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Authors

Marks, Morgan A
Chaturvedi, Anil K
Kelsey, Karl
et al.

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Association of marijuana smoking with oropharyngeal and oral tongue cancers: Pooled analysis from the INHANCE Consortium

Morgan A. Marks[1], **Anil K. Chaturvedi**[1], **Karl Kelsey**[2], **Kurt Straif**[3], **Julien Berthiller**[3,4], **Stephen M Schwartz**[5], **Elaine Smith**[6], **Annah Wyss**[7], **Paul Brennan**[3], **Andrew F. Olshan**[7], **Qingyi Wei**[8], **Erich M. Sturgis**[8], **Zuo-Feng Zhang**[9], **Hal Morgenstern**[10], **Joshua Muscat**[11], **Philip Lazarus**[11], **Michael McClean**[12], **Chu Chen**[5], **Thomas L. Vaughan**[5], **Victor Wunsch-Filho**[13], **Maria Paula Curado**[14], **Sergio Koifman**[15], **Elena Matos**[16], **Ana Menezes**[17], **Alexander W. Daudt**[18], **Leticia Fernandez**[19], **Marshall Posner**[20], **Paolo Boffetta**[14,21], **Yuan-Chin Amy Lee**[22], **Mia Hashibe**[22], and **Gypsyamber D'Souza**[23,*]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD

[2]Department of Community Health, School of Medicine, Brown University, Providence, RI

[3]International Agency of Research on Cancer, Lyon, France

[4]Hospices Civils de Lyon, Pole Information Medicale Evaluation Recherche, Lyon, F-69424, France; Universite Lyon 1, Equipe d'Accueil 4129, France

[5]Fred Hutchinson Cancer Research Cancer, Seattle, WA

[6]University of Iowa College of Public Health, Iowa City, IA

[7]School of Public Health, University of North Carolina, Chapel Hill, NC

[8]Department of Head and Neck Surgery and Epidemiology, University of Texas M.D. Anderson Cancer Center, Houston, TX

[9]UCLA School of Public Health, Los Angeles, CA

[10]Departments of Epidemiology and Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI

[11]Penn State College of Medicine, Hershey, PA

[12]Boston University School of Public Health, Boston, MA

[13]Faculdade de Saude Publica, Universidade de Sao Paulo, Sao Paulo, Brazil

[14]International Prevention Research Institute, Lyon, France

[15]Escola Nacional de Saude Publica, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil

[16]Institute Oncology Angel H. Roffo, University of Buenos Aires, Buenos Aires, Argentina

[17]Universidade Federal de Pelotas, Pelotas, Brazil

[18]Hospital de Clinicas de Porto Alegre, Port Alegre, Brazil

[19]Institute of Oncology and Radiobiology, Havana, Cuba

[20]Johns Hopkins School of Medicine, Baltimore, MD

[21]The Tisch Cancer Institute Mount Sinai School of Medicine, New York, NY

[*]Corresponding author: Name: Dr. Gypsamber D'Souza, Address: Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Rm. E6132B, Baltimore, MD 21205, Phone: (410) 502-2583, gdsouza@jhsph.edu.

[22]University of Utah School of Medicine, Salt Lake City, UT

[23]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

Background—The incidence of oropharyngeal and oral tongue cancers have increased over the last twenty years which parallels increased use of marijuana among individuals born after 1950.

Methods—Pooled analysis of individual-level data from nine case-control studies from the U.S. and Latin America in the INHANCE consortium. Self-reported information on marijuana smoking, demographic, and behavioral factors was obtained from 1,921 oropharyngeal cases, 356 oral tongue cases, and 7,639 controls.

Results—Compared with never marijuana smokers, ever marijuana smokers had an elevated risk of oropharyngeal (adjusted odds ratio [aOR]: 1.24; 95% confidence interval [CI]: 1.06, 1.47) and a reduced risk of oral tongue cancer (aOR: 0.47; 95% CI: 0.29, 0.75). The risk of oropharyngeal cancer remained elevated among never tobacco and alcohol users. The risk of oral tongue cancer decreased with increasing frequency (p_{trend}=0.005), duration (p_{trend}=0.002), and joint-years of marijuana use (p_{trend}=0.004), and was reduced among never users tobacco and alcohol users. Sensitivity analysis adjusting for potential confounding by HPV exposure attenuated the association of marijuana use with oropharyngeal cancer (aOR: 0.99; 95% CI: 0.71, 1.25), but had no effect on the oral tongue cancer association.

Conclusions—These results suggest that the association of marijuana use with Head and Neck Carcinoma may differ by tumor site.

Impact—The associations of marijuana use with oropharyngeal and oral tongue cancer are consistent with both possible pro- and anti-carcinogenic effects of cannabinoids. Additional work is needed to rule out various sources of bias, including residual confounding by HPV infection and misclassification of marijuana exposure.

Keywords

marijuana; oropharynx; oral tongue; INHANCE; human papillomavirus

Introduction

Head and neck squamous cell carcinomas, which include cancers of the oral cavity, oropharynx, and larynx, are the sixth most common cancers worldwide with an estimated annual burden of 355,000 deaths and 633,000 incident cases (1). In addition to traditional risk factors, such as tobacco and alcohol use, human papillomavirus (HPV) infection has recently been established as a major etiologic factor for a subset of Head and Neck Squamous Cell Carcinomas—cancers arising from the oropharynx, including the base of tongue, tonsil, and other parts of the pharynx (2). The incidence of a majority of head and neck cancer subsets (i.e. cancers of lip, oral cavity, larynx, hypopharynx, and nasopharynx) has declined significantly during the past 2 decades in the U.S. and other developed countries, largely due to declines in cigarette smoking (3, 4). In contrast to this overall pattern, the incidence of oropharyngeal and oral tongue cancers has significantly increased during the same period, especially among individuals <45 years of age (4–6). While increases in oropharyngeal cancer incidence are attributed to increased acquisition of oral HPV through changes in sexual behaviors among recent birth cohorts (7), the reasons underlying increasing oral tongue cancer incidence are largely unknown. Notably, HPV infection is not currently believed to play a major role in the etiology of oral tongue cancers (8).

Marijuana use has significantly increased among individuals born after 1950 (9, 10), raising the hypothesis of a role of marijuana use as a risk factor for oropharyngeal and oral tongue cancer development (11). A recent case-control study reported that marijuana use was strongly associated with increased risk of HPV-positive oropharyngeal cancer (12). Conversely, a case-control study of HNSCC demonstrated an inverse association of marijuana use on cancers of the oral cavity (13). However, epidemiologic studies that have examined the association of marijuana use with Head and Neck Squamous Cell Carcinomas have been inconsistent (14–20).

We therefore investigated the association of marijuana use with risk of oropharyngeal and oral tongue cancers in a large pooled analysis consisting of 9 case-control studies that were part of the International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Material & Methods

Subject inclusion and cancer site classification

The INHANCE pooled data (version 1.4) used in this study included nine case-control studies containing information on marijuana use comprising 2,395 cases (2,002 oropharyngeal and 393 oral tongue) and 7,798 controls. After subjects in these nine studies with data missing on age, sex, race/ethnicity, tobacco use, alcohol use and marijuana use (70 cases and 159 controls) were excluded, there were 2,325 cases and 7,639 controls. Tumor sites were classified using the International Classification of Diseases for Oncology 2nd edition (ICD-0-2). Oropharyngeal cancer outcomes included tumors of the oropharynx (C10.0–C10.9), base of tongue (C0.19), tonsils (C09.0–C09.9, C02.4), soft palate (C05.1), and uvula (C05.2). Oral tongue cancer included tumors of the dorsal surface (C02.0), border (C02.1) and ventral surface (C02.2) of the tongue. All tumors were restricted to squamous cell carcinomas (SCC) using histologic codes provided by the ICD-0-2 (8050–8084). Of the 2,325 cases, 2,286 (98%) were SCC (1,921 oropharynx and 365 oral tongue). Due to the small number of cases (n<25 cases), Baltimore [HOTSPOT], Los Angeles, North Carolina (2002–2006) and Tampa sites were dropped from oral tongue cancer analyses leaving 356 oral tongue cases and 4,321 controls for these analyses.

Characteristics of the individual studies included in the pooled data are presented in Supplemental Table 1. Three out of the nine studies were hospital based (Baltimore [HOTSPOT], Houston, and Latin America). Seven studies frequency matched controls to cases (Boston, Houston, Latin America, North Carolina (2002–2006), Seattle, Seattle-LEO, and Tampa), and two studies performed individual matching (Baltimore[HOTSPOT], and Los Angeles). All studies matched controls to cases on age and sex. Some studies additionally matched on race & ethnicity (Baltimore[HOTSPOT], Houston, Latin America, North Carolina (2002–2006), and Tampa), neighborhood (Boston and Los Angeles), and city of residence (Latin America). Studies conducted interviews face to face with either self-administered (Boston, North Carolina (2002–2006)), interviewer-administered (Los Angeles, Houston, Tampa, Latin America, Seattle, Seattle-LEO), or computer assisted self interview (Baltimore[HOTSPOT]) questionnaires Individual-level data from each study were standardized as previously described (15). Anonymized data from individual studies were pooled; each data item was checked for illogical or missing values; inconsistencies were resolved by local site (21).

Marijuana Exposure Measurement

All studies included in this analysis collected data on lifetime marijuana use from cases and controls, including duration of use and frequency of use. Four of the studies (Houston, Tampa and Seattle-LEO [Vaughan], and Baltimore [HOTSPOT])) asked each subject to report the average frequency of marijuana use over their lifetime, while the remaining five

studies (Seattle (1985–1995) [Schwartz], Latin America, Boston, Los Angeles, and North Carolina (2002–2006)) obtained information about marijuana use during different periods of the subject's lifetime. For these later five studies the lifetime average frequency of marijuana use was calculated by weighting the frequency of each specific period by the duration of that period relative to the total years of marijuana use. For analysis, marijuana use was defined as ever/never, frequency of use per week (never, >0–3, >3 joints/week) and duration of use (never, >0–10, >10 years). Lastly, a "joint-year" variable was created as a measure of cumulative marijuana exposure, and defined as the number of joints per day multiplied by the duration of marijuana use in years and was categorized into a-priori categories (never, >0–1 joint-years vs. 2–10 joint-years vs. >10 joint-years). Four out of the nine studies (Latin America, Tampa, Los Angeles, and North Carolina (2002–2006)) defined marijuana use specifically as smoking marijuana whereas the remaining five studies defined marijuana use in any form.

Tobacco Consumption

All studies collected information on tobacco use including ever vs. never use of cigarettes and cigars/pipes. In six out of nine studies (Seattle (1985–1995) [Schwartz], Seattle-LEO [Vaughan], North Carolina (2002–2006), Los Angeles, Houston, and Boston) ever smoking cigarettes was defined as anyone smoking at least 100 cigarettes in their lifetime. Three studies (Tampa, Latin America, and Baltimore [HOTSPOT]) defined ever smoking cigarettes as smoking one or more cigarettes per day for greater than or equal to one year. Lastly, "pack-years" of cigarette smoking was created as a cumulative measure of cigarette smoking duration and intensity and treated as a continuous variable in the analysis. For each study, pack-years was directly calculated by multiplying the number of cigarettes smoked by the age of initiation and cessation of smoking (i.e. duration). Cigar and Pipe use was defined as ever vs. never. Four studies (Seattle (1985–1995) [Schwartz], North Carolina (2002–2006), Los Angeles, and Seattle-LEO [Vaughan]) defined ever cigar/pipe use as use for six months or greater at anytime in the past. Two studies (Latin America and Tampa) defined ever cigar/pipe use as smoking once per day for at least one year or more. One study (Boston) defined ever pipe use as ever smoking 12 ounces of tobacco and cigar use as smoking one cigar per week for at least one year. Lastly, two studies (Houston and Baltimore [HOTSPOT]) collected "ever vs. never" information from questionnaire data without defining a frequency or duration of use cut-off.

Alcohol Consumption

Alcohol consumption was defined as ever vs. never for all studies. Ever use of alcohol was defined as either greater than four or more drinks in a year (Seattle (1985–1995) [Schwartz] and Baltimore [HOTSPOT]), greater than or equal to one drink per week for greater than or equal to one year (Tampa and Houston), greater than either one (Latin America) or four drinks per month (North Carolina (2002–2006)), or ever consumed in a lifetime (Boston). Total alcohol consumption (i.e. alcohol-years) was calculated as the total volume of pure ethanol consumed from beer, wine, and liquor multiplied by the age of initiation and cessation (i.e. duration) (22). Total alcohol consumption was treated as a continuous variable in all analyses.

Statistical Analysis

Odds ratio (OR) and 95% confidence intervals (95% CI) were estimated using logistic regression to assess the association between marijuana use and oropharyngeal and oral tongue cancer diagnosis. Given that all the case-control studies included in this analysis utilize incident cases derived from open and dynamic populations, the odds ratio estimated in this study approximates the relative risk. To control for heterogeneity in effects across study, study indicator was included as a random effects intercept term in all regression

models. We tested for heterogeneity across study using a log likelihood ratio test for the goodnesss of fit of the model with and without a product term for marijuana use and study. Furthermore, we quantified the among-study variability of the association of ever marijuana use with both cancer outcomes by estimating the population effects interval (PEI) which is derived from the point estimate of the association and the τ^2 estimated from meta-regression analysis (calculated as the odds ratio for the association of ever marijuana use with each cancer outcome plus or minus 1.96 times the square root of the estimate of τ^2). Regression models were adjusted for age (continuous), sex, education (none, <junior high, some high school, high school graduate, vocational, some college, ≥college, missing), race/ethnicity (White non-Hispanic, Black, Hispanic, Asian, Other, Latin American), pack-years of cigarette smoking (continuous), ever pipe/cigar smoking (ever, never), and intensity of alcohol drinking (continuous). The Tampa study was excluded from analyses on duration and frequency of marijuana use because there were insufficient cases and controls in each category of marijuana use.

For subjects with missing data on education level (82 cases and 255 controls), multiple imputation analysis was performed. Logistic regression was used to predict education level using age, sex, race/ethnicity, study, and case-control status. Five imputations were created and a summary estimate for the association of marijuana use and cancer outcomes was calculated using logistic regression using the MI ESTIMATE command in STATA. Analysis excluding individuals with missing educational status demonstrated similar associations of marijuana use with cancer (data not shown).

Sub-group analyses

Tobacco and alcohol use is a recognized risk factor for both oropharyngeal and oral tongue cancers and is strongly correlated with marijuana use (23, 24). Therefore, sub-group analyses were performed to further assess the presence of residual confounding by smoking status by restricting the study sample to never tobacco users/never drinkers. Given the relatively small number of oral tongue cancer cases who were NSND, light smokers and light drinkers were categorized as never tobacco users/never drinkers for this analysis. The potential multiplicative interaction of tobacco and alcohol use on the association of marijuana use and cancer outcomes were compared by the inclusion of a product term of marijuana use and tobacco/alcohol use in the logistic regression model to estimate the ratio of odds ratios (ROR). In addition, the additive interaction of tobacco and alcohol use on the association of marijuana use with cancer outcomes was also tested through estimation of the Relative Excess Risk due to Interaction (RERI) using a generalized linear model (25).

Because sexual behaviors (which increase the likelihood of HPV exposure) and marijuana use could be highly correlated, we conducted two separate analyses to evaluate the potential confounding effects of HPV on the observed associations of marijuana use with risk of oropharyngeal cancer. First, analyses were stratified by HPV 16 L1 serologic status. Data on HPV L1 antibodies were available in four studies: Boston, Latin America, Houston, and Seattle (1985–1995) [Schwartz]. Second, given the absence of either detailed information on oral sexual behaviors or oral HPV status in a majority of studies, we utilized external information to indirectly adjust the marijuana-oropharyngeal cancer association for confounding by HPV using the methods described by Steenland and Greenland (26) **(See Statistical Appendix)**. These analyses utilized external information on the association of marijuana use with oral HPV prevalence (derived from the NHANES 2009/2010 study: prevalence among never-users (4%), the association of current marijuana use and oral HPV infection (OR: 2.87 (95% CI:1.85, 4.46), and the association of oral HPV infection with oropharyngeal cancer risk (derived from the literature: (OR:12.3 (95% CI: 5.4, 26.4)) to calculate a bias factor (27, 28). The observed marijuana-oropharyngeal cancer association

was then divided by the bias factor to estimate an adjusted OR which accounted for confounding by HPV.

The studies included in this analysis primarily collected information on marijuana use using interviewer or self-administered questionnaires. Therefore, differential misclassification of the reporting of marijuana use between cancer cases and controls is a possibility. To estimate the potential effect of reporting bias, simple probabilistic sensitivity analyses were conducted based on methods previously described (29, 30). Sensitivity and specificity estimates used in this analysis were derived from the literature on misreporting of marijuana use in a variety of populations (31, 32).

Results

Oropharyngeal cancer

Study Sample characteristics—There were 1,921 oropharyngeal cancer cases from nine studies with the majority from Houston (20.3%), Latin America (19.9%), North Carolina (17.9%), and Boston (11.9%) (Table 1). Compared to controls, oropharyngeal cancer cases were more likely to be male (80.4% vs. 69.2%) and white non-hispanic (69.5% vs. 65.1%). Oropharyngeal cancer cases were more likely than controls to ever use tobacco products (79.7% vs. 62.1%) or alcohol (87.7% vs. 74.4%). Lastly, oropharyngeal cancer cases were more likely than controls to report >50 pack-years of cigarette smoking (24.2% vs. 10.9%) and >60 drink-years of alcohol use (46.3% vs. 22.9%).

Association of marijuana use and oropharyngeal cancer—Ever smoking marijuana was reported by 21% of oropharyngeal cancer cases compared to 15% of controls (Table 2). After adjusting for demographic factors, tobacco and alcohol use, the risk of oropharyngeal cancer was significantly elevated among ever marijuana users (aOR: 1.24 [95%CI:1.06, 1.47]; p=0.009). Similarly, the risk of oropharyngeal cancer were significantly elevated among those with higher frequency of marijuana use (p-trend=0.046), and longer duration of marijuana use (p-trend=0.031). The risk of oropharyngeal cancer remained elevated among longer duration marijuana users when duration of use was treated as a continuous variable on either an absolute (p=0.003) and log-transformed (p=0.024) scale as well as using category means (p=0.037) (Supplemental table 2). However, there was significant heterogeneity of these associations by study-site for ever marijuana use (Figure 1).

Effect of tobacco/alcohol consumption on marijuana-oropharyngeal cancer association—The positive association of marijuana use and oropharyngeal cancer could potentially be explained by increased consumption of tobacco and alcohol, known risk factors for oropharyngeal cancer, among marijuana users as compared to non-users. However, marijuana use remained associated with an elevated risk of oropharyngeal cancer among both never-tobacco-smoker/never-drinkers (aOR: 2.11 [95%CI: 0.97, 4.62]) and ever-tobacco-smoker/ever-drinkers (aOR:1.47 [95% CI:1.24, 1.73]) (Table 3). There was no evidence of a statistical interaction of the effect of marijuana use on oropharyngeal cancer by smoking/drinking status on a multiplicative scale (ROR). However, the association of marijuana use with oropharyngeal cancer was marginally lower among ever smokers/drinkers as compared to never smokers/drinkers on a additive scale among those reporting marijuana use at a frequency of <3 times/week (RERI:−0.42 [95% CI: −0.79, −0.04]) or among those with a cumulative use of 0–1 joint-years (RERI: −0.34 [95% CI: −0.67, −0.01]).

Effect of HPV exposure status on marijuana-oropharyngeal cancer association—HPV 16 L1 antibody status was available in 4 of the 9 studies (Boston, Houston, Latin America, and Seattle [Schwartz]) making up 665 oropharyngeal cancer cases and 2,133 controls. The adjusted association of marijuana use with oropharyngeal cancer prior to considering HPV antibody status in these four studies was null (aOR: 0.89 [95% CI: 0.65, 1.19]). Additional adjustment of these 4 studies for HPV 16 L1 serostatus did not significantly alter the odds ratio (aOR: 0.87 [95% CI: 0.66, 1.16]). We nevertheless observed a significant interaction between ever marijuana use and HPV16 L1 antibody status ($p_{interaction}<0.001$). Among individuals seronegative for HPV16 L1 antibodies, ever marijuana use was associated with significantly decreased risk of oropharyngeal cancer (aOR: 0.54 [95% CI: 0.34, 0.85]). In contrast, among HPV16 seropositive individuals ever marijuana use was positively, but not significantly associated with oropharyngeal cancer (aOR: 1.19 [95% CI: 0.72, 1.98]) (Supplemental Table 3). This qualitative difference in the odds ratio was similar among those reporting 2–10 ($p_{interaction}=0.016$) and >10 ($p_{interaction}=0.001$) joint-years of marijuana use on a multiplicative scale. On an additive scale, the relative odds was significant higher among HPV 16 seropositive individuals only among ever marijuana users (RERI: 2.09 [95% CI: 0.86, 3.32]).

We then performed indirect adjustment of the OR for the association of ever marijuana use and oropharyngeal cancer diagnosis for confounding by oral HPV infection status (Table 4). These analyses indicated that, under plausible assumptions of the difference in oral HPV prevalence by marijuana use status and the association of HPV infection with oropharyngeal cancer risk, confounding by oral HPV infection could potentially explain the observed association of marijuana use with oropharyngeal cancer risk ($OR_{indirect\ adjustment}$: 0.99 [95% CI: 0.71, 1.25]).

Sensitivity analyses that corrected for differential misclassification in which there was greater under-reporting of marijuana exposure (reduced sensitivity) among cases strengthened the association with oropharyngeal cancer, whereas greater under-reporting among controls attenuated the association (Supplemental Table 4). In contrast, correction for non-differential misclassification resulted in a slight strengthening of the association of marijuana with oropharyngeal cancer.

Lastly, analyses that excluded both base of tongue and tonsil cancers, subsets of oropharynx cancers that are strongly associated with HPV infection, resulted in an attenuation of the odds ratios and loss of statistical significance ($OR_{ever\ vs.\ never}$: 0.98 [95% CI: 0.77, 1.26]).

Oral tongue cancer

Study Sample Characteristics—There were 356 oral tongue cancer cases from five studies with the majority from Houston (31.1%) and Seattle [Schwartz] (25.9%) (Table 1). As compared to controls, oral tongue cancer cases were more likely to be female (34.6% vs. 26.1%), white non-hispanic (77.5% vs. 56.0%), and have some college education (30.4% vs. 21.3%) and slightly younger (55 vs. 57 years). Oral tongue cancer cases were more likely to ever use of tobacco products (73.9% vs. 65.2%) or alcohol (81.7% vs. 75.7%). Lastly, oral tongue cancer cases were more likely than controls to report >50 pack-years of cigarette smoking (23.9% vs. 11.8%) and >60 drink-years of alcohol use (35.9.3% vs. 28.2%).

Association of marijuana use and oral tongue cancer—Ever marijuana use was reported among 7% of oral tongue cancer cases as compared to 10% of controls (Table 2). After adjustment for demographic factors, tobacco and alcohol use, the risk of oral tongue cancer was significantly reduced (i.e. was more protective) among ever marijuana users (aOR: 0.47 [95%CI:0.29, 0.75], p=0.001). Similarly, the risk of oral tongue cancer was significantly reduced among those with higher frequency of marijuana use ($p_{trend}=0.005$),

longer duration of marijuana use (p_{trend}=0.002), and higher cumulative joint-years of marijuana exposure (p_{trend}=0.004). These associations remained significant when these exposure metrics were treated as continuous on either an absolute or logarithmic scale or defined based on the means of the each category for each variable (Supplemental Table 2). The strength of the association of ever marijuana use and oral tongue cancer did not differ significantly by study site (p_{study}=0.922; Figure 1) and no single study had a significant impact on the directionality or strength of the association. The strong inverse association of marijuana use on oral tongue cancer was similar among never tobacco smokers and ever tobacco smokers/ever drinkers (Supplemental Table 5).

Sensitivity analyses that corrected for differential misclassification in which there was greater under-reporting of marijuana exposure (reduced sensitivity) among cases attenuated the association with oral tongue cancer whereas greater under-reporting among controls strengthened the association (Supplemental Table 4). Correction for non-differential misclassification resulted in a slight attenuation of the association of marijuana with oral tongue cancer.

Discussion

The rising incidence of oropharyngeal and oral tongue cancers over the last twenty years has paralleled trends of increasing use of marijuana among individuals born after 1950 (4, 11, 33). Therefore, we initially hypothesized that marijuana use could, in part, have contributed to the rising incidence of these cancers. Using pooled data from 9 case-control studies that contributed to the INHANCE consortium, we found evidence of a possible positive association of marijuana use with oropharyngeal cancer and a negative association with oral tongue cancer..

Our findings of a positive association of marijuana use and oropharyngeal cancer while in agreement with two prior studies (12, 20) contrasts with findings from five studies that showed no association (14–16, 18, 19). The possibility of a true association of marijuana use with oropharyngeal cancer risk was supported in the present study by the consistency of the observed associations with multiple measures of marijuana use including ever use, duration and frequency of use and was unaffected across strata of smoking and drinking. However, the inconsistent association across studies in this pooled analysis combined with an attenuation in the association after adjustment for smoking and drinking make the effect of residual and unmeasured confounding highly plausible.

Differential exposure to HPV infection among marijuana smokers as compared to non-smokers could be one source of potential confounding to explain the association of marijuana use with oropharyngeal cancer, as marijuana users engage more frequently in risky sexual behaviors leading to higher rates of sexually transmitted infections (34, 35). We had serologic information on HPV 16 from four studies. Unfortunately, the association of marijuana use and oropharyngeal cancer among these four studies was not representative of all the studies included in the pooled analysis, although stratified analyses among these four studies by HPV 16 L1 serostatus revealed a modest positive association of ever and long duration marijuana use oropharyngeal cancer among seropositive individuals. Therefore, we attempted to estimate the potential confounding effect of HPV on this association using plausible estimates of the association of HPV infection on oropharyngeal cancer risk as well as differences in oral HPV prevalence by marijuana usage. This approach revealed a substantial and nearly complete attenuation of the association of marijuana use with oropharyngeal cancer risk. Lastly, the association of marijuana use appeared to be specific for those oropharyngeal cancers most likely to be HPV-associated: non-smoker/non-drinkers, and those with tonsil or base of tongue sites. These data suggest that the positive

association of marijuana use and oropharyngeal cancer may be dependent on exposure to HPV. In lieu of more definitive information on tumor HPV infection status among cases and oral HPV infection status among cases and controls, the role of marijuana use as a potential risk factor in oropharyngeal cancer cannot be determined.

We observed that marijuana use was strongly inversely associated with oral tongue cancer specifically, which is similar to what has been reported previously among oral cavity cancers in general (9, 13, 15). This association remained robust across all marijuana use metrics, was strengthened after adjustment for tobacco and alcohol use, and was consistent across the five studies that had sufficient numbers of cases. Given that a very small fraction of oral cavity cancers are attributed to HPV (8), it is not surprising that marijuana use remained strongly inversely associated with oral tongue cancer even after adjustment for HPV (data not shown). Lastly, the inverse association appeared to be strongest amongst individuals <50 years of age, which are the same individuals that have the greatest observed per year increases in oral tongue cancer incidence (Supplemental Table 6). Therefore, this association may reflect a true inverse association of marijuana use on oral tongue cancer.

The major bioactive cannabinoid compound found in marijuana smoke, Δ (9) -tetrahydrocannabinol (Δ (9) -THC), has been shown to have both pro- and anti-carcinogenic capabilities. This cannabinoid functions primarily through engagement of specific cell surface receptors CB1, expressed on a range of cell types (36) and CB2 present primarily on a variety of immune cells, particularly those found in the human tonsil (37). Engagement of these receptors on immune cells has been shown to suppress pro-inflammatory cytokine production and enhance anti-inflammatory cytokine production (38, 39) leading to reduced host immune responses to infectious agents as well as suppression of anti-tumor immunity (40–42). Conversely, Δ (9) -THC has also been shown in epithelial cell lines to have distinct antitumor effects through arrest of uncontrolled cell growth, enhancement of apoptosis, and downregulation of angiogenesis and cellular migration (43–45). As a result, this cannabinoid has been investigated as a potential therapeutic agent in the treatment of glioma, breast and prostate cancers (46, 47). Interestingly, the anti-tumor effect of this cannabinoid is mediated through the same CB1 and CB2 receptors. The effects of tetrahydrocannabinol (Δ (9) -THC) and other cannabinoids on modulating tumorigenesis may be cell and tissue specific based on receptor expression profiles. This may help explain the differing associations of marijuana smoke with oropharyngeal and oral tongue cancers. Lastly, the presence of other carcinogenic compounds present in marijuana smoke may also play a role in driving the association.

Differences in the measurement of marijuana use, study sample recruitment, and measurement of demographic and other risk factors for Head and Neck Squamous Cell Carcinoma across the studies included in this analysis may have contributed to the heterogeneity observed across study sites. However, this heterogeneity was observed only for oropharyngeal cancer and not oral tongue cancer. Nevertheless, we included in our logistic regression models a random-effects term for each study to account for the heterogeneity of the association of marijuana use with oropharyngeal cancer outcomes. Furthermore, we acknowledge the possibility that misclassification in the measurement of marijuana use between cases and controls may explain some of these findings. Misclassification of marijuana exposure due to the use of self-administered or interviewer administered questionnaires has been suggested previously to be significant source of error in the observed association with head and neck cancers (9). Sensitivity analyses that modeled the effects of differential and non-differential misclassification of marijuana exposure demonstrated that correction for misclassification did alter the strength of the association with each cancer outcome (Supplementary table 4). Therefore, it cannot be ruled

out that either differential or non-differential misreporting of marijuana exposure may explain the observed associations of marijuana use with oropharynx and oral tongue cancers.

This pooled analysis of nine case-control studies conducted in the US and Latin America is the largest to date to investigate the relationship of marijuana use specifically with cancers of the oropharynx and oral tongue. The differing associations of marijuana use on oropharyngeal and oral tongue cancers observed in this study provides some epidemiologic support for the biological effect of cannabinoids as both a pro- and anti-carcinogenic agent. However, given the strong association of HPV on orpoharyngeal cancer not measured in this study, the modest attenuated effect of marijuana on these caners may well be explained by confounding by HPV. Additional studies focusing on cannabinoid receptor expression profiles and downstream effector functions across cell types involved in tumorigenesis of these cancers may yield important etiologic information as to the role of marijuana on head and neck cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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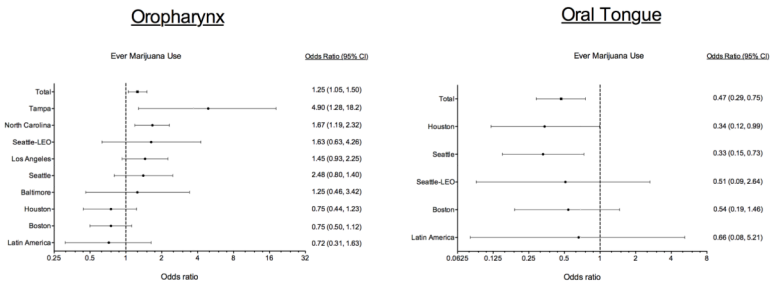

Figure 1.

Forest plots for study specific associations of ever marijuana marijuana use with oropharyngeal and oral tongue cancer among studies in the INHANCE consortium (Reference group is “Never users”) [95% Population effect interval $(PEI)_{[Oropharyngeal\ cancer]}$ = (0.81, 1.94)]; 95% Population effect interval $(PEI)_{[Oral\ tongue\ cancer]}$ = (0.38, 0.57)].

Table 1

Characteristics of oropharyngeal and oral tongue cases and controls, INHANCE Consortium

Characteristic	Oropharynx† n(%)		Oral Tongue†† n (%)	
	Cases (n=1,921)	Controls (n=7, 639)	Cases (n=356)	Controls (n=4, 321)
Study				
Baltimore[HOTSPOT]	69 (3.6)	71 (1.0)	-----	-----
Boston	230 (11.9)	659 (8.6)	30 (8.4)	659 (15.2)
Houston	388 (20.3)	865 (11.3)	115 (32.4)	865 (20.0)
Latin America	383 (19.9)	1, 643 (21.5)	53 (14.9)	1, 643 (38.0)
Los Angeles	152 (7.9)	1, 001 (13.1)	-----	-----
North Carolina	345 (17.9)	1, 357 (17.8)	-----	-----
Seattle[a]	168 (8.8)	607 (7.9)	96 (26.9)	607 (14.1)
Seattle-LEO[b]	129 (6.8)	547 (7.2)	62 (17.4)	547 (12.7)
Tampa	57 (2.9)	889 (11.6)	-----	-----
Age (years)				
<40	65 (3.4)	496 (6.5)	40 (11.2)	281 (6.5)
40–44	138 (7.2)	526 (6.9)	22 (6.2)	299 (6.9)
45–49	273 (14.2)	774 (10.1)	42 (11.8)	485 (11.2)
50–54	375 (19.5)	1, 269 (16.6)	44 (12.4)	638 (14.8)
55–59	402 (20.9)	1, 408 (18.4)	60 (16.8)	728 (16.9)
>=60	668 (34.8)	3, 166 (41.5)	148 (41.6)	1, 890 (43.7)
Sex:				
Male	1,544 (80.4)	5, 288 (69.2)	233 (65.5)	3, 208 (74.2)
Female	377 (19.6)	2, 351 (30.8)	123 (34.5)	1, 113 (25.8)
Race				
White non-Hispanic	1, 334 (69.5)	4, 971 (65.1)	276 (77.5)	2, 420 (56.0)
Black	132 (6.9)	563 (7.4)	7 (1.9)	119 (2.9)
Hispanic	45 (2.3)	341 (4.5)	10 (2.8)	86 (1.9)
Asian	17 (0.9)	88 (1.2)	8 (2.3)	26 (0.6)
Other	10 (0.5)	33 (0.4)	2 (0.6)	27 (0.6)
Latin American	383 (19.9)	1, 643 (21.5)	53 (14.9)	1, 643 (38.0)
Education				
No education	1 (0.1)	14 (0.2)	0 (0)	12 (0.3)
<Junior High School	369 (19.2)	1, 389 (18.2)	53 (14.9)	1, 266 (29.3)
Some high school	263 (13.7)	649 (8.5)	62 (17.4)	407 (9.4)
High school graduate	376 (19.6)	1, 315 (17.2)	59 (16.6)	592 (13.7)
Vocation, some college	425 (22.1)	1, 898 (24.8)	108 (30.4)	922 (21.3)
>=College	433 (22.5)	2, 160 (28.3)	71 (19.9)	910 (21.1)
Missing	54 (2.8)	214 (2.8)	3 (0.8)	212 (4.9)
Tobacco Smoking status				
Never	390 (20.3)	2, 893 (37.9)	93 (26.1)	1, 503 (34.8)

Characteristic	Oropharynx† n(%)		Oral Tongue†† n (%)	
	Cases (n=1,921)	Controls (n=7, 639)	Cases (n=356)	Controls (n=4, 321)
Ever	1, 531 (79.7)	4, 746 (62.1)	263 (73.9)	2, 818 (65.2)
Pack-Years of cigarette use				
1–10	213 (11.1)	1, 264 (16.5)	41 (11.5)	672 (15.5)
11–20	164 (8.5)	840 (11.0)	40 (11.2)	509 (11.7)
21–30	220 (11.5)	692 (9.1)	27 (7.7)	432 (10.0)
31–40	248 (12.9)	635 (8.3)	35 (9.8)	391 (9.1)
41–50	202 (10.6)	439 (5.8)	35 (9.8)	268 (6.2)
51+	465 (24.2)	835 (10.9)	85 (23.9)	509 (11.8)
Missing	19 (0.9)	41 (0.5)	0 (0)	37 (0.9)
Cigar/Pipe smoking status				
Never	1, 631 (84.9)	6, 705 (87.8)	312 (87.6)	3, 800 (87.9)
Ever	232 (12.1)	918 (12.0)	43 (12.1)	515 (11.9)
Missing	58 (3.0)	16 (0.2)	1 (0.3)	6 (0.2)
Alcohol drinking status				
Never	237 (12.3)	1, 955 (25.6)	65 (18.3)	1, 050 (24.3)
Ever	1, 684 (87.7)	5, 684 (74.4)	291 (81.7)	3, 271 (75.7)
Drink-Years of alcohol consumption				
1–20	400 (20.8)	2, 480 (32.5)	80 (22.5)	1, 175 (27.2)
21–30	117 (6.1)	496 (6.5)	22 (6.2)	304 (7.0)
31–40	84 (4.5)	370 (4.8)	23 (6.4)	227 (5.3)
41–50	840(4.2)	283 (3.7)	12 (3.4)	165 (3.7)
51–60	57 (2.9)	233 (3.1)	15 (4.2)	149 (3.5)
60+	890 (46.3)	1, 754 (22.9)	128 (35.9)	1, 218 (28.2)
Missing	56 (2.9)	68 (0.9)	11 (3.1)	33 (0.8)
HPV 16 Antibody Status†††				
Negative	398 (55.2)	1, 735 (74.5)	106 (44.7)	1, 735 (74.5)
Positive	239 (33.2)	426 (18.3)	59 (24.9)	426 (18.3)
Missing	84 (11.6)	167 (7.2)	72 (30.4)	167 (7.2)

†**ICD-9:** 141.0, 141.6, 145.3, 145.4, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9; **ICD-10:** C01.0, C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.8, C10.9.

††**ICD-9:** 141.1, 141.2, 141.3; **ICD-10:** C02.0, C02.1, C02.2

†††L1 serologic results available for Houston, Latin America, Boston, and Seattle(Schwartz) studies only;

*a*Schwartz et al.;

*b*Vaughan et al.;

*c*HOTSPOT

Table 2

Association of marijuana use with oropharyngeal and oral tongue cancer in the INHANCE Consortium

Marijuana use	Oropharyngeal				Oral Tongue†			
	Cases	Controls	uOR (95% CI)	aOR** (95% CI)	Cases	Controls	uOR (95% CI)	aOR** (95% CI)
Ever use								
Never	1, 511	6, 455	1.0	1.0	331	3, 909	1.0	1.0
Ever	410	1, 184	1.76 (1.52, 2.03)	1.24 (1.06, 1.47)	25	412	0.63 (0.41, 0.98)	0.47 (0.29, 0.75)
P (Interaction by study)			<0.001	<0.001			0.823	0.922
Freq of use (per week)*								
Never	1, 458	5, 576	1.0	1.0	331	3, 909	1.0	1.0
<=3	235	774	1.70 (1.42, 2.04)	1.24 (1.02, 1.52)	13	170	0.61 (0.34, 1.11)	0.47 (0.25, 0.89)
>3	137	311	1.94 (1.56, 2.42)	1.19 (0.94, 1.52)	9	161	0.64 (0.32, 1.27)	0.47 (0.23, 0.95)
Missing	34	89			3	81		
P for trend			<0.001	0.046			0.061	0.005
P (Interaction by study)			<0.001	<0.001			0.405	0.413
Duration of use (years)*								
Never	1, 458	5, 576	1.0	1.0	331	3, 909	1.0	1.0
<=10	191	662	1.45 (1.20, 1.75)	1.11 (0.91, 1.36)	14	255	0.56 (0.32, 0.98)	0.43 (0.23, 0.77)
>10	166	419	2.01 (1.63, 2.47)	1.28 (1.02, 1.61)	8	146	0.57 (0.27, 1.19)	0.44 (0.21, 0.94)
Missing	49	93			3	11		
P for trend			<0.001	0.031			0.022	0.002
P (Interaction by study)			<0.001	<0.001			0.479	0.675
Cumulative exposure (joint-year)*								
Never	1, 458	5, 576	1.0	1.0	331	3, 909	1.0	1.0
>0–1	113	491	1.42 (1.12, 1.81)	1.12 (0.87, 1.45)	8	101	0.55 (0.26, 1.15)	0.39 (0.18, 0.88)
2–10	129	306	1.98 (1.57, 2.48)	1.34 (1.04, 1.71)	9	125	0.77 (0.38, 1.55)	0.64 (0.31, 1.29)
>10	89	207	1.88 (1.44, 2.46)	1.14 (0.85, 1.52)	4	105	0.44 (0.16, 1.21)	0.31 (0.11, 0.89)
Missing	75	170			4	81		
P for trend			<0.001	0.055			0.040	0.004

Marijuana use	Oropharyngeal				Oral Tongue†			
	Cases	Controls	uOR (95% CI)	aOR** (95% CI)	Cases	Controls	uOR (95% CI)	aOR** (95% CI)
P (Interaction by study)			<0.001	<0.001			0.117	0.151

*Tampa excluded

**Models adjusted for age (continuous), sex, race (white vs. black vs. Hispanic vs. asian vs. other), education-level (imputed) (No education vs. <=Junior high school vs. Some high school vs. High school graduate vs. Technical school, some college vs. >=College graduate), ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking, alcohol-year. Study was included as a random intercept.

†Tampa, North Carolina, Baltimore, and Los Angeles excluded

Table 3

Association of marijuana use and oropharyngeal[†] cancer among never tobacco smokers/never drinkers vs. ever smoker/drinkers in the INHANCE Consortium

Marijuana use variables	Never Tobacco Smokers and Never Drinker			Ever Tobacco Smokers and or Ever Drinkers			ROR (95% CI)	RERI (95% CI)
	Cases	Controls	aOR (95% CI)*	Cases	Controls	aOR (95% CI)*		
Ever use								
Never	103	732	1.0	981	3, 232	1.0		
Ever	11	41	2.11 (0.97, 4.62)	386	1, 102	1.47 (1.24, 1.73)	0.58 (0.28, 1.26)	−0.48 (−1.43, 0.47)
P (Interaction by study)			0.011			<0.001		
Freq of use (per week)*								
Never	103	732	1.0	981	3, 232	1.0		
<=3	8	33	2.35 (0.92, 5.99)	227	741	1.48 (1.21, 1.81)	0.59 (0.24, 1.43)	−0.42 (−0.79, −0.04)
>3	2	6	1.61 (0.31, 8.50)	127	274	1.57 (1.23, 2.01)	0.79 (0.15, 4.14)	−0.53 (−4.77, 3.71)
Missing	1	2		32	87			
P for trend			0.117			<0.001		
P (Interaction by study)			0.004			<0.001		
Duration of use (years)*								
Never	103	732	1.0	981	3, 232	1.0		
<=10	7	31	1.82 (0.72, 4.62)	179	610	1.27 (1.03, 1.56)	0.63 (0.26, 1.54)	−0.43 (−1.12, 0.26)
>10	3	9	2.66 (0.63, 11.24)	160	400	1.66 (1.32, 2.09)	0.60 (0.12, 2.97)	−0.28 (−1.77, 1.21)
Missing	1	1		47	92			
P for trend			0.080			<0.001		
P (Interaction by study)			0.032			<0.001		
Cumulative exposure (joint-year)*								
Never	103	732	1.0	981	3, 232	1.0		
>0–1	5	29	1.57 (0.53, 4.66)	107	462	1.27 (0.98, 1.64)	0.70 (0.25, 1.54)	−0.34 (−0.67, −0.01)
2–10	3	7	2.83 (0.66, 12.1)	125	289	1.66 (1.29, 2.12)	0.66 (0.12, 3.46)	−0.53 (−1.88, 1.13)
>10	2	3	3.94 (0.59, 26.3)	81	183	1.48 (1.10, 1.99)	0.30 (0.05, 1.05)	−2.25 (−10.4, 5.9)
Missing	1	2		73	168			

Marijuana use variables	Never Tobacco Smokers and Never Drinker			Ever Tobacco Smokers and or Ever Drinkers			ROR (95% CI)	RERI (95% CI)
	Cases	Controls	aOR (95% CI)*	Cases	Controls	aOR (95% CI)*		
P for trend			0.037			<0.001		
P (Interaction by study)			0.027			<0.001		

*Tampa excluded

¶Models adjusted for age (continuous), sex, race (white vs. black vs. Hispanic vs. asian vs. other), education-level (imputed) (No education vs. <=Junior high school vs. Some high school graduate vs. Technical school, some college vs. >=College graduate), ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking,, alcohol-year. Study was included as a random intercept.

†**ICD-9:** 141.0, 141.6, 145.3, 145.4, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9; **ICD-10:** C01.0, C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.8, C10.9.

Table 4

Sensitivity analysis of the effect of HPV-exposure on the association of EVER Marijuana use and oropharyngeal cancer

Prevalence of HPV among Marijuana never users	Adjusted Odds Ratio†	Bias Factor**
2%	1.13 (0.84, 1.33)	1.56
3%	1.05 (0.76, 1.28)	1.68
4%	**0.99 (0.71, 1.25)**	**1.78**
5%	0.95 (0.68, 1.21)	1.85
6%	0.92 (0.66, 1.19)	1.91

† Assuming an odds ratio of 12.3 (95% CI: 5.4, 26.4) for the association of oral HPV infection and oropharyngeal cancer (Reference: D'Souza et al. NEJM 2007) and an estimated odds ratio for the association of current marijuana use and oral HPV prevalence of 2.87 (95% CI:1.85, 4.46) (Gillison et al. JAMA 2012).

* **Bolded** denotes most relevant scenario based on reported oral HPV prevalence among marijuana never users and the reported increased prevalence of oral HPV among current marijuana users reported in the NHANES.

** Compared with unadjusted model