smokeless Tobacco)

How many years have you used (did you use) it? ☐☐

What is the most that you have ever used in one day?
○ 1/2 pack or less ○ 1 pack ○ 1-2 packs ○ More than 2 packs

How much do you currently use each day?
○ None ○ 1/2 pack or less ○ 1 pack ○ 1-2 packs ○ More than 2 packs

Have you changed your use since your biopsy?
○ I quit before my biopsy ○ No ○ Yes - I've reduced how much I use ○ Yes - I've quit

---

Smokeless tobacco (chew or snuff)

Have you ever used this product? ○ Yes ○ No (SKIP TO NEXT SECTION - Pipes or cigars)

How many years have you used (did you use) it? ☐☐

What is the most that you have ever used in one day?
○ less than 1 hour ○ 1-5 hours ○ 6-12 hours ○ More than 12 hours

How much do you currently use each day?
○ None ○ less than 1 hour ○ 1-5 hours ○ 6-12 hours ○ More than 12 hours

Have you changed your use since your biopsy?
○ I quit before my biopsy ○ No ○ Yes - I've reduced how much I use ○ Yes - I've quit

---

*This questionnaire was partially modeled off the Alaskan Native Medical Center Tobacco Use Questionnaire.
www.anthc.org/cs/chs/tobacco/upload/FINAL-ANMC-Tobacco-use-questionnaire-May-08.PDF

Questionnaire - Page 2 ID:

Pipes or Cigars

Have you ever used this product? ○ Yes ○ No (SKIP TO NEXT SECTION - Alcoholic Drinks)

How many years have you used (did you use) it? ☐☐

What is the most that you have ever used in one day?
○ 1 cigar or pipe load ○ 1-3 cigars or pipe loads ○ 4 or more cigars or pipe loads

How much do you currently use each day?
○ None ○ 1 cigar or pipe load ○ 1-3 cigars or pipe loads ○ 4 or more cigars or pipe loads

Have you changed your use since your biopsy?
○ I quit before my biopsy ○ No ○ Yes - I've reduced how much I use ○ Yes - I've quit

Alcoholic Drinks

Have you ever used this product? ○ Yes ○ No

How many years have you used (did you use) it? ☐☐

What is the most that you have ever used in one day?
○ less than one drink ○ 1-5 drinks ○ more than 5 drinks

How much do you currently use each day?
○ None ○ less than one drink ○ 1-5 drinks ○ more than 5 drinks

Have you changed your use since your biopsy?
○ I quit before my biopsy ○ No ○ Yes - I've reduced how much I use ○ Yes - I've quit

Please return this questionnaire in the provided stamped envelope.

Thank you for your time and consideration!

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