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BOSTON UNIVERSITY

HENRY M. GOLDMAN SCHOOL OF DENTAL MEDICINE

DISSERTATION

TOBACCO USE AND DENTAL CARIES: TOBACCO USE STATUS, PRODUCT TYPES, AND MEDIATION BY SALIVA FLOW RATE

by

LAYLA WALEED ABULJADAYEL

BDS, University of King Abdulaziz, School of Dental Medicine, 2011

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Science in Dentistry

Department of Health Policy and Health Services Research

2017

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Approved by

First Reader: ______________________________

Elizabeth A. Kaye, PhD, MPH

Professor, Department of Health Policy & Health Services Research.

Second Reader: ______________________________

Raul I. Garcia, DMD, MMedSc.

Professor and Chair, Department of Health Policy & Health Services Research

Director, Northeast Center for Research to Evaluate and Eliminate Dental Disparities (CREEDD).

Third Reader: ______________________________

Corinna Culler, RDH, DrPH.

Assistant Professor, Department of Health Policy & Health Services Research

Director, School-based Programs.

Fourth Reader: ______________________________

Astha Singhal, D.M.D, Ph.D.

Assistant Professor, Department of Health Policy & Health Services Research.

“Smoking is one of the leading causes of statistics.”

Fletcher Knebel

DEDICATION

In memory of

my dear Grandfather Ramzi Edrees

& To my love

Abdulraheem and Layal Alwafi

& To my family

for their infinite love and trust

ACKNOWLEDGMENTS

It is a real pleasure to have reached this moment after the long route of processing this dissertation. This dissertation was not written and completed alone, therefore, it owes very much to all the people with whom I have travelled through this journey. Their knowledgeable and/ or moral support, encouragement and guidance are greatly appreciated. I wish to offer my most heartfelt thanks to the following people.

First and foremost I want to thank my advisor Prof. Elizabeth Kaye. Thank you for the advice, support, time, patience, and willingness that make my doctorate experience productive and stimulating.

To Prof. Raul Garcia. As the chair of the department, you have been an ever present beacon of knowledge and support. Thank you for all comments and feedbacks despite your busy schedule.

To Asst. Prof. Corinna Culler. Thank you for being there for us since the first year in the program. As the director of school-based programs, if there is one thing I want to imitate from you, it is your advocacy on oral health care for children.

To Asst. Prof. Astha Singhal. Thank you very much for your time, valuable advice and excellent guidance in the statistical analysis.

I would like to express my gratitude to Assoc. Prof. Woosung Sohn, director of the program. Thank you for all of the meetings and chats over the years. Thank you for your advice and guidance from the very early stage of the program. In addition, I would like to thank Ms. Thayer Scott. Thank you for keeping your office door open and available for all the times when I needed it. Thank you for being a positive influence in the department. Thank you for the breathing exercises to refresh our minds all the time.

Furthermore, I would like to express my sincere thanks and appreciation to my country Saudi Arabia for this golden opportunity with this scholarship, a once-in-a-lifetime chance to pursue my education. I am looking forward to returning to my home, my country and to using this extensive experience and expertise to serve my country.

I am deeply thankful to my family for their love and support, specially my younger siblings: Kahlid, Abdulmaleek, Ramzi and Ibrahim. Special thanks for my one and only sister, Rabab, for all her encouragement and motivations. My second family, my in-laws, have always supported me throughout my education and I really appreciate it. Thank you for all prayers and love.

My deepest gratitude and love for my father, Eng. Waleed Abuljadayel, for allowing me to follow my ambitions throughout my childhood. Thank you, dad, for challenging me all time and for giving me your warrior spirit, which are blessings because they expand my potentials.

My heartfelt thanks go to a special person, who I can honestly say that without her unconditional intervention, support and prayers this dissertation would not exist. Mom, Sana Edrees, I cannot thank you enough for being my mom, best friend and role model. Thank you.

I am extremely grateful for my grandmother, Sobhia Gabish, the mother of all, whose blessings have enabled me to accomplish my research work successfully and for the strength that keep us standing. Thank you for every skill I got it in my life, starting from my first walking steps to many more. Allah bless you!

Finally, and most importantly, I wish to thank wholeheartedly my husband Abdulraheem Alwafi. Thanks for always being on my side during the past 12 years. Thank you for supporting me in both my achievements and my failures. Thank you for making me who I am today. I'm the luckiest lady on earth to have you as mine and to grow old with you with all these successes. Prominently, thank you for giving me the opportunity to be a mother of the most gorgeous daughter, Layal.

Layal, words can't express how grateful I am for having you in my life. You are the most precious gift from Allah. You were there, inside me, sharing me every moment while doing this dissertation from very scratch, so thank you for all your sacrifices. I love you my baby! And I am very proud of you!

Oh Allah, make me be the reason for my family happiness and pride!

TOBACCO USE AND DENTAL CARIES:

TOBACCO USE STATUS, PRODUCT TYPES, AND MEDIATION

BY SALIVA FLOW RATE

LAYLA WALEED ABULJADAYEL

Boston University, Henry M. Goldman School of Dental Medicine, 2017

Major Professor: Elizabeth A. Kaye, Professor, Department of Health Policy & Health Services Research, Boston University Henry M. Goldman School of Dental Medicine

ABSTRACT

Objectives: Despite declining tobacco consumption in the U.S., it remains a public health concern. The aim of this study was to assess the impact of tobacco consumption, different tobacco products and smoking duration on dental caries risk among different populations.

Methods: National Health and Nutrition Examination Survey data were used in an epidemiological cross-sectional study of a representative sample of U.S. civilian non-institutionalized population to investigate the influence of tobacco use and different tobacco products on caries prevalence among adolescents and adults. The outcomes were DMFT and DFT indices. Data from the Dental Longitudinal Study (DLS), a closed-panel prospective cohort study of oral health and aging, was used in longitudinal design to determine if changes in tobacco use status change the risk of developing new caries in adult men. Caries increment was used as an outcome. In addition, a cross-sectional study, using DLS, evaluated the association between smoking duration and caries prevalence,

and to determine if it is mediated by unstimulated saliva flow rate. DMFS was used as an outcome. Descriptive and bivariate analyses were conducted on dental caries outcomes by tobacco use status and product consumption. Multiple regression, GEE, and mediation analyses were conducted controlling for confounders.

Results: Active tobacco use was significantly associated with dental caries, with the highest caries prevalence compared to passive or non-use among adolescents and adults (P-value <.0001). Among adolescents, passive tobacco users had higher caries prevalence than non-tobacco users. In the DLS, continuous use, quitting and starting/ restarting tobacco use between examinations were all associated with higher caries increments (p-value <0.01). Smoking duration was significantly associated with caries prevalence as long smoking duration (31- 70 years) had on average 14 more DMFS than nonsmokers (p-value= 0.0002) and USFR may partially mediate this relation by about 8.70%.

Conclusion: Dental caries was significantly associated with active tobacco use among adolescents and adults. Caries prevalence is also high among adolescents passively exposed to tobacco. In adult men, continuous tobacco use was associated with higher caries increments. Long-term smoking was associated with high caries prevalence and this relation could be partially mediated by unstimulated saliva flow rate.

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LIST OF ABBREVIATIONS

CDC .... Centers for Disease Control

DFS .... Decayed and Filled Surfaces

DFT .... Decayed and Filled Teeth

DLS .... Dental Longitudinal Study

DMFS .... Decayed, Filled, Missing Surfaces

DMFT .... Decayed, Filled, Missing Teeth

NHANES .... National Health and Nutrition Examination Survey

USFR .... Unstimulated Saliva Flow Rate

VA .... Veterans Affairs

WHO .... World Health Organization

INTRODUCTION

Overview of Tobacco Use and Dental Caries

Dental caries (tooth decay) is one of the most common chronic infectious bacterial diseases to which people are susceptible throughout their lifetime[1]. Worldwide, 60–90% of school children and almost 100% of adults have dental caries, often leading to pain and discomfort.[2] The distribution of dental caries is uneven in different populations, with the highest prevalence of decay in the developing world as a result of a huge deficiency in public health measures including disparities in dental service utilization, low public health awareness, lack of use of fluoride or high consumption of cariogenic products[3]. In the United States, 21% of children 6 to 11 and 92% of adults 20 to 64 years old have had dental caries in their permanent teeth according to a CDC, 2015 report[4].

The etiology of dental caries is complex, with factors acting at distinct levels. Factors range from the narrowest circumstances of an individual's oral cavity environment (tooth alignment, bacteria presence, impaired salivary function) to health behaviors (tooth-brushing frequency, food habits) and community level influences (community water fluoridation, dental care access, and exposure to toxins such as lead[5, 6])

Dental caries negatively impacts not only on individual's oral health, but also the quality of life and systemic health[7]. In some cases it can lead to fatal complications as when in 2007 a 12-year-old Maryland boy died from a severe brain infection that resulted after his dental caries went untreated[8].

Therefore, one of the main oral health objectives in Healthy People 2020 objectives is to reduce the proportion of dental caries among adolescents aged 13 to 15 years from 53.7% to 48.3% and among adults 35 years and older from 82.8% to 74.5%.

To date, most public health efforts aimed at addressing the caries epidemic have focused on tooth-level factors and interventions (e.g., topical fluorides, dental sealants). Comparatively, less research has been conducted on the socioeconomic[9], environmental[10], political[1], and oral healthcare provider[11],[12] determinants of oral health.

Tobacco use is a worldwide problem. One-third of the world‘s population above the age of 15 years uses tobacco products, which equals over 800 million people, according to the WHO[13]. Although the tobacco use trend has declined in the United States since 1965[14], the national oral health objectives in Healthy People 2020 have emphasized reducing consumption and exposure to all tobacco products among all age groups[15]. Goals include reducing the percentage of adolescents who use tobacco from 26% to 21% and to increase smoking cessation attempts by adult smokers from 50.2% to 80%. Reducing the proportion of adolescents who are exposed to secondhand smoke from 45.5% to 41% is an objective as well.

Tobacco consumption is represented by different methods and products available on the market, any of which contains the addictive drug nicotine [16],[17]. After green

tobacco leaves have been harvested, they are dried, cured and ground up to use in different ways: 1) inhaling the smoke from burning tobacco leaves, called "smoking tobacco" or 2) consuming the leaf powder orally or nasally, called "smokeless tobacco". Smoking tobacco includes cigarettes, cigars and pipes. Cigarettes, the most commonly used smoking tobacco product, are made from tobacco leaves rolled in a thin paper cylinder. Cigars are made of air-cured or dried tobacco leaves that have been aged and fermented in a long process during which the bacteria cause chemical changes in the leaf compounds. These end-product compounds give cigars their unique taste and smell, but also make them as highly carcinogenic as cigarettes[18]. Pipe tobacco is placed in the chamber or bowl of a pipe and lit, and the smoke is inhaled through the connecting stem.

Smokeless products include chewing tobacco and snuff. Chewing tobacco is tobacco that has been shredded, twisted, or compacted into bricks that is placed in the mouth, cheek, or inner lip. It is either held in place, sucked or chewed. It is available as paste or powder. It is sometimes referred to as "spit" tobacco because users spit out the built-up tobacco juices and saliva. Snuff tobacco is finely cut or powdered and is available loose, in dissolvable lozenges or strips, or in small pouches similar to tea bags. Users place a pinch or pouch between the cheek and gums and hold it in place.

Any direct use of any type of these products is considered "active" tobacco use, while exposure to these products by inhaling the smoke from an active smoker leads to "passive" tobacco use. To accurately distinguish between active and passive tobacco use,

many researchers prefer to use cotinine level in body fluids as an index of tobacco exposure. Cotinine is the primary metabolic substance of nicotine in the body. It could be measured in serum, urine, saliva and hair and its half-life is about a week[19].

Many management guidelines for systemic diseases state that patients should be strongly advised not to use tobacco as it is obviously demonstrated to be a strong risk factor or causal factor for many diseases. For example, cancer, asthma, heart diseases and HIV-related infections are all increased in tobacco users[20-22]. The harmful effects of tobacco are not limited to systemic diseases but also involve many oral health complications. Tobacco use is one of the behavioral risk factors that is associated with oral cancer, oral mucosal lesions[23], periodontal disease[24-26], and cleft lip and palate[27]. On the other hand, the association between tobacco use and dental caries is still not verified.

The association between tobacco use and dental caries has been a controversial subject for many years; while Hirsch et al. 1991 & Ylostalo et al. 2004 stated that there is a positive correlation between the tobacco use and caries prevalence[28] [29], Johnson et al., 2000 concluded that smoking protects from caries. This conclusion was based on observations that smokers have higher concentrations of thiocyanate [30], a chemical product present in tobacco smoke and in normal saliva that was once thought to inhibit oral bacteria growth.

Previous studies that investigated the association between tobacco use and dental caries have many limitations, as earlier cross-sectional studies had small sample sizes or segmented population groups regarding age, gender or region. The majority of studies looked at a limited variety of products, measuring tobacco status by cigarette use only. Many previous cohort studies were also limited to just cigarette products, or had short follow-up periods. The longest cohort studies that assessed the relation between tobacco use and dental caries were 8 years for adolescent[31] and 4 years for adult age group[32]. Another limitation of previous studies is that the mediation effect of saliva flow rate on the relation between tobacco use and dental caries has not been evaluated.

Not only is tobacco use itself harmful for our body, but duration of use is related to severity of systemic health issues such as lung cancer[33], cardiovascular diseases[34], oral, pharyngeal and esophageal cancers[35], tooth loss[36], periodontitis[37] and dental caries[38]. Extent of caries may also be impacted by smoking duration.

The biological mechanism of how tobacco use could lead to dental cares is still unclear. Several factors have been proposed to explain, directly or indirectly, the mechanism of increased caries prevalence in smokers. For instance, some studies indicated that nicotine in tobacco stimulates the growth of Streptococcus Mutans bacteria in vitro[39]. Others showed that poor oral hygiene habits, high sugar consumption habits or poor dental prevention are significantly higher in tobacco users than nonusers[40]. Another potential pathway that was suggested by research to justify how tobacco use

could increase caries, is through reducing the quantity or quality of saliva. Saliva quantity has been found to be one of the strongest salivary biomarkers for an increased risk of developing caries[41]. Altered saliva flow rate has been shown to be associated with oral malodor[42], tooth loss[43], periodontitis and caries[44]. Furthermore, some researchers concluded that saliva flow rate could be modified by tobacco use. Salivary fluid is the first biological fluid that is exposed to tobacco products and these products contain toxic substances that could modify saliva properties[45]. As a result, there is a possible mediation effect of saliva flow rate on the association between tobacco use and dental caries. While Johnson et al, 2000 and Lie et al 2001suggested that there was no significant difference in saliva flow rate between smokers and non-smokers[30, 46], Rad et al, 2010, showed that mean USFR in long-term smokers was significantly lesser than in non-smokers among Iranian adults[45].

Therefore, this dissertation is composed of three different studies that evaluated several aspects of tobacco use and its association with dental caries development:

Study 1: Association between tobacco use status (active, passive, none) and tobacco products with dental caries prevalence among US population, NHANES (2001-2012)

Study 2: Association between changes in tobacco use status and new caries development among adult men over a period of 40 years (1969-2008), Dental Longitudinal Study (DLS)

Study 3: Association between smoking duration and dental caries among US men adults: unstimulated saliva flow rate as key mediator, cross-sectional study (DLS)

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CHAPTER ONE

Association between tobacco use status (active, passive, none) and tobacco products with dental caries prevalence among US population, NHANES (2001-2012)

Abstract:

Objectives: To analyze the association of tobacco use status (active, passive, none) and different tobacco products (smoking; cigarettes, cigar or pipe/ smokeless; chewing or snuff/ combined more than one product) with dental caries prevalence among US adolescents and adults.

Methods: Data from the 2001-2012 National Health and Nutrition Examination Surveys were used. Participants were aged 12 years and older. Active tobacco use was defined as a detectable cotinine level above 10 ng/mL, passive use as serum cotinine level between 0.05 and 10 ng/mL and non-use as a serum cotinine level ≤0.05 ng/mL. Self-reported use of different tobacco product types was assessed by questionnaire. Associations of smoking status and different products with total caries prevalence (decayed, filled, missing teeth; DMFT index) and (decayed and filled teeth; DFT index) were examined in bivariate and linear regression analyses controlling for potential confounders. Analyses were performed separately for adolescents (age 12-19) and adults (age 20+).

Results: The overall mean (± SD) DMFT and DFT were 2.55 ± 0.08 and 2.49 ± 0.08, respectively, for adolescents, and 11.36 ±7.73 and 7.03±5.40, respectively, for adults. After adjusting for potential confounders, tobacco use status was a strong independent risk indicator for dental caries. Among adolescents, DMFT was significantly higher in active users (3.62±0.28) and passive users (3.2±0.19) compared to nonusers (2.45± 0.22). Similarly, mean DFT was 3.43±0.26 in active adolescent smokers, 3.06±0.18 in passive, and 2.34±0.21 in nonsmokers. Among adults, DMFT was higher in active users (9.46±0.37) than passive (8.50±0.28) or nonsmokers (8.91±0.30). Similarly, DFT was higher in active adult smokers (5.31±0.20) than passive (4.95±0.18) or nonsmokers (5.34±0.19). Independent factors associated with increased dental caries prevalence were being Mexican American, living below the poverty level, having health insurance, dental visit within 1 year, poor oral hygiene, and high sugar intake. For adults, being married, having less than a high school education and moderate alcohol intake were additional confounders that were associated with dental caries. Using different tobacco products (smoking, smokeless and combined) was not statistically significantly associated with dental caries for either adolescents or adults after adjusting for possible confounders.

Conclusions: These results suggest that dental caries is more prevalent among active tobacco users of all age groups compared to non-users. Caries prevalence is

also high among adolescents passively exposed to tobacco. For active tobacco users, there was no statically significant difference between tobacco products in their harmful effects on caries prevalence.

Introduction

Dental caries is a preventable infectious disease that affects about 100% of adults and between 60% and 90% of children of the world's population. Three in five US adolescents aged 12-19 had experienced dental caries in permanent teeth and 15 % had untreated tooth decay[1][2]. Caries also affects US adults, with 9 out of 10 over the age of 20 having some degree of tooth-root decay according to CDC survey in 2012 [3].

Dental caries is a multifactorial disease. Oral cavity factors such as tooth condition, bacterial presence and saliva malfunctioning, health behaviors such as oral hygiene, sugar and carbohydrate consumption, and social factors such as insurance availability and dental care access all contribute to dental caries development[4-7]. Another health behavior that could affect dental caries is tobacco use[8, 9].

Tobacco use is a significant health hazard. Despite many governmental and non-governmental efforts worldwide to control tobacco use, several diseases as well as death rates from smoking continue to grow to reach millions of people ever year[10]. Tobacco use in the U.S. has declined since 1965; however, 36.5 million US adults 18 years and older were current smokers in 2015 and 2,100 US youth start smoking every day, according to the CDC [11][12]. Tobacco use is defined as using any product that contains the addictive drug nicotine. It can be smoked, as in cigarette, cigar or

pipes, or consumed orally or nasally in powder form (smokeless tobacco such as chewing tobacco and snuff). Any direct usage of any type of these products is counted as “active tobacco use”, while inhaling the smoke from an active smoker leads to “passive tobacco use”. For accurate differentiation between active and passive tobacco use status, the preferred method is measurement of cotinine levels, the primary metabolite of nicotine, in the body as an index of nicotine exposure.

Active or passive tobacco use leads to many general diseases as well as oral diseases such as oral cancer, periodontal disease[13], and tooth loss [14, 15]. An association between tobacco use and dental caries has been investigated, however, this association remains inconclusive.

The objectives of this study, therefore, were to compare caries prevalence between active, passive, and non-users of tobacco, and to examine caries prevalence among users of different tobacco products (smoking, smokeless and combined) in a nationally representative sample of U.S adolescents and adults.

Materials and Methods

Data Source and Participants:

Three cycles of the National Health and Nutrition Examination Survey (NHANES 2001-2002, 2003-3004 and 2011-2012) that included full dental examinations and

serum cotinine level were used for this study. NHANES is a stratified multistage probability sample of the civilian non-institutionalized population in the 50 states of the U.S. and the District of Columbia that represent the whole nation. The technical details of NHANES national survey, including sampling design, smoking questions, oral health examination data and laboratory measurements can be accessed at www. Cdc.gov/nchs/nhanes.htm. NHANES participants received standardized dental examinations conducted by trained dental examiners, had blood draws for biological biomarkers and were interviewed on a variety of health practices, including tobacco use. Of the 30,917 people who participated in the 3 cycles, 22,075 participants were 12 years of age or older. Among those, 14,930 participants had a completed dental caries examination, self-reported their tobacco use and had laboratory results for serum cotinine level.

Primary exposure variable – Recent Tobacco Use

In this study we had two independent variables: tobacco use status and tobacco use products, which were determined from serum cotinine measurements and responses to questions of recent tobacco use questionnaire, which were collected at the mobile examination center.

Cotinine values are reported in nanograms per milliliter (ng/mL). The laboratory lower detection limit for cotinine is 0.015 ng/mL. Self-reported tobacco use was obtained using the following questions: "During the past 5 days, including today, did you use any smoking products (cigarettes, cigar, pipe), smokeless tobacco products

that are placed in the mouth or nose (include chewing tobacco, snuff) (Please do not include nicotine replacement products like patches, gum, lozenge, or spray which are considered products to help you stop smoking (Yes – No)", and "Which of these products did you use? (cigarettes, cigar, pipe, chewing tobacco, snuff)" and multiple answers was applicable. No information on the amount or frequency of the tobacco use was available.

The tobacco use status was categorized to three main groups based on the serum cotinine levels according to the healthy people objectives 2020 definition of tobacco use status [16]. Active tobacco users were defined as those who had a serum cotinine level ≥ 10 ng/mL. Passive tobacco users had a serum cotinine level between 0.05 and 10 ng/mL and non-users had a serum cotinine level ≤0.05 ng/mL.

For tobacco use products, we had four different groups according to questions asked about tobacco products used in the past 5 days. Tobacco products used were cigarettes, cigar +/-pipe, smokeless tobacco (chewing +/- snuff) and combination use of cigarette, cigar/pipe, and smokeless product types.

Primary outcome – Dental Caries Prevalence

Trained dental examiners assessed the conditions of all teeth and tooth surfaces, except for third molars, using a surface reflecting mirror and No. 23 explorer. No radiographs were taken. Dental examiners recorded untreated dental decay at the

cavitated level. Two caries indices were used as outcome measures of caries prevalence: the sum of decayed, missing due to disease, and filled/crowned permanent teeth (DMFT Index), and number of decayed and filled/crowned permanent teeth (DFT Index).

Covariates

Covariates that were examined were those believed to be important or previously found to be associated with dental caries. Age, gender, race/ethnicity, socioeconomic status, poverty level, educational level (adults only), insurance, marital status (adults only), self-reported oral health assessment, last dental visit, and reason of last dental visit were obtained from questionnaires. Sugar intake (grams/day) was obtained from the one-day diet recall. Average number of alcoholic drinks/day in the past 12 months intake (adults only) was obtained from a questionnaire and categorized into no use, moderate use (1-2 drinks for men, 1 drink for women), or heavy use (3+ drinks for men, 2+ drinks for women).

Statistical analysis:

All analyses were performed separately for adolescents aged 12-19 years (n= 4,746) and for adults aged 20 years and older (n=10,159). Survey multivariable linear regression analyses assessed the associations between tobacco use status and

tobacco use products with DMFT and DFT controlling for possible confounders found in bivariate analyses. For adolescents, these variables were gender, race, poverty level, time of last dental visit, reason for last dental visit and self-reported oral health. Adult caries mean were adjusted for the same covariates plus education, marital status, sugar and alcohol intake. Pairwise t-tests for contrast were used to compare different tobacco use groups to non-tobacco users. All analyses were conducted using survey procedures in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) that account for the complex, multistage sampling design and use sampling weights to be representative of US population. The significance level was defined as 2-tailed alpha =<0.05.

Results

Among adolescents, males and females were approximately equally represented, the majority were Non-Hispanic White, lived at or above the Federal poverty level, had health insurance, visited a dentist in the past year and had very good oral health. The most common reason for a dental visit was a regular check-up or periodic teeth cleaning. Mean DFT and DMFT were similar, approximately 2.5 teeth. The majority (46%) of adolescents were non-tobacco users, 41.3% were passive tobacco users and 12.7% were active users (Table 1.1). Among those who use tobacco actively, the majority smoked cigarettes only. Few adolescents used other smoked or smokeless products, while nearly 19% used a combination of products.

Among adults, males and females were equally represented, the majority were Non-Hispanic White, had income at or above the Federal poverty level, were married, had a high school education or less, had health insurance, visited a dentist in the past year and had good oral health (Table 1.2). The most common reason for a dental visit was a regular check-up or periodic teeth cleaning. Most of the adults were moderate drinkers. As in the adolescent group, the majority of adults did not use tobacco (48.7%), however, the percentages of active and passive tobacco users were approximately equal. Among active tobacco users, the majority smoked cigarettes only. Compared to adolescents, more adults used smokeless products and few used a combination of products. Mean sugar intake among adults was lower than among adolescents.

Bivariate analysis for adolescents and adults indicated that DMFT and DFT were statistically associated with tobacco use status (p- value <.001) and further adjustment for gender, race, poverty level, last dental visit, reasons of last dental visit and general oral health conditions did not change the results. Overall, active tobacco users had the the highest caries prevalence in both age groups: DMFT and DFT means were 3.62 ± 0.28 and 3.43 ± 0.26, respectively, for adolescents and 9.46 ± 0.37 and 5.33 ± 0.20, respectively, for adults. Mean DMFT and DFT were lower among adolescent passive smokers (3.21 ± 0.19 and 3.06 ± 0.18, respectively) than active smokers, but still higher than their non-tobacco using peers (Table 1.3). Even

though adult passive smokers had lower mean DMFT and DFT than nonsmokers, the differences were not statistically significant (Table 1.4).

For tobacco products, there was no significant difference between caries prevalence and different tobacco products among both age groups after controlling for possible cofounders. However, adolescents who consumed more than 1 product simultaneously had the highest caries prevalence. Adults who smoked cigar or pipe had the highest dental caries prevalence (Table 1.5).

Discussion

The main objective of this study was to examine the associations between tobacco use status and different tobacco product types and caries prevalence using two dental caries indices, DMFT and DFT, among adolescents and adults in the U.S. The results showed that for both age groups, active tobacco users had the highest caries levels. We found different results for passive smokers by age group. Among adolescents, passive tobacco users had higher caries prevalence than non-tobacco users whereas in the older age group, passive tobacco users had fewer caries than non-tobacco users, however, this different is not statically significant.

Our study also showed that, although not statistically different, combining more than one tobacco products had the highest DMFT and DFT means for adolescents,

however, among adults, consuming cigar and pipe had the highest DMFT and DFT means. Reasons for this trend need to be studied in the future.

Few studies have assessed the association between tobacco use and dental caries among the U.S. population. Ditmyer et al., 2013, conducted an 8 year cohort study on adolescents in Nevada state and showed similar trend for caries incidence among different tobacco use status, with active cigarette users having higher DMFT than nonusers[17]. Voelker et al, 2013, conducted a clinical trial on adult patients receiving care in a dental hygiene clinic at the University of Missouri-Kansas City. They included salivary properties (saliva buffering capacity, salivary pH, flow rate and saliva consistency) in their analyses and found a strong relationship between caries risk and different smoking status (active, passive, former, and none). However, they depended on self-reported cigarette smoking status only without asking for other tobacco products or taking serum cotinine level into consideration[18]. Iida et al, 2009 also used NHANES data to analyze the effect of passive tobacco use on oral health of female adults. They showed that smoking cigarettes was a strong an independent risk indicator for dental caries. The differences between the Iida et al. study and ours is that their sample was limited to participants age 44 years and younger, only females, used different smoking status classifications (current, former, never) and a different serum cotinine level cutoff point (15 ng/mL). Also, different tobacco products were not examined. However, they showed a similar trend of caries prevalence and smoking, with current

smokers having the highest mean DMFS, but their results were not statistically significant[8].

Our findings regarding passive smoking and dental caries agree with the literature, although many reported on a younger age group than ours. A study using NHANES data by Aligne, et al, 2003, on 4- 11 year old children showed that having tobacco exposure (cotinine level >0.2 but <10 ng/mL) was not a significant risk factor for caries[19]. Ayo-Yusuf et al, 2007, conducted a study on 13-15 year old South African adolescents who were passive smokers regarding to their self-reported smoking status, which makes this study very close to our adolescent age group. They found passive smokers had significantly higher caries than nonsmokers[20]. Another study, Tanaka et al, 2010 from Japan, showed that passive smoking among teenagers (6-15 years old), through exposure to cigarette smoking from family members at home, had higher DFT prevalence than their non-smoking peers in smoke-free homes[21].

To the best of our knowledge, this is the only study that assessed the relation between U.S adult passive tobacco users (20 years and older) and caries prevalence. Therefore, more investigations should be done for this age group and reasons for having higher DMFT/DFT among non-tobacco use users than passive users should be examined in the future.

For the association between tobacco products and dental caries, cross-sectional studies of different tobacco products and caries conducted in and outside of the U.S. have given discrepant results. Tomar et al., 1999, who used NHANES III data, found that chewing tobacco users had the highest mean DFT compared to cigarette, cigar/pipe, and combined smokers, and were four times as likely to have prevalent root caries than those who never used tobacco. In contrast, we found that among adults, cigar and pipe smokers had the highest caries prevalence and smokeless tobacco users had the least, however, this was not statistically significant. These differences may be due to using different NHANES datasets, gender (males only) or tobacco use status categorization (smokeless, former, never)[22].

For studies of adolescents outside the U.S., our results agree with a study from Saudi Arabia, which showed those using a combination of products had higher DMFT scores, but no statistically significant difference in the prevalence of caries between different tobacco products [23].

Our ability to categorize the tobacco use status had limitations that were associated with the validity of serum cotinine level. The one week half-life made it difficult to distinguish between former and never tobacco users. Although we tried to verify tobacco use status with a biological measure, i.e., cotinine levels, concerns still remain, as individuals with high passive smoking exposures might present high cotinine levels that overlap with those of active smokers. Cotinine is the primary

metabolite element of nicotine. Nicotine has only a half-life of only several hours in blood, therefore, cotinine, which is typically detectable in blood plasma up to one week, is preferable as an indicator for nicotine. Another limitation of this study is that tobacco product questions asked about the products used only in the past 5 days; this might not capture other products used before this time period. Other limitations of this study are the cross-sectional study design and lack of information on quantity of tobacco products used. Prevalence of use of cigars, chewing tobacco/snuff, and combined products was low (23% prevalence for adolescents and 10% for adults). Future studies might be able to gain a better understanding of the dose-dependent effect of active and passive tobacco use on caries. The case definition of DMFT used in this study, by including teeth missing due to caries, might have led to overestimation of the true extent of caries if participants were not certain of the reason any teeth were lost. However, we also examined the decay component separately, with similar results.

A major strength of this study is that it used data from a large, nationally representative sample of US population. To our knowledge, this is the first study that examined the association of tobacco use and dental caries in a broad age range of the U.S. population using serum cotinine level as a basic measure to differentiate between active, passive and non- tobacco users and to compare the effect of different tobacco products on dental caries prevalence.

Conclusion

In conclusion, these results suggest that dental caries is more prevalent among active tobacco users of all age groups compared to non-users. Caries prevalence is also high among adolescents passively exposed to tobacco. This result emphasizes the need for dental professionals to address tobacco use with their patients, especially younger population and to provide appropriate interventions and recommendations for tobacco cessation. Clearly, more collaborative research is needed to determine the mediators that could be a part of tobacco-caries causal chain

Table 1.1 Frequencies of tobacco use status and covariates among US adolescents (12-19 years old, 2001-2012). n=4,746.

Variables	Weighted Frequencies	Weighted Percentages
Tobacco use Status		
Active tobacco use	560	12.7
Passive tobacco use	2177	41.3
Non-tobacco use	2009	46.0
Active tobacco use products		
Cigarette	447	75.0
Cigar / Pipe	27	3.1
Chewing tobacco and Snuff	9	1.5
Combination tobacco products	77	18.7
Gender		
Male	2412	51.0
Female	2334	49.0
Race/ Ethnicity		
Non-Hispanic White	1301	60.5
Non-Hispanic Black	1530	14.6
Other Hispanic	251	6.6
Mexican American	1343	12.1
Other, including multi-racial	321	6.3
Poverty Level		
Below poverty level	1654	26.8
At or above the poverty level	3092	73.2
Health Insurance		
Yes	3809	86.8
No	890	13.2
Last Dental visit		
1 Year or less	3263	76.0
More than 1 Year	1290	22.0
Never	182	1.9
Reason for dental visit		
Check-up, examination or cleaning	3371	74.9
Bothering or hurting	653	10.9
Other reasons	722	14.2
General condition of mouth and teeth		
Very good	1363	44.2
Good	1569	37.5
Fair	765	14.8
Poor	172	3.5

Sugar intake (gm/day) *	154 ∓ 93	-
DMFT*	2.55 ∓ 0.08	-
DFT*	2.49 ∓ 0.08	-

* Mean ∓SE

Table 1.2 Frequencies of tobacco use status and covariates among US adults (20 years and older, 2001-2012). n=10,159.

Variables	Weighted Frequencies	Weighted Percentage
Tobacco use Status		
Active tobacco use	2492	26.2
Passive tobacco use	2709	25.1
Non-tobacco use	4958	48.7
Active tobacco use products		
Cigarette	2163	85.2
Cigar / Pipe	116	4.4
Chewing tobacco and Snuff	146	7.8
Combination tobacco products	67	2.7
Gender		
Male	5089	50.0
Female	5070	50.0
Race/ Ethnicity		
Non-Hispanic White	4722	70.6
Non-Hispanic Black	2133	10.2
Other Hispanic	637	5.4
Mexican American	1806	8.1
Other, including multi-racial	861	5.7
Poverty Level		
Below poverty level	2445	18.3
At or above the poverty level	7714	81.7
Education		
High school or less	4764	38.5
Some college degree	2980	32.2
College graduate above	2410	29.3
Health Insurance		
Yes	7840	80.8
No	2257	19.2
Last Dental visit		
1 Year or less	5785	62.2
More than 1 Year	4116	36.4
Never	243	1.4
Reason for dental visit		
Check-up, examination or cleaning	5502	60.4
Bothering or hurting	2967	26.1
Other reasons	1690	13.5

General condition of mouth and teeth		
Very good	2471	29.4
Good	3628	36.7
Fair	2620	22.5
Poor	1431	11.5
Alcohol use		
No use	1398	12.97
Moderate	6243	77.10
Heavy	720	9.92
Marital Status		
Married	5500	57.0
Widowed	668	4.3
Divorced – Separated	1233	11.6
Never married	2007	19.6
Living with partner	745	7.6
Sugar intake (gm/day) *	125 ∓ 84	-
DMFT*	11.36 ∓ 7.73	-
DFT*	7.03 ∓ 5.40	-

* Mean ∓SE

Table 1.3 Survey multivariable linear regression analyses, adjusted mean DMFT and DFT by tobacco use status among adolescents and adults

	Adjusted* Mean DMFT	SE	p-value	Adjusted* Mean DFT	SE	p-value
Tobacco use status						
Adolescents (12-19 Y)			<0.001			<0.01
Active tobacco user	3.62	0.28		3.43	0.26	
Passive tobacco user	3.21	0.19		3.06	0.18	
Non-tobacco use user	2.45	0.22		2.34	0.21	
Adults (20^{+} Y)			<0.001			0.03
Active tobacco user	9.46	0.37		5.33	0.20	
Passive tobacco user	8.50	0.28		4.95	0.18	
Non-tobacco use user	8.91	0.30		5.32	0.19	

* Adolescent means adjusted for gender, race, poverty level, time of last dental visit, reason for last dental visits and self-reported oral health. Adult means adjusted for same covariates plus education, marital status, sugar and alcohol intake.

Table 1.4 Differences between tobacco use status by adjusted mean DMFT and DFT among adolescents and adults

	Adjusted* Mean DMFT Difference	SE	p-value	Adjusted* Mean DFT Difference	SE	p-value
Tobacco use status						
Adolescents (12-19Y)						
Active Vs non-tobacco	1.20	0.33	0.01	1.12	0.34	0.02
Passive Vs non-tobacco	0.78	0.20	0.01	0.73	0.20	0.01
Adults (20+ Y)						
Active Vs non-tobacco	0.11	0.27	0.04	-0.35	0.15	0.02
Passive Vs non-tobacco	-0.59	0.19	0.69	-0.48	0.15	0.07

* Adolescent means adjusted for gender, race, poverty level, time of last dental visit, reason for last dental visits and self-reported oral health. Adult means adjusted for same covariates plus education, marital status, sugar and alcohol intake.

Table 1.5 Survey multivariable linear regression analysis, adjusted mean DMFT and DFT by active tobacco use products among adolescents and adults

	Adjusted* Mean DMFT	SE	p-value	Adjusted* Mean DFT	SE	p-value
Tobacco use products						
Adolescents (12-19 Y)			0.12			0.11
Cigarette	3.8	0.48		3.42	0.46	
Pipe and Cigar	3.8	0.48		3.75	0.58	
Chewing tobacco and Snuff	1.77	0.48		1.01	1.31	
Combination tobacco use	4.26	0.39		4.03	0.70	
Adults (20+ Y)			0.18			0.06
Cigarette	10.05	0.81		5.25	0.28	
Pipe and Cigar	10.45	0.88		6.55	0.61	
Chewing tobacco and Snuff	8.38	1.09		5.37	0.55	
Combination tobacco use	8.32	1.31		4.49	0.70	

* Adolescent means adjusted for gender, race, poverty level, time of last dental visit, reason for last dental visits and self-reported oral health. Adult means adjusted for same covariates plus education, marital status, sugar and alcohol intake

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CHAPTER TWO

Association between changes in tobacco use status and new caries development among adult men over a period of 40 years (1969-2008), Dental Longitudinal Study (DLS)

Abstract

Objectives: To determine if changes in tobacco use status will change the risk of developing new dental caries in adult men.

Methods: Data were obtained from the VA Dental Longitudinal Study, a retrospective cohort study with dental examinations approximately every 3 years up to 40 years. Participants were 1,033 men aged 49 ± 9 years at baseline from the greater Boston, New England area. Clinical assessments of caries were carried out by a dental examiner and tobacco use was obtained from questionnaires at each examination. Caries prevalence at baseline was computed as number of decayed, missing or filled surfaces (total DMFS) and the caries increment (new DMFS) between each examination was computed from new and recurrent caries events. Men were categorized at baseline as active cigarette user, active cigar/pipe user, or nonuser, and between exams by whether their status did not change, they quit, or started/restarted tobacco use. Adjusted mean total DMFS and caries increment were compared among categories of tobacco status using general linear models and

repeated measures generalized estimating equations, controlling for possible confounders.

Results: At baseline, mean DMFS was higher in active cigarette users (26.23 ±1.0 surfaces) and active cigar/pipe smokers (24.59 ±1.0 surface) compared to non-users (22.03±1.0), P-value <.0001. Use of any tobacco product during follow-up was strongly associated with having new caries lesions compared to nonsmokers (P-value <0.0001). Cigarette products had stronger effect on caries lesion development than cigars or pipes.

Conclusions: Dental caries prevalence and incidence are higher among tobacco users than nontobacco users. Active cigarette and cigar/pipe usage were found to be significant and risk factors for dental caries.

Introduction

During the last several decades, changes in lifestyle and health behaviors, including tobacco use, have occurred as industrialization and market globalization increased. In the United States, cigarette smoking accelerated in the 1930s and 1940s but has declined dramatically since the 1960s following the first US Surgeon General's report on smoking and health in 1964 and subsequent restrictions on tobacco advertising and use in public[1]. In contrast to cigarettes, the prevalence of cigar and pipe smoking has been rising, especially for adolescents[2].Cigar merchandising has increased 50 percent since 1993[3]. Despite the trends for both types of tobacco products, men who use tobacco increase their risk of dying from bronchitis and emphysema by 17 times[4].

Using different tobacco products, whether cigarettes, cigar or pipe, has a significant impact on the oral health status of populations as well[5]. Dental caries is a multi-factorial disease; the oral cavity environment, individual behaviors, and social determinants all can contribute to caries development. During the last decade, researchers have focused on the host and microbial factors in the oral cavity environment and their interactions to identify risk factors for dental caries. However, few studies have assessed smoking, as a health behavior, as cariogenic factor. Two systematic reviews concluded that tobacco use could be a behavioral risk factor for dental caries but the evidence was insufficient[6, 7]. It has been

reported that tobacco users tend to brush their teeth less frequently[8] and consume more sugary products[7] than nonsmokers.

Cigarettes are not the only tobacco products that have negative effect on health. Smoking other products such as cigar or pipe were found to be related to bladder cancer, chronic obstructive pulmonary disease and coronary heart disease, even in participants who had never smoked cigarettes[9-11]. Cigars, similar to cigarettes, are wrapped tobacco leaves, but unlike cigarettes, they go through a prolonged process of fermentation and they don't typically have filters. A single cigar has the nicotine equivalent of an entire pack of cigarettes[12].

Pipes have a unique design for consuming tobacco, which puts tobacco leaves in a bowl at the end of a stem that connects the bowl to the mouthpiece. Unlike cigarettes and cigars, pipes have less nicotine per gram and are considered less harmful - but the tobacco is also unfiltered and risk is not zero[13]. The effect of smoking other tobacco products such as cigar or pipe on oral health is less well documented, as most studies focused mainly on periodontal disease, alveolar bone loss or tooth loss[3, 14]

Smoking cessation is a main public health goal. Former cigarette users have lower incidence of oral cancer[15], tooth loss[16], oral cancer than current cigar users[17]. Quitting pipe smoking also showed a decrease in risk of oral cancer compared to

continuing use[18]. However, the relation between using or quitting any of these tobacco products and dental caries in still unclear.

The main aim of this study is to examine associations between tobacco use and product type and dental caries prevalence, and determine if changings in tobacco use status will change the risk of developing new dental caries in adult men.

Martials and Methods

Data Source and Participants:

The Veterans Affairs Dental Longitudinal Study (DLS) began in 1969 with volunteers drawn from the 2,280 participants in the VA Normative Aging Study, a closed-panel interdisciplinary study of aging in over 2000 community-dwelling men in the Greater Boston Metropolitan Area. The DLS is a prospective descriptive study of oral health that enrolled 1,231 men, ages 21 to 84 and in good medical health. As part of the DLS, they receive comprehensive dental examination and complete questionnaires on dental care, smoking, health and lifestyle every 2 to 4 years (cycle). The DLS cohort is almost entirely non-Hispanic white veteran males, who are not patients of the VA healthcare system. They receive their medical and dental care from the private sector.

Data for this study were obtained from dental examinations between 1969 and 2008 (12 cycle). Mean follow-up time is 21±11 years (range, 2 to 40 years). Participants with no teeth at baseline (N=73), no at least one follow-up (N=112), or missing data on key exposure and outcome variables (N=13) were excluded, leaving a total sample of N= 1,033 men.

Written informed consent was acquired from each participant at each examination. The study was approved by institutional review boards at Boston University Medical Center and the VA Boston Healthcare System

Oral Examination

Dentist examiners performed the clinical assessment of caries and restorations for each tooth at each examination cycle. An explorer was used to probe the tooth surface. Non-cavitated surfaces, discolored and penetrable by probing, were scored as level 1 caries, whereas cavitated surfaces were scored as level 2. Restorations and caries on five coronal and four root surfaces per tooth were recorded. Full-mouth intraoral radiographs were taken at each oral examination and radiographic decay was recorded. A surface was considered as one carious lesion surface in this study whether the caries lesion was detected on clinical examination or on radiograph, was level 1 or level 2, or was present on the coronal or root surface. The examiners also noted whether saliva was limited or copious.

<u>Primary exposure variables – Current Tobacco Use Status</u>

Tobacco use data were available for all examination years (1969 – 2008) from smoking questionnaires administered during the dental examination, providing information about smoking status (current, former or not) and the type of tobacco product (cigarette, cigar, and pipe) usage. Tobacco use status was conducted at two assessment points; baseline and follow-up and it relied only on self-reported tobacco use status from the smoking questioner. Tobacco use status at baseline was divided into three categories: active cigarette user, active cigar/pipe user, or non-smoker. Men who reported former smokers were classified as non-smoker as they were a small number. Change in tobacco status at each follow-up examination for each type of tobacco product was further categorized as continuous nonsmoker, continuous user, quit using, or started/restarted use. Men who used a combination of cigarettes and other products were classified as primarily cigarette smokers.

Primary outcome – Dental Caries

Caries prevalence

The first outcome in this study was the prevalence of dental caries at baseline was computed as the number of decayed, missing or filled surfaces (Total DMFS).

Caries Increment

The second outcome was new dental caries development on surfaces at risk as measured by caries increment (new DMFS). A surface was considered at risk of

caries development if free of clinical and radiographic evidence of caries. Incident caries events were computed at each examination. An incident caries event was defined as decay, restoration, or crown on a surface that was sound at the prior examination, and a recurrent caries event as a restoration plus decay on a surface that was restored but free of caries (excluding crowns) at the prior examination. A reversal was recorded when a surface with decay or restorations transitioned to completely sound at the next examination. The caries increment between examinations was defined as the number of incident caries events minus the number of reversals per subject. Caries increments between each pair of examinations were adjusted for reversals using the method described by Beck et al, 1995[19]. Third molars were excluded from the caries increment.

Covariate Variables

Covariates examined were those believed to be important or previously found in the literature review to be associated with dental caries. They were demographic variables (age, educational level, and marital status), oral health assessments (number of tooth surfaces at risk of caries, tooth brushing frequency, dental treatment and cleaning in past year (yes/no) and saliva condition (limited, copious)), and alcohol intake (<2 or >= 2 drinks day).

Statistical analysis:

Results of the Kolmogorov-Smirnov test (p-value=<0.01) showed that total DMFS and caries increment were skewed, therefore, negative binomial analysis was required for the bivariate and multivariate analyses. Bivariate analysis for total DMFS at baseline and means and frequencies of the covariates among tobacco use categories were compared using general linear models or the Chi-square test. For the first outcome, adjusted means of total DMFS among the tobacco use categories were evaluated with generalized linear model (GLM) and controlled for age, number of tooth surfaces at risk of caries, dental treatment in the past year, saliva condition and alcohol intake.

For the secondary exposure, change in tobacco use status, we computed a lagged variable describing change in tobacco use status in relation to status at the previous examination. The manual elimination technique was used to remove the least significant variables (p-value=>.0.05) and build the final models. Repeated measures multivariable analyses were conducted with generalized estimating equations (GEE) that assumed a negative binomial distribution and an autoregressive within-subject correlation matrix, and were adjusted for age, time at risk, number of tooth surfaces at risk of caries, dental treatment past year, and alcohol intake. Data from up to 12 examinations per participant were used. The dependent variable was caries increment between each examination. Additionally,

we conducted contrast analyses to determine the statistical significance of differences between nonsmokers and other categories of tobacco use status.

Mean total DMFS and new DMFS values obtained from the negative binomial analyses were back-transformed into original units for presentation in the tables. All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). The significance level was defined at 2-tailed alpha =0.05.

Results

Baseline characteristics of this cohort study are presented in Table 2.1. The majority of the men were not actively smoking tobacco at enrollment into the DLS. Active cigarette smokers were the youngest, had the fewest teeth remaining, and fewest surfaces at risk. There were no significant differences in brushing frequency or dental prophylaxis visits among the groups. However, active smokers of any product type were less likely to have received dental treatment in the past year than nonsmokers. Active cigarette smokers were more likely to have limited saliva and drink 2 or more alcoholic drinks/day than nonsmokers. Active cigar/pipe users were the highest educated group.

At baseline, the unadjusted mean total DMFS was significantly different among the tobacco use groups, and there was a trend toward higher DMFS in the cigarette smokers (Table 2.2). After adjustment for age, number of tooth surfaces at risk of caries, dental treatment in the past year, saliva condition, and alcohol intake, the results showed that non-tobacco users had a significantly lower mean DMFS than active cigarette or cigar/pipe users. The contrast analyses were consistent with the significant association between cigarette use and cigar use and non-tobacco use use (p-value <.05).

Figure 2.1 shows the changes in tobacco use over time among men who were followed in this study. At baseline, more than 60% of the cohort were nonsmokers, 23% were cigarette users and 15% were cigar/pipe users. Of those who participated in at least seven examinations, at approximately the midpoint of the follow-up, the percent of nonsmokers had increased to 90%, and by the twelfth examination, 98% were nonsmokers. As time progressed, cigar or pipe smoking became more prevalent than cigarette smoking.

Results of the multivariate repeated measures analysis are shown in Table 2.3 Compared to nonsmokers, caries increments were significantly greater in men who used cigarettes, whether continuously (P=<0.01), quitting (P<0.001) or starting/restarting (P=0.01) between examinations, after adjusting for age, time at

risk, tooth surfaces at risk of caries, dental treatment past year, and alcohol intake. There was also a trend for continuous pipe/cigar smokers and men who started smoking cigars or pipes to also have higher caries increments than nonsmokers (p-value <.05).

Discussion

This study was a retrospective cohort study of men who were followed up to 40 years between 1969 and 2008. The baseline examinations began shortly after the U.S. Surgeon General released the first report detailing the harmful effects of cigarette smoking on health. At baseline, a substantial percentage of the participants were either current cigarette users or former cigarette smokers [3], and active cigarette use continued to decline over follow-up, paralleling the national trends. The main objectives of this study were to examine if short-term changes in tobacco use status or product type will change the risk of developing new caries lesions. The main findings were that active cigarette use was significantly associated with caries prevalence and changing in tobacco use status was associated with new caries increment. Compared to nonsmokers, caries increments were increased among men who smoked cigarettes, cigar or pipe continuously or for part of the study. Men who quit or started/restarted smoking had high caries increments similar to continuous smokers because the short interval between examinations, generally occurred 2 to 4 years, was not long enough to minimize the carry-over effect of tobacco.

Caries increment was associated with age and lack of dental cleaning or treatment in the previous year. On the other hand, new caries development was not significantly associated with saliva condition nor alcohol consumption.

Nationally, although cigarette use has been declining since 1961 [20], cigar consumption has shown a 50% increase since 1993 as a result of cigarette smokers switching to cigars in response to publicity about the negative impacts of cigarettes and to increased marketing of cigars[21] Interestingly, the same trend was seen in our study, as there was remarkable decrease in prevalence of cigarette use after baseline and an increase in cigar/pipe use among the men who continued to participate in the study.

Few prospective studies of tobacco and caries have been previously conducted. One cohort study was consistence with our results showed that smoker elderly subjects who followed for 3 years to assess using tobacco and developing new DFS had significantly higher caries incidence and severity than non-smoke[22].

Other cohort studies assessed the relation between dental caries and cigarette use only. They conducted a study in Finland for 4 years (2001-2005) in adults and their results showed daily cigarette smoking was not significantly associated with DMFT

increment, which is in disagreement with our results[23]. Another two Swedish longitudinal studies reported findings similar to ours. Holmén et al 2013, studied an adolescent population and reported that DMFS increments were significantly higher among those who ever used tobacco than never users after 6 years of follow-up[24].
Furthermore, another 3-year cohort study conducted by Ambrosius et al, 2005, on female adolescents found that smoking habits were significantly associated with higher DMFS in eighth grade students[25].

Strengths of the present study include the longitudinal observational study design with long follow-up time and use of radiographs for comprehensive caries detection. On general, extensive data on caries risk factors were conducted, which allowed various cofounders to be controlled for in our analysis.

The results from this study should be interpreted in the light of some study limitations. First, information on tobacco use status relied on self-reports. Self-reports of tobacco use are accurate in most studies. However, to improve accuracy, biochemical assessment as cotinine level in body fluids, should be considered[26]. Second, that quantity of tobacco products was not used in the analyses because of much missing data regarding this information. Third, this cohort is all male, mostly white veterans, so the results are not representative of the U.S population

Conclusion

In conclusion, these results suggest that dental caries prevalence and incidence are higher among tobacco users than nontobacco users. Active cigarette and cigar/pipe usage were found to be significant and risk factors for dental caries.

This result highlights the need for dental professionals to address tobacco use with their patients, including cigar and pipe smoking. More collaborative research is needed to determine the effect of tobacco usage on dental caries in younger age groups.

Table 2.1 Baseline characteristics of VA Dental Longitudinal Study participants by tobacco use status (n=1,033)

	Nonsmoker	Active cigarette	Active cigar/pipe	p-value
N	643	233	157	
Age *	49.1±8.9	44.8±7.3	49.8±8.6	<0.001
No of teeth present (Excluding 3rd molars)*	23.0±5.1	21.7±5.6	22.4±4.9	<0.001
No of tooth surfaces at risk of caries*	104.3±27.8	98.5±28.8	101.6±26.6	<0.001
Highest level of education				<0.01
High school	27.7	39.1	32.5	
Some college	40.0	39.6	31.2	
College or professional school	32.4	21.9	36.3	
Brushing frequency				0.34
Never	1.6	0.9	3.2	
Once per day	54.6	56.5	58.6	
Twice per day	43.9	42.7	38.2	
Dental treatment last year				0.03
Yes	94.4	89.7	90.5	
No	5.6	10.3	9.5	
Dental cleaning last year				0.48
Yes	84.9	81.5	83.4	
No	15.1	18.5	16.6	
Saliva condition				<0.01
Normal	84.5	73.9	84.0	
Limited	15.5	26.1	16.0	
Drink >=2 alcoholic drinks a day				<0.01
No	83.4	72.6	81.7	
Yes	16.6	27.4	18.3	

*Mean ± SD.

Table 2.2 Mean Total DMFS at baseline by tobacco use status (n=1,033)

	Total DMFS			
Tobacco use status	**Unadjusted Mean ± SE**	**p-value**	**Adjusted* Mean ± SE**	**p-value**
At Baseline		0.02		<.0001
Active cigarette use	26.50 ± 1.02		26.23 ± 1.03¥	
Active cigar/pipe use	24.96 ± 1.95		24.59 ± 1.02	
Non-tobacco use	22.56 ± 1.02		22.03 ± 1.02	

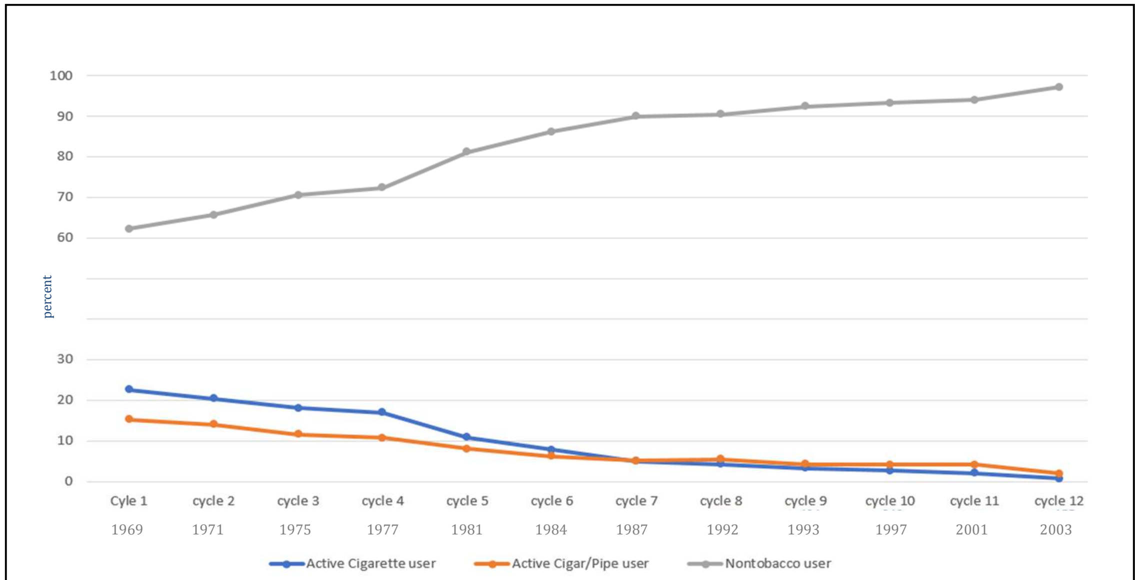
* Adjusted for: age, tooth surfaces at risk of caries, dental treatment in past year, saliva condition and alcohol intake.
¥ Significantly different from mean of non-tobacco users, pairwise t-test P ≤ .05

Table 2.3 Adjusted caries increment (new DMFS) by change in tobacco use status between examinations

	Change in tobacco use status	Adjusted* Caries Increment (New DMFS) Mean ± SE	p-value
At Follow-up			<0.0001
Cigarette Use	Continuous cigarette use	18.01 ± 0.73¥	
	Quit cigarette use	18.03 ± 0.80	
	Start / restart cigarette use	17.19 ± 0.88	
Cigar/Pipe Use	Continuous cigar/pipe use	17.26 ± 0.75¥	
	Quit cigar/pipe use	17.29 ± 0.80	
	Start/ restart cigar/pipe use	17.46 ± 0.84¥	
Non-tobacco use	Continuous Non-tobacco use	16.80 ± 0.71	

* Adjusted for: age, tooth surfaces at risk of caries, dental treatment in past year, saliva condition and alcohol intake.
¥ Significantly different from mean of non-tobacco users, pairwise t-test P ≤ .05

Figure 2.1: Trend of tobacco use status among our sample over 40 years of follow-up



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CHAPTER THREE

Association between smoking duration and dental caries among US men adults: unstimulated saliva flow rate as key mediator

Abstract

Objectives: To investigate the association between smoking status and duration with dental caries prevalence in adults and to analyze the mediation effect of saliva flow rate in this relationship.

Methods: A cross-sectional analysis of baseline data from the VA Dental Longitudinal Study. Participants were n=1,048 men aged 50.5±8.8 years from the greater Boston, New England area. Clinical assessments of caries were carried out by a dental examiner and history of tobacco use was obtained from a questionnaire. Smoking status was self-reported as never or ever smoked tobacco and smoking duration was recorded in years. Caries prevalence was computed as mean number of decayed, missing or filled surfaces (total DMFS). Unstimulated salivary flow rate (USFR, ml/min) was measured. The association between DMFS and smoking duration was conducted using multivariable negative binomial regression controlling for age. Mediation analyses, indirect effect and the Sobel test were conducted for USFR. Finally, the magnitude of mediation effect was calculated.

Results: At baseline, 75.6% of the men (n =815) had ever smoked cigarettes, cigars or pipes. The overall mean DMFS for ever smokers was 69.09 ± 31.54, and was

greater among subjects who had longest smoking duration (76.24 ± 1.02, p-value =0.0002) compared with those smoked for shortest smoking duration (62.14 ± 1.03). In addition, USFR was also associated with smoking duration as long-term smokers had 0.12 ± 0.03 mL/min lower saliva flow rate than short-term smokers. USFR was significantly associated with DMFS (p-value= <.0001) as each ml increases in saliva flow, there was a 1.00 ± 1.000 decrease in DMFS mean. The Sobel test indicated that USFR was a marginally insignificant partial mediator for those who smoked for 31 to 70 years by about 8.7%.

Conclusion: Ever smoking cigarettes, cigars or pipes was significantly associated with caries prevalence, and prevalence increased as smoking duration increased. Although, saliva flow was associated with both smoking duration and caries prevalence, it only partially mediated the relationship between smoking duration and caries prevalence among long-term smokers (31- 70 Y).

Introduction

Much clinical and epidemiological evidence exists regarding the harmful impact of tobacco use on general health as well as oral health[1]. Numerous studies have shown that cigarette smoking leads to increased incidence and severity of oral cancer, periodontal diseases and tooth loss[2-4]. Cigar and pipe smoking could also be risk factors for periodontal diseases and tooth loss[5]. However, the association between smoking tobacco and dental caries is still unclear.

Dental caries is a multifactorial infectious disease that affects about 90% of adolescents and almost all adults worldwide[6]. Nearly 91% of US adults have prevalent dental caries in their permanent teeth[7]. Tobacco use could be a health behavior that causes dental caries. Several biological mechanisms have been proposed as logical explanations for this association. These include disturbances in saliva function, low saliva flow rate, and altered pH or buffering capacity[8, 9]. Saliva is a complex and essential body fluid that has a significant role in maintaining oral health. Saliva amount and its components are important for tooth cleaning, retarding demineralization and promoting remineralization of hard tooth tissues. Inadequate salivary buffering action and decreased oral pH can lead to caries development[10].

Saliva is the first biological fluid that is exposed when tobacco is consumed and the many toxic elements in smoke are responsible for structural and functional

alterations in saliva[11]. There are few studies that assessed the effect of smoking tobacco on saliva amount, however, the evidence is inconclusive. Some studies concluded that long-term tobacco use is associated with decreased saliva flow rate, but others concluded there are no significant changes in tobacco users' saliva flow rate compared to non-tobacco use users[12, 13]. Any effect of tobacco on the salivary gland and flow rate may be dependent on the duration of exposure. The purpose of this study was to investigate the association between smoking use (status and duration) and dental caries prevalence and to determine whether this association is mediated by unstimulated whole saliva flow rate.

We have two hypotheses:

Hypothesis 1: Caries prevalence is expected to be positively associated with smoking status; smokers will prevalence more caries lesions than never smokers.

Hypothesis 2: Caries prevalence is expected to be positively associated with smoking duration: smokers who use tobacco for longer periods will have more caries lesions. In addition, this association is mediated by USFR.

Materials and Methods

Data Source and Participant:

The Veterans Affairs Dental Longitudinal Study (DLS) began in 1969 with volunteers drawn from the 2,280 participants in the VA Normative Aging Study, a closed-panel interdisciplinary study of aging in over 2000 community-dwelling men in the Greater Boston Metropolitan Area. The DLS is a prospective descriptive study of oral health that enrolled 1,231 men, ages 27 to 84 and in good medical health, between 1969 and 1973. As part of the DLS, they receive comprehensive dental examination and complete questionnaires on dental care, smoking, health and lifestyle every 2 to 4 years. The DLS cohort is almost entirely non-Hispanic white veteran males, who are not patients of the VA healthcare system. They receive their medical and dental care from the private sector.

Written informed consent was acquired from all participants. The study was approved by institutional review boards at Boston University Medical Center and the VA Boston Healthcare System.

Inclusion criteria for this study were being dentate, completion of a smoking history questionnaire, and completing a saliva flow measurement. The initial saliva flow measurements were obtained at either examination cycle 1 or 2 and are considered the baseline for this study. The number of men who met these criteria was 1,048.

Oral Examination

Dentist examiners performed the clinical assessment of caries and restorations for each tooth at each examination cycle. An explorer was used to probe the tooth surface. Non-cavitated surfaces, discolored and penetrable by probing, were scored as level 1 caries, whereas cavitated surfaces were scored as level 2. Restorations and caries on five coronal and four root surfaces per tooth were recorded. Full-mouth intraoral radiographs were taken at each oral examination and radiographic decay was recorded. A surface was considered as one carious lesion surface in this study whether the caries lesion was detected on clinical examination or on radiograph, was level 1 or level 2, or was present on the coronal or root surface.

Unstimulated saliva collection was made at random in the morning or afternoon, at least 1.5 hour postprandially. Collections of whole saliva were made by instructing the subjects to accumulate the saliva in their mouths and to expectorate every 30 seconds into a 50 ml tube graduated to 0.5 ml. They were frequently reminded to refrain from swallowing the saliva while the collection was made. The subjects were also instructed not to engage in any oral activity. A 5 minute clearance sample was collected first, followed by the 10 minute experimental sample for unstimulated salivary flow rate (USFR) [14].

Exposure variables – Smoking use

Data on current and former tobacco use, duration of use and type of smoked product used (cigarette, cigar, and pipe) were obtained from the smoking questionnaire.

Smoking status was categorized as never smoked tobacco or ever smoked (current and former smokers of cigarettes, cigars and/or pipes). Those men who ever smoked were further categorized by duration tertile (1-15 years, 16-30 years, or 31-70 years).

Primary outcome – Dental Caries Prevalence

The prevalence of dental caries prevalence was computed as the number of decayed, missing or filled surfaces (total DMFS). Third molars were excluded from all analyses.

Primary mediator – Unstimulated Saliva Flow Rate

The mean of unstimulated saliva flow rate (USFR) was calculated for each participant. Its range in this study was (0.02 - 3.00 mL/min)

Covariate Variables

Covariates examined were those believed to be important or previously found in the literature review to be associated with dental caries and salivary flow. They

were age, color of a 24-hour urine sample (clear, yellow or amber) as an indicator for body hydration, diuretic drug use (yes/no), diabetes diagnosis (yes/no) assessed by the study physician, and alcohol intake (<2 or >= 2 drinks day) taken from the Cornell Medical Index questionnaire [15].

<u>Statistical analysis:</u>

To test the first hypothesis, bivariate associations of smoking status and smoking duration with DMFS, USFR and covariates were examined with the Pearson correlation coefficients and analyses of variance. Multivariable associations between smoking status, smoking duration and DMFS were performed using generalized linear model GLM, specifying a negative binominal distribution for DMFS and USFR. The regression coefficient in the negative binominal models, after transformation from the log scale, represents the ratio of number of DMF surfaces in a smoking exposure category (ever smoked, moderate or long-term smoking) relative to the reference group. Multivariable associations were followed by mediation analyses as described below.

Mediation analysis

The common conceptual framework effect introduced by Baron and Kenny in 1986 [16] was used for testing the presence of mediation by USFR on the association between smoking duration and caries. It assumes that true mediation occurs when the mediator variable (USFR) is significantly associated with both the predictor (smoking duration) and the outcome (DMFS) variables. Four steps were performed

to test the mediation effect using multivariable regression models, controlling for covariates that were significant at $p < 0.05$ in the bivariate analyses (in our study, only age).

For mediation analyses, we tested the hypothesis that alterations in DMFS over different smoking durations would be mediated by USFR. These analyses consist of four steps (Figure 1); first step, to demonstrate the association between smoking duration and the caries prevalence, we constructed a regression model with smoking duration as independent variable and the outcome measure (DMFS) as the dependent variable. Secondly, to demonstrate the association between smoking duration and the mediator (USFR), we constructed a regression model with the USFR as the dependent variable and smoking duration as an independent variable. Thirdly, to demonstrate the association between caries prevalence and USFR, we constructed a regression model with DMFS as the dependent variable, and the USFR as an independent variable.

Lastly, to demonstrate the effect of smoking duration on DMFS after adjusting for the mediator (USFR), we constructed a regression model with both smoking duration and USFR as independent variables and DMFS as the dependent variable. In all four steps, we controlled for age as it had significant associations with both DMFS and USFR in bivariate analyses. This step is called the direct effect of the mediator.

The indirect effect and Sobel tests were performed to examine the statistical significance of the mediation effect. Finally, to evaluate the magnitude of the mediation effect, the percentage change in the regression coefficient was computed according to the following formula[17, 18]:

$$PC = \frac{(\beta_{adjusted\ for\ age} - \beta_{adjusted\ for\ age\ and\ USRF})}{(\beta_{adjusted\ for\ age} - 1)} \text{ x } 100.$$

All analyses were conducted using SAS 9.3 (*SAS Institute Inc., Cary, NC, USA*. The significance level was defined at 2-tailed alpha =0.05.

Results

The average age of the study sample was 50.5 ± 8.8 (range = 31 - 84 years). Three quarters of the participants had ever smoked cigarettes, cigars or pipes (n=845). However, information on smoking duration was available for 815 participants. The overall mean DMFS among all smokers was 69.14 ± 31.55 and their mean USFR was 0.59 ± 0.33 mL/ min (range = 0.04 -2.2 mL/min). The mean DMFS and USFR among never smokers (n=233) were 57.77 ± 26.23 and 0.60 ± 0.37 mL/min (range 0.02- 3.00 mL/min), respectively.

Smoking status was significantly associated with DMFS independently of age. Never smokers had significantly lower DMFS than ever smokers (Table 3.1). However, smoking status was not associated with USFR.

Diuretic drug use, hydration status, diabetes diagnosis and alcohol intake were not significantly associated with smoking duration, DMFS or USFR (p-value > 0.05). Only age was related to DMFS (0.78±0.12 surface increase per 1 year increase in age, p-value <0.001) and to USFR (0.36 ± 0.13 ml/min decrease per 1 year increase in age, p-value =0.01).

Although USFR and smoking status were not related, USFR was significantly related to smoking duration, so our further analyses examined the role of USFR as a mediator between smoking duration and total DMFS. Consistent with the trend with ever/never smoking status, smoking duration was positively associated with DMFS. Participants with the longest smoking duration had 14 more decayed, filled or missing surfaces than those with the shortest duration. Smoking duration was also inversely associated with USFR (Table 3.2).

As there was a significant association between USFR and DMFS (for each 1 ml increase in saliva flow, there was a 1.00 ± 1.001 decrease in DMFS, p-value<0.0001), we went further and assessed the mediation effect of unstimulated saliva flow rate in the smoking duration – DMFS relationship.

Table 3.3 presents the results of the mediation analysis. Men who smoked 16-30 years had 1.11 times more DMFS than men who smoked 1-15 years; after accounting for USFR, this ratio decreased to 1.10 but was not significantly different

from the reference group (Sobel p-value= 0.25). Men who smoked 31-70 years had 1.23 times more DMFS than the reference group, and after accounting for USFR, this ratio decreased to 1.21, and was marginally insignificantly different from the reference group (Sobel test p-value = 0.07). Unstimulated saliva flow rate may partially mediate the association between caries prevalence and long smoking duration (31 -70 years) by about 8.70%

Discussion

Our findings showed that there are significant associations between smoking status and duration with caries prevalence. Never smokers had dramatically lower DMFS compared to ever smokers. Among men who had ever smoked, participants with the longest smoking duration had the highest number of DMFS independently of age and salivary flow rate. To our knowledge, the present study has the longest smoking period showing the effect of smoking duration on dental caries. As our participants were mostly older adults, some of them used tobacco since they were 14 years old (smoking for 70 years maximum), which gives our study a strength for having prolonged smoking duration. Our results are consistent with findings from previous cohort studies which demonstrated an association between smoking duration and caries prevalence. Bernabé et al., 2014, showed a different conclusion, i.e., that smoking (cigarette, cigar or pipe) for four years was not independently associated with caries development (DT) among Finnish adults[19]. However, Drake

et al, agreed with our results that smoking cigarettes for 3 years were related to the development of new DFS among elderly subjects[20].

The mechanism of how tobacco use could lead to dental cares is still unclear but several factors that could explain the mechanism of the increase in caries prevalence in smokers directly or indirectly have been suggested. For instance, some studies indicated that nicotine in tobacco stimulates the growth of Streptococcus Mutans bacteria in vitro[21]. Others demonstrated that poor oral hygiene habits, high sugar consumption or lack of preventive dental visits are more common in tobacco users than nonusers [22]. Another potential pathway that has been suggested is through the effect of tobacco on reducing the quantity or quality of saliva. Saliva quantity has been found to be one of the strongest salivary biomarkers for an increased risk of developing caries[23]. The literature shows that the average flow rate of unstimulated whole saliva in individuals is about 0.2-0.7 ml/min[24] and it is considered an independent caries risk factor when USFR is lower than 0.1 mL/min[25]. Pedersen et al., 2005 concluded that subjects with reduced salivary flow had higher DMFS [26], a finding that is consistent with ours. In contrast, a study conducted by Lenander-Lumikari and Loimaranta 2000, showed that there was no correlation between salivary flow rate and caries experience[27]. Few previous studies addressed the salivary flow – caries relationship among smokers. Findings by Rad et al. and Petrušić et al. were parallel with ours, as they confirmed that long-term smoking significantly reduced SFR and increased cervical caries lesions[28, 29]. However, Voelker et al., 2013, concluded that there was no

relation between caries risk and saliva flow in cigarette smokers, and Hugoson et al., 2012, showed that in tobacco users there was no association between their dental caries and saliva secretion rate [30, 31].

The relationship between smoking and the salivary flow rate is also uncertain. Our findings are consistent with one prior cross-sectional study that demonstrated an association between smoking and decreased USFR. Rad et al., 2010, showed that mean USFR in long-term smokers was significantly lower than in non-smokers[28]. However, Konić-Ristić et al. 2015, found opposite results, as in that study, smoking did not affect unstimulated salivary flow rate[32]. Duration of smoking may be a key factor in demonstrating a relationship. Studies suggest that while there is an increase in the activity of salivary glands during active tobacco use [33], as smoking duration increases, the function of these glands declines and the SFR is reduced [34] resulting in decreased quantity of saliva among long-term tobacco users[28].

Our study may be the first to address the mediation effect of saliva flow in the relationship between smoking and dental caries. However, we found that unstimulated saliva flow rate only partially and weakly mediated the association between long smoking duration and caries prevalence, suggesting other important mediators need to be identified or may be with larger sample size with stronger power to detect the differences.

There are some limitations in this study. First, the cross-sectional design did not allow us to establish a temporal order of the independent variable (smoking duration), the mediator variable (USFR) and the outcome variable (DMFS). However, although cohort studies are preferred for mediation analysis, all other study designs, as well as cross-sectional, can still test the mediation effect[35]. Second, our results are based on a sample of white male veterans in New England. Thus the findings might not be applicable to other populations. In addition, there may be other confounders that influence saliva secretion and DMFS, such as medications (antidepressants, antihistaminic, and antihypertensive drugs) [36, 37] and other medical conditions (renal failure, anorexia) [38] that were not present or prevalent in our study sample. The study also has several strengths. The dental examinations consisted of a whole-mouth x-ray and detailed surface-by surface assessment by calibrated examiners, and numerous potential confounders were available in the data for evaluation.

The findings from the present study have potential policy implications. As it is shown that using tobacco could lead to dental caries, smoking cessation and prevention programs should be an essential component in the dental practice. All dental practitioners need to be aware of the association between smoking and dry mouth as well as caries development so they will be more prepared to boost their patients to quit tobacco use.

Conclusion

In conclusion, using tobacco in the form of cigarettes, cigars or pipes and long-term smoking were clearly associated with increased caries prevalence among adults. This relation could be partially mediated by the unstimulated saliva flow rate. Thus, smoking should be relevant to be included in the clinical caries risk assessment of individuals as well as for the community.

Table 3.1 Bivariate and multivariate analysis of smoking status with DMFS and USFR (n=1048).

	Smoking status at Baseline		
	Never (N=233)	**Ever (N=815)**	**P- value**
DMFS			
Unadjusted	57.77 ± 26.22	69.14 ± 31.54	<.0001
Age-adjusted	56.86 ± 26.22	69.09 ± 31.54	<.0001
USFR			
Unadjusted	0.61 ± 0.37	0.59 ± 0.33	0.79
Age-adjusted	0.61 ± 0.36	0.60 ± 0.33	0.66

Table 3.2 Multivariate analysis of smoking duration among ever smokers with DMFS and USFR among smokers (n=815)

Characteristics	N	DMFS* Mean ±SD	p-value	USFR* Mean ±SD	p-value
Smoking Duration			0.0002		<0.001
1-15 years	277	62.14 ± 1.03		0.65 ± 0.33	
16-30 years	275	68.81± 1.02		0.60 ± 0.35	
31-70 years	263	76.24 ± 1.02		0.53 0.30	

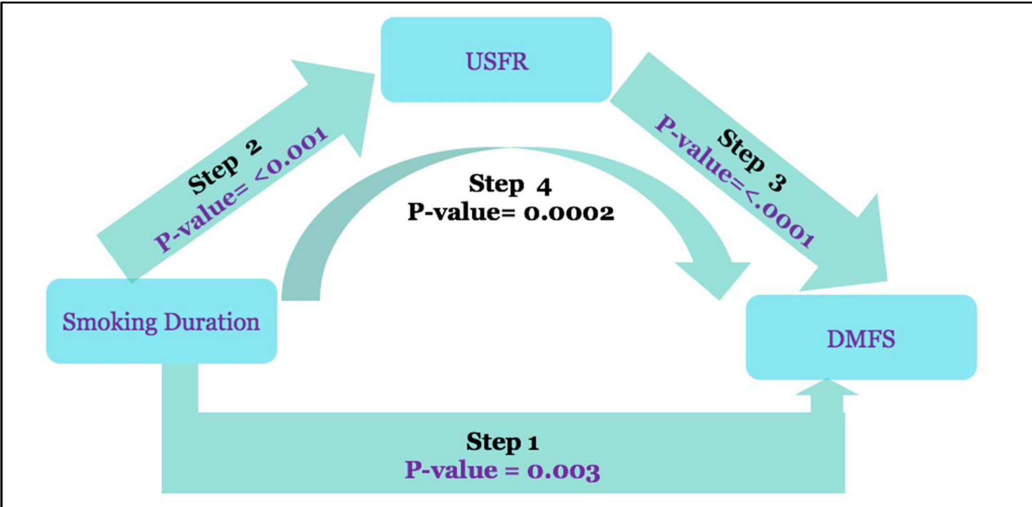
* Adjusted for: age

Table 3.3 Multivariate analysis of smoking duration and DMFS among ever smokers, excluding and including USFR as a mediator (n=815)

	Ratio of DMFS* Excluding USFR $\beta \pm$ SE (p-value)	Ratio of DMFS* Including USFR $\beta \pm$ SE (p-value)	Percent change in β	Sobel test – Z-value (p-value)
Smoking Duration				
1-15 years	Ref	Ref		
16-30 years	1.11 ± 0.04 (0.02)	1.10 ± 0.04 (0.01)	9.09%	1.15 (0.25)
31-70 years	1.23 ± 0.04 (0.0003)	1.21 ±0.04 (0.0001)	8.70%	1.83 (0.07)

* Adjusted for: age

Figure 3.1 Baron and Kenny four step mediation analyses



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CONCLUSION AND DENTAL PUBLIC HEALTH IMPLICATIONS

In conclusion, caries prevalence was significantly associated with tobacco use status (active, passive and non-tobacco use use) among both adolescents and adults. Data from 2001-2012 National Health and Nutrition Examination Surveys demonstrated that adolescent passive users had higher dental caries than non-tobacco users. For tobacco products consumption, there was no statistically significant difference in caries prevalence among different tobacco products. However, adolescent users who consumed more than one product at a time had the highest dental caries prevalence.

In contrast to the findings among adolescents, the NHANES data showed that adult passive users had lower caries prevalence to non-tobacco use users, however, this finding was not statistically significant. Active tobacco users had the highest caries prevalence at all ages. These findings were confirmed in cross-sectional analyses of the Dental Longitudinal Study (DLS) cohort of adult men.

In prospective analyses, new caries development was significantly associated with tobacco use status of any type of smoking tobacco product (cigarettes, cigar or pipe), whether the use was continuous or not. Finally, our results showed that as smoking duration increases, the prevalence of caries is increased and unstimulated saliva flow rate is decreased. Saliva flow rate could partially mediate this association, however it only partially mediated the association between long-term

smoking duration and caries. More research is needed to verify other potential mechanisms for this association.

According to the results of this dissertation, we would like to have sufficient evidence of the association between tobacco use and dental caries among adolescents and adults to emphasize the important role of dentists and dental hygienists in tobacco cessation, as they are in an excellent position to play a major role in this issue. Dental practitioners could easily identify tobacco users in the dental office, they could help the public and policymakers to understand the chronic nature of tobacco use, and they could support cessation services for all people, especially adolescents who are the main target group for tobacco advertisements. This could be done when dentists include tobacco use in the clinical caries risk assessment for each patient in every clinic.

Dental professionals should learn how to help tobacco users to implement the correct method for tobacco cessation as a mandatory part of the health care delivery system. In addition, dental public health providers should include tobacco cessation programs in community health plans for oral health. In conclusion, each dental provider should help each individual to be tobacco free, which will improve the health and well-being of millions of U.S individuals.

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