Research Article

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Association of Marijuana Smoking with Oropharyngeal and Oral Tongue Cancers: Pooled Analysis from the INHANCE Consortium

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Abstract

Background: The incidence of oropharyngeal and oral tongue cancers has increased over the last 20 years which parallels increased use of marijuana among individuals born after 1950.

Methods: A pooled analysis was conducted comprising individual-level data from nine case–control studies from the United States 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 OR (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 was reduced among never users of tobacco and alcohol. 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 anticarcinogenic 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.
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Introduction

Head and neck squamous cell carcinomas (HNSCC), which include cancers of the oral cavity, oropharynx, and larynx, are the sixth most common cancers worldwide with an estimated annual burden of 3,55,000 deaths and 6,33,000 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

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major etiologic factor for a subset of HNSCC—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 United States 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 less than 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 HNSCCs 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.

Materials and 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 second edition (ICD-02). 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-02 (8050–8084). Of the 2,325 cases, 2,286 (98%) were SCC (1,921 oropharynx and 365 oral tongue). Because of 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 Supplementary Table S1. 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 and 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, and 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, whereas 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). Finally, 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

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 one year or more. Finally, "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 were 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 versus 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 6 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. Finally, two studies [Houston and Baltimore (HOTSPOT)] collected "ever versus never" information from questionnaire data without defining a frequency or duration of use cutoff.

Alcohol consumption

Alcohol consumption was defined as ever versus 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 one year or more (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; ref. 22). Total alcohol consumption was treated as a continuous variable in all analyses.

Statistical analysis

ORs 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 ORs 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 goodness 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 ORs 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).

Subgroup 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, subgroup 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 non-smoker non-drinker, 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 ORs (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 (ref. 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 with 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%). Finally, oropharyngeal cancer cases were more likely than controls to report more than 50 pack-years of cigarette smoking (24.2% vs. 10.9%) and more than 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 with 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 was 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 ($P = 0.037$; Supplementary Table S2). However, there was significant heterogeneity of these associations by study-site for ever-marijuana use (Fig. 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 with never smokers/drinkers on a additive scale among those reporting marijuana use at a frequency of less than 3 times per 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 before 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 ORs (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; Supplementary Table S3). This qualitative difference in the OR 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

Table 1. Characteristics of oropharyngeal and oral tongue cases and controls, INHANCE Consortium

	Oropharynx[a], *n* (%)		Oral tongue[b], *n* (%)	
Characteristic	**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[c]	168 (8.8)	607 (7.9)	96 (26.9)	607 (14.1)
Seattle-LEO[d]	129 (6.8)	547 (7.2)	62 (17.4)	547 (12.7)
Tampa	57 (2.9)	889 (11.6)	—	—
Age, y				
<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)
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)

(Continued on the following page)

Table 1. Characteristics of oropharyngeal and oral tongue cases and controls, INHANCE Consortium (Cont'd)

	Oropharynx[a], *n* (%)		Oral tongue[b], *n* (%)	
Characteristic	**Cases (*n* = 1,921)**	**Controls (*n* = 7,639)**	**Cases (*n* = 356)**	**Controls (*n* = 4,321)**
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[e]				
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)

[a]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.
[b]ICD-9: 141.1, 141.2, 141.3; ICD-10: C02.0, C02.1, C02.2.
[c]Schwartz and colleagues.
[d]Vaughan and colleagues.
[e]L1 serologic results available for Houston, Latin America, Boston, and Seattle (Schwartz) studies only.

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 (Supplementary Table S4). In contrast, correction for non-differential misclassification resulted in a slight strengthening of the association of marijuana with oropharyngeal cancer.

Finally, 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 ORs 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 with 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%). Finally, oral tongue cancer cases were more likely than controls to report more than 50 pack-years of cigarette smoking (23.9% vs. 11.8%) and more than 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 with 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 on the basis of the means of the each category for each variable (Supplementary Table S2). The strength of the association of ever marijuana use and oral tongue cancer did not differ significantly by study site ($P_{study} =$

Table 2. Association of marijuana use with oropharyngeal and oral tongue cancer in the INHANCE Consortium

	Oropharyngeal				Oral tongue[c]			
Marijuana use	**Cases**	**Controls**	**uOR (95% CI)**	**aOR[b] (95% CI)**	**Cases**	**Controls**	**uOR (95% CI)**	**aOR[b] (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
Frequency of use (per week)[a]								
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_{trend}			<0.001	0.046			0.061	0.005
P (interaction by study)			<0.001	<0.001			0.405	0.413
Duration of use, y[a]								
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_{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)[a]								
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_{trend}			<0.001	0.055			0.040	0.004
P (interaction by study)			<0.001	<0.001			0.117	0.151

[a]Tampa excluded.

[b]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, and alcohol-year. Study was included as a random intercept.

[c]Tampa, North Carolina, Baltimore, and Los Angeles excluded.

0.922; Fig. 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 (Supplementary Table S5).

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 (Supplementary Table S4). 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 20 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

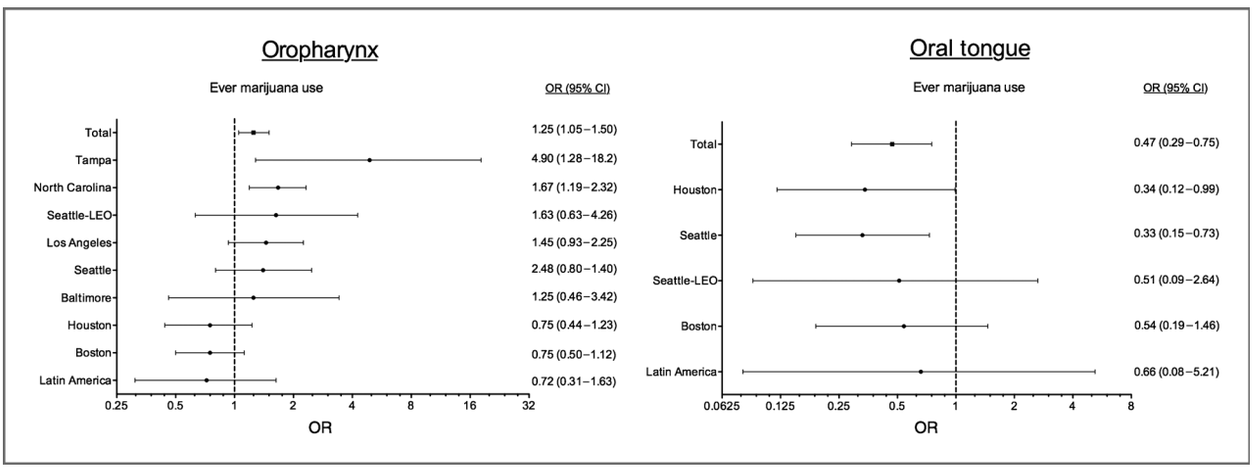

Figure 1. Forest plots for study-specific associations of ever marijuana use with oropharyngeal and oral tongue cancer among studies in the INHANCE consortium [reference group is "Never users"; 95% $PEI_{(Oropharyngeal\ cancer)} = 0.81–1.94$; 95% $PEI_{(Oral\ tongue\ cancer)} = 0.38–0.57$].

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 with 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. Finally, 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). Finally, the inverse association appeared to be strongest amongst individuals less than 50 years of age, which are the same individuals that have the greatest observed per year increases in oral tongue cancer incidence (Supplementary Table S6). 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 anticarcinogenic 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 proinflammatory cytokine production and enhance anti-inflammatory cytokine production (38, 39) leading to reduced host immune responses to infectious agents as

Table 3. Association of marijuana use and oropharyngeal[a] cancer among never tobacco smokers/never drinkers versus ever smoker/drinkers in the INHANCE Consortium

	Never tobacco smokers and never drinkers			Ever tobacco smokers and/or ever drinkers				
Marijuana use variables	**Cases**	**Controls**	**aOR (95% CI)[b]**	**Cases**	**Controls**	**aOR (95% CI)[b]**	**ROR (95% CI)**	**RERI (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		
Frequency of use (per week)[c]								
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_{trend}			0.117			<0.001		
P (interaction by study)			0.004			<0.001		
Duration of use, y[c]								
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_{trend}			0.080			<0.001		
P (interaction by study)			0.032			<0.001		
Cumulative exposure (joint-year)[c]								
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			
P_{trend}			0.037			<0.001		
P (interaction by study)			0.027			<0.001		

[a]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.

[b]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, and alcohol-year. Study was included as a random intercept.

[c]Tampa excluded.

well as suppression of antitumor 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 antitumor 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. Finally, 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

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	aOR[a] (95% CI)	Bias factor[b]
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

NOTE: Data given in bold denote 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.

[a]Assuming an OR of 12.3 (95% CI, 5.4–26.4) for the association of oral HPV infection and oropharyngeal cancer [D'Souza and colleagues (27)] and an estimated OR for the association of current marijuana use and oral HPV prevalence of 2.87 [95% CI,1.85–4.46; Gillison and colleagues (28)].

[b]Compared with unadjusted model.

and other risk factors for HNSCC 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 nondifferential misclassification of marijuana exposure demonstrated that correction for misclassification did alter the strength of the association with each cancer outcome (Supplementary Table S4). Therefore, it cannot be ruled out that either differential or nondifferential 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 United States 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 biologic effect of cannabinoids as both a pro- and anticarcinogenic 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.

Disclosure of Potential Conflicts of Interest

G. D'Souza has a commercial research grant from Merck Inc. No potential conflicts of interest were disclosed by the other authors.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
2. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet 2004;363:1488–9.
3. Blomberg M, Nielsen A, Munk C, Kjaer SK. Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites. Int J Cancer 2010;129:733–41.
4. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612–9.
5. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer 2005;103:1843–9.
6. Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, Hackman T, et al. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. J Clin Oncol 2011;29: 1488–94.
7. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–301.
8. Lingen MW, Xiao W, Schmidt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol 2012;49:1–8.
9. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. Alcohol 2005;35:265–75.
10. Johnson RA, Gerstein DR. Initiation of use of alcohol, cigarettes, marijuana, cocaine, and other substances in US birth cohorts since 1919. Am J Public Health 1998;88:27–33.
11. Schantz SP, Yu GP. Head and neck cancer incidence trends in young Americans, 1973–1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg 2002;128:268–74.
12. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008;100:407–20.
13. Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, et al. A population-based case-control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res 2009;2: 759–68.
14. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and cancer of the head and neck: case-control study. Otolaryngol Head Neck Surg 2008;138:374–80.
15. Berthiller J, Lee YC, Boffetta P, Wei Q, Sturgis EM, Greenland S, et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev 2009;18:1544–51.
16. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England. J Oral Pathol Med 2004;33: 525–32.
17. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya KA. Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol 2003;39:106–14.
18. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004;40:304–13.
19. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res 2004;64:4049–54.
20. Zhang ZF, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 1999;8:1071–8.
21. Conway DI, Hashibe M, Boffetta P, Wunsch-Filho V, Muscat J, La Vecchia C, et al. Enhancing epidemiologic research on head and neck cancer: INHANCE - The international head and neck cancer epidemiology consortium. Oral Oncol 2009;45:743–6.
22. Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Dal Maso L, Herrero R, et al. Type of alcoholic beverage and risk of head and neck cancer–a pooled analysis within the INHANCE Consortium. Am J Epidemiol 2009;169:132–42.
23. Edwards S, Carne C. Oral sex and the transmission of viral STIs. Sex Transm Infect 1998;74:6–10.
24. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis 2005;41:67–74.
25. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am J Epidemiol 2009;169:756–60.
26. Steenland K, Greenland S. Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. Am J Epidemiol 2004;160:384–92.
27. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944–56.
28. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009–2010. JAMA 2012;307:693–703.
29. Rothman K, Greenland S. Modern Epidemiology. Baltimore, MD: Lippincott Williams & Wilkins; 1998. p. 347–50.
30. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol 1996;25:1107–16.
31. Buchan BJ, L Dennis M, Tims FM, Diamond GS. Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction 2002;97(Suppl 1):98–108.
32. Trivers KF, Mertens AC, Ross JA, Steinbuch M, Olshan AF, Robison LL. Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (United States and Canada). Paediatr Perinat Epidemiol 2006;20:110–8.
33. Miech R, Koester S. Trends in U.S., past-year marijuana use from 1985 to 2009: an age-period-cohort analysis. Drug Alcohol Depend 2012;124:259–67.
34. Parks KA, Collins RL, Derrick JL. The influence of marijuana and alcohol use on condom use behavior: findings from a sample of young adult female bar drinkers. Psychol Addict Behav 2012;26:888–94.
35. Bryan AD, Schmiege SJ, Magnan RE. Marijuana use and risky sexual behavior among high-risk adolescents: trajectories, risk factors, and event-level relationships. Dev Psychol 2012;48:1429–42.
36. Gertsch J, Raduner S, Altmann KH. New natural noncannabinoid ligands for cannabinoid type-2 (CB2) receptors. J Recept Signal Transduct Res 2006;26:709–30.
37. Berglund BA, Boring DL, Howlett AC. Investigation of structural analogs of prostaglandin amides for binding to and activation of CB1 and CB2 cannabinoid receptors in rat brain and human tonsils. Adv Exp Med Biol 1999;469:527–33.
38. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 2005;5:400–11.
39. Klein TW, Newton C, Larsen K, Lu L, Perkins I, Nong L, et al. The cannabinoid system and immune modulation. J Leukoc Biol 2003;74: 486–96.
40. Cabral GA, Dove Pettit DA. Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. J Neuroimmunol 1998;83:116–23.
41. McKallip RJ, Nagarkatti M, Nagarkatti PS. Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J Immunol 2005;174:3281–9.
42. Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP, et al. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. J Immunol 2000;165:373–80.
43. Flygare J, Sander B. The endocannabinoid system in cancer-potential therapeutic target? Semin Cancer Biol 2008;18:176–89.
44. Greenhough A, Patsos HA, Williams AC, Paraskeva C. The cannabinoid delta(9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT

survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. Int J Cancer 2007;121:2172–80.

45. Whyte DA, Al-Hammadi S, Balhaj G, Brown OM, Penefsky HS, Souid AK. Cannabinoids inhibit cellular respiration of human oral cancer cells. Pharmacology 2010;85:328–35.

46. Parolaro D, Massi P. Cannabinoids as potential new therapy for the treatment of gliomas. Expert Rev Neurother 2008;8:37–49.

47. Guindon J, Hohmann AG. The endocannabinoid system and cancer: therapeutic implication. Br J Pharmacol 2011;163:1447–63.