Marijuana Smoking and the Risk of Head and Neck Cancer: Pooled Analysis in the INHANCE Consortium

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Abstract

Background: **Marijuana contains carcinogens similar to tobacco smoke and has been suggested by relatively small studies to increase the risk of head and neck cancer (HNC). Because tobacco is a major risk factor for HNC, large studies with substantial numbers of never tobacco users could help to clarify whether marijuana smoking is independently associated with HNC risk.**

Methods: **We pooled self-reported interview data on marijuana smoking and known HNC risk factors on 4,029 HNC cases and 5,015 controls from five case-control studies within the INHANCE Consortium. Subanalyses were conducted among never tobacco users (493 cases and 1,813 controls) and among individuals who did not consume alcohol or smoke tobacco (237 cases and 887 controls).**

Results: **The risk of HNC was not elevated by ever marijuana smoking [odds ratio (OR), 0.88; 95% confidence intervals (95% CI), 0.67-1.16], and there was no increasing risk associated with increasing frequency, duration, or cumulative consumption of marijuana smoking. An increased risk of HNC associated with marijuana use was not detected among never tobacco users (OR, 0.93; 95% CI, 0.63-1.37; three studies) nor among individuals who did not drink alcohol and smoke tobacco (OR, 1.06; 95% CI, 0.47-2.38; two studies).**

Conclusion: **Our results are consistent with the notion that infrequent marijuana smoking does not confer a risk of these malignancies. Nonetheless, because the prevalence of frequent marijuana smoking was low in most of the contributing studies, we could not rule out a moderately increased risk, particularly among subgroups without exposure to tobacco and alcohol.** (Cancer Epidemiol Biomarkers Prev 2009;18(5):1544–51)

Introduction

Marijuana (*Cannabis sativa*) is the most commonly used illegal drug in the world. It is estimated that about 160 million people consume marijuana each year, which is about 4% of the world population ages 15 to 64 years (1). Because it is mainly consumed by smoking and its combustion products include tobacco carcinogens, such as nitrosamine and polycyclic aromatic hydrocarbons (benzo[*a*]pyrene and phenols; refs. 2, 3) at levels that can be higher than derived from cigarettes (4), it has been suspected to be causally associated with cancers of the lung, head and neck, and bladder (5). One small study observed an increased risk of upper aerodigestive tract cancers for ever marijuana smoking, with a dose-response relationship for both frequency and duration of smoking (6). This association was not observed among never tobacco users and never alcohol users, but the numbers in these categories were low. The study used blood donors as controls; if these individuals tended to have less marijuana use than typical in the source population, a spurious positive association would result. On the other hand, five studies, one on head and neck cancer (HNC) in New Zealand (7), one on upper aerodigestive tract cancers in Los Angeles (8), two on oral cavity cancer conducted in South England (9), and one on oral cavity cancers in the United States (10), did not observe any association with ever smoking marijuana.

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The INHANCE Consortium was established in 2004 based on the collaboration of research groups leading large molecular epidemiology studies of HNC that were ongoing or recently completed. This consortium was established to explore potential HNC risk factors that were difficult to evaluate in individual studies. The aim of this pooled analysis was to investigate the association between the risk of HNC and marijuana smoking, particularly in individuals who did not smoke tobacco or drink alcohol. Focusing on this subgroup may allow clarification on whether marijuana smoking is independently associated with HNC risk.

Materials and Methods

The INHANCE pooled data (version 1.1) included 18 individual case-control studies of HNC, of which 5 had information on marijuana smoking comprising 4,085 cases and 5,125 controls. The results on marijuana smoking from the Los Angeles study (601 head and neck cases and 1,040 controls) and from the Seattle study (435 cases and 615 controls), included in this pooled data set, have already been published (8, 10). After subjects in these five studies with data missing on age, sex, race/ethnicity, or marijuana status and cases with missing information on the site of origin of their cancer were excluded (56 cases and 110 controls), there were 4,029 cases and 5,015 controls available for the pooled analysis.

The tumor subsite distribution of cases was as follows: 981 oral cavity, 1,397 pharynx (1,165 oropharynx and 232 hypopharynx), 435 oral cavity or pharynx not otherwise specified, 1,159 larynx, and 57 head and neck not otherwise specified. Two studies restricted case eligibility to squamous cell carcinomas (SCC; Tampa and Houston studies). For other studies that provided the International Classification of Diseases for Oncology, 2nd edition, histologic coding for each tumor (Seattle, Los Angeles, and Latin America studies), we used the codes to identify SCC cases. Of the 4,029 HNC cases, 3,818 were SCCs (95%).

Characteristics of the individual studies included in the pooled data are presented in Table 1. Three of the five studies were hospital-based case-control studies. Four of the studies frequency matched controls to cases based on age and sex. The Latin America study additionally matched on study center. The Los Angeles study individually matched controls to cases based on age decade, sex, and neighborhood. All interviews were conducted face to face with structured questionnaires. Questionnaires were collected from all individual studies to assess the comparability of the data and wording of interview questions. Anonymized data from individual studies were pooled; each data item was checked for illogical or missing values; inconsistencies were resolved.

Data on whether an individual had smoked marijuana smoking, and at what frequency and length of time, were collected differently across studies. The questions asked for assessing marijuana smoking were the following: ''Have you ever used marijuana?'' (Los Angeles, Seattle, and Houston studies), ''Have you ever smoked marijuana at least once per week for 6 months?'' (Latin America study), and ''Have you ever smoked marijuana at least once a day for one year's time?'' (Tampa study).

The Houston and Tampa studies asked each subject to report the frequency and years of marijuana use average over his/her lifetime, whereas three studies (Seattle, Latin America, and Los Angeles) obtained information about different periods of marijuana smoking over the subject's lifetime; for these three studies, the lifetime average was calculated by weighting the frequency of the specific period by the duration of that period and total years of marijuana smoking were calculated by summing across the durations of the individual periods. A ''joint-year'' variable was created and defined as the number of joints per day multiplied by the duration of marijuana smoking in years.

Statistical Analysis. The association between marijuana smoking and the risk of HNC was assessed by computing odds ratios (OR) and 95% confidence intervals (95% CI) from unconditional logistic regression models for each case-control study. To adjust for potential confounders, the models included age (categorical), sex, education (categorical), race/ethnicity, study center, pack-years (continuous), duration of smoking pipe (continuous), duration of smoking cigar (continuous), and duration of alcohol drinking in years (continuous).

Stratified analyses were conducted by subsite of HNC (oral cavity, pharynx, oral cavity/pharynx not otherwise specified, and larynx). Additional analyses were restricted to never tobacco users (493 cases and 1,813 controls), never alcohol drinkers (568 cases and 1,505 controls), and

Table 1. Summary of individual studies in INHANCE pooled data version 1.1

Study location	Recruitment period	Cases			Controls*	
		Source	Participation rate	Age eligibility	Source	Participation rate
Seattle, WA	1985-1995	Cancer registry	54%, 63% †	18-65	Random digit dialing	63%, 61% †
Tampa, FL	1999-2003	Hospital	98%	≥18	Cancer screening clinic—healthy	90%
Los Angeles, CA	1999-2004	Cancer registry	49%	18-65	Neighborhood	68%
Houston, TX	2001-2006	Hospital	95%	>18	Hospital visitors	80%
Havana, Buenos Aires, Brazil	2000-2003	Hospital	95%	15-79	Hospital—patients	86%

*All studies frequency matched controls to cases, minimally on age and sex. Additional frequency matching factors included center (Latin America), ethnicity, and neighborhood (Los Angeles study).

† Two response rates are reported because data were collected in two population-based case-control studies: the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

Table 2. Characteristics of HNC cases and controls

	Cases			Controls		
	Total	No. ever marijuana smokers*	% ever marijuana smokers	Total	No. ever marijuana smokers*	% ever marijuana smokers
Total	4,029	408	10.1	5,015	744	14.8
Study						
Seattle	407	68	16.7	607	103	17.0
Tampa	207	5	2.4	897	4	0.4
Los Angeles	416	244	58.7	1,002	543	54.2
Houston	829	49	5.9	865	64	7.4
Latin America						
Buenos Aires	334	0	0.0	188	5	2.7
Havana	196	1	0.5	176	2	1.1
Goiania	391	7	1.8	242	4	1.7
Pelotas	128	1	0.8	225	0	0.0
Porto Alegre	191	2	1.0	152	1	0.7
Rio de Janeiro	428	12	2.8	241	7	2.9
Sao Paulo	502	19	3.8	420	11	2.6
Age categories						
<40	162	39	24.1	347	90	25.9
40-<45	281	53	18.9	455	131	28.8
45-<50	526	115	21.9	643	156	24.3
50-<55	690	95	13.8	945	208	22.0
55-<60	805	92	11.4	992	136	13.7
≥60	1,565	14	0.9	1,633	23	1.4
Sex						
Women	785	66	8.4	1,547	213	13.8
Men	3,244	342	10.5	3,468	531	15.3
Race						
White non-Hispanic	1,526	280	18.3	2,684	558	20.8
Black	145	52	35.9	271	71	26.2
Hispanic	141	27	19.1	328	68	20.7
Asian + other	47	10	21.3	88	17	19.3
Latin American †	2,170	42	1.9	1,644	30	1.8
Education						
<Junior high school	1,722	46	2.7	1,310	29	2.2
Some high school	441	66	15.0	390	49	12.6
High school graduate	475	77	16.2	666	128	19.2
Vocational, some college	606	126	20.8	1,159	242	20.9
≥College	480	90	18.8	1,278	296	23.2
Missing	305	3	1.0	212	—	—
Tobacco smoking status						
Never	493	57	11.6	1,813	221	12.2
Ever	3,536	351	9.9	3,196	522	16.3
Missing	—	—		6	1	
Alcohol drinking status						
Never	568	34	6.0	1,505	80	5.3
Ever	3,457	373	10.8	3,506	663	18.9
Missing	4	1		4	1	

*Ever marijuana smoking was defined differently in the studies: the Seattle, Houston, and Los Angeles studies (''ever'' use), Latin America study (≥once per week for 6 mo), and Tampa study (≥once per day for 1 y).
† The Latin America study did not assess race/ethnicity; thus, we classified the subjects as a separate category ''Latin Americans.''.

never tobacco and never alcohol drinkers (237 cases and 887 controls) based on the definitions described previously (11).

For subjects missing data on education level (305 cases and 212 controls), we applied multiple imputations (five imputations) with the PROC MI procedure in Statistical Analysis System. We used the logistic regression model (12) to predict education level with age, sex, race/ethnicity, study, and case/control status for the Latin American and North American regions separately. The logistic regression results to assess summary estimates for marijuana smoking for the five imputations were combined by using the PROC MIANALYZE procedure.

We tested for heterogeneity between studies for each analysis using a log likelihood ratio test. We compared the model with and without a product term between marijuana smoking and the study indicator. We then compared twice the difference between the log likelihood of these two models to a χ^2 distribution with degree of freedom equal to the number of studies minus one. When the heterogeneity P was <0.05, study-specific estimates were included in a two-stage random-effects logistic regression model. Influence analyses were conducted, with exclusion of each study one at a time, to evaluate if the magnitude of the estimate was dependent on any one study.

Results

Approximately 10% of cases and 15% of controls were ever marijuana smokers (Table 2). The greatest proportion of ever marijuana smokers was observed in the Los

Table 3. Marijuana smoking and the risk of HNC

	Case	Controls	OR* (95% CI)
Total	4,029	5,015	
Marijuana smoking			
Never	3,538	4,199	1.00 (reference)
Ever	402	736	0.88 (0.67-1.16)
Missing	89	80	
P for heterogeneity			0.07
Frequency of marijuana smoking (times per day) †			
Never	3,339	3,319	1.00
0-1	298	630	0.87 (0.61-1.25)
>1-3	49	61	0.71 (0.35-1.47)
>3	42	42	0.87 (0.40-1.89)
Missing	94	66	
P for trend			0.26
P for heterogeneity			0.03
Duration of marijuana smoking (in years) †			
Never	3,339	3,319	1.00 reference
>0-5	150	319	0.81 (0.53-1.23)
>5-10	65	129	0.87 (0.48-1.57)
>10-20	74	145	0.82 (0.46-1.44)
>20	100	140	0.94 (0.53-1.66)
Missing	94	66	
P for trend			0.77
P for heterogeneity			0.36
Cumulative exposure (joint-year) †,‡			
Never	3,339	3,319	1.00 (reference)
>0-2	208	476	0.89 (0.60-1.31)
>2-5	36	77	0.70 (0.31-1.56)
>5	145	180	0.86 (0.54-1.37)
Missing	94	66	
P for trend			0.22
P for heterogeneity			0.04

*Random-effects estimates. Adjusted for age (categorical), sex, race, education level, study, pack-year (continuous), alcohol duration (continuous), duration of smoking pipe (continuous), and duration of smoking cigar (continuous). Likelihood heterogeneity test by study.
† Tampa study excluded.
‡ A joint-year is the number of joints per day multiplied by the duration of marijuana smoking in years (1 joint-year being equivalent to 1 joint per day for 1 y or 365 joints lifetime).

Angeles study (58.7% of the cases and 54.2% of the controls). There were higher proportions of marijuana smokers among white men, subjects 45 to 55 years old, and subjects with an education level greater than college. Among never tobacco users, 13.9% of cases and 29.7% of controls reported ever smoking marijuana. Among never alcohol drinkers, 8.4% of cases and 10.8% of controls reported ever smoking marijuana.

We did not observe an association with ever marijuana smoking and the risk of HNC (OR, 0.88; 95% CI, 0.67-1.16; Table 3). Figure 1 shows a forest plot of the study-specific estimates of the risk of HNC associated with marijuana smoking. All five studies failed to detect an association between HNC and marijuana smoking. Only the Tampa study had an OR above three, whereas the other studies showed OR below one.

When we restricted the analysis to studies with similar definitions of ''ever use'' (Los Angeles, Seattle, and Houston studies), we did not observe an association between ever marijuana smoking and HNC risk (OR, 0.85; 95% CI, 0.53-1.35). When we applied a specific cutoff definition of marijuana smoking to 1 joint per day for 1 year, we similarly did not observe an association for ever marijuana smoking. In addition, we did not observe any dose-response trend for frequency of marijuana smoking, marijuana smoking duration, or cumulative marijuana consumption in these analyses. The Tampa study was excluded from the analysis on duration and frequency of marijuana smoking because there were not enough cases or controls in each category of frequency and duration of marijuana smoking to calculate these estimates. Heterogeneity was detected between studies for the associations of frequency of marijuana smoking and joint-years of marijuana smoking with risk of HNCs.

Increased risks were not observed by ever, frequency, duration, or cumulative marijuana smoking for any HNC subsite (Table 4). For pharyngeal cancers, the Tampa and Seattle studies were excluded from the analysis on frequency of marijuana use and the Seattle study was excluded for the analysis on duration and cumulative consumption because there were not enough cases or controls in the categories of frequency and duration of marijuana smoking. For oropharyngeal cancer, we observed an increased risk associated with ever marijuana smoking (OR, 1.40; 95% CI, 1.05-1.87), but a dose-response relationship was not detected.

In the analysis restricted to never tobacco users (353 cases and 1,017 controls; Table 5), the Tampa study was not included because all marijuana smokers were also tobacco users. The Latin America study was also excluded because no cases and only one control smoked marijuana without using tobacco. No association between smoking marijuana and the risk of HNC was observed among never tobacco users. Among never alcohol drinkers, an increased risk was observed for subjects who smoked marijuana for more than 20 years (*P* trend = 0.05) and for subjects who smoked more than

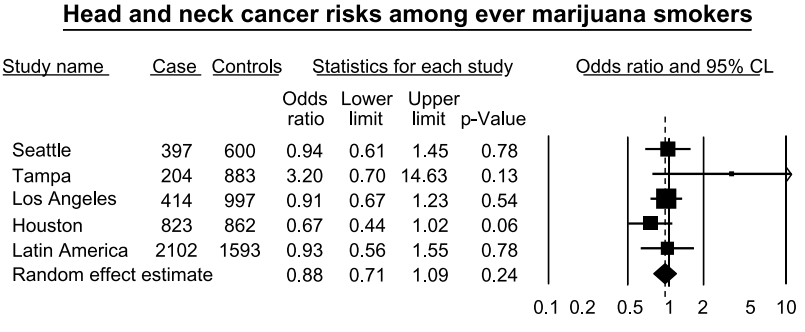

Figure 1. The risk of HNC associated with ever marijuana smoking by study. ORs were adjusted on age, sex, race/ethnicity, education level, study, pack-years of tobacco smoking, years of alcohol drinking, years of cigar smoking, and years of pipe smoking.

Table 4. Marijuana smoking and the risk of HNC stratified by subsite of cancer

	Oral cavity			Pharynx*,†			Larynx‡		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total	981	5,015		1,397	5,015		1,159	4,408	
Marijuana smoking									
Never	877	4,199	1.00 (reference)	1,177	4,199	1.00 (reference)	1,063	3,701	1.00 (reference)
Ever	77	736	0.74 (0.55-1.00)	192	736	1.13 (0.76-1.68)	72	634	0.98 (0.69-1.39)
Missing	27	80		28	80		24	73	
P for heterogeneity			0.33			0.03			0.62
Frequency of marijuana smoking (times per day)									
Never	877	4,199	1.00 (reference)	988	2,821	1.00 (reference)	1,063	3,701	1.00 (reference)
0-1	59	631	0.76 (0.54-1.07)	113	534	1.05 (0.49-2.22)	47	535	0.88 (0.57-1.34)
>1-3	10	61	0.63 (0.30-1.30)	22	56	1.01 (0.28-3.64)	11	56	1.08 (0.54-2.18)
>3	7	43	0.64 (0.27-1.52)	14	41	0.82 (0.19-3.61)	12	42	1.05 (0.51-2.15)
Missing	28	81		24	59		26	74	
P for trend			0.04			0.71			0.99
P for heterogeneity			0.85			<0.01			0.55
Duration of marijuana smoking (in years)									
Never	877	4,199	1.00 (reference)	1,124	3,319	1.00 (reference)	1,063	3,701	1.00 (reference)
>0-5	29	319	0.64 (0.42-0.99)	75	319	1.08 (0.63-1.85)	20	278	0.65 (0.38-1.11)
>5-10	16	129	0.83 (0.46-1.50)	28	129	1.01 (0.46-2.24)	12	111	1.10 (0.56-2.14)
>10-20	18	145	0.80 (0.46-1.40)	36	145	1.07 (0.51-2.26)	10	111	0.85 (0.41-1.76)
>20	13	143	0.74 (0.39-1.39)	45	140	1.31 (0.62-2.76)	28	134	1.42 (0.84-2.38)
Missing	28	80		26	66		26	73	
P for trend			0.15			0.66			0.32
P for heterogeneity			0.93			0.23			0.69
Cumulative exposure (joint-year)									
Never	877	4,199	1.00 (reference)	1,124	3,319	1.00 (reference)	1,063	3,701	1.00 (reference)
>0-2	41	476	0.73 (0.50-1.08)	97	476	1.15 (0.68-1.94)	31	406	0.84 (0.52-1.36)
>2-5	9	77	0.68 (0.32-1.46)	21	77	1.29 (0.45-3.75)	3	66	0.31 (0.09-1.07)
>5	26	182	0.73 (0.46-1.16)	66	180	1.03 (0.47-2.26)	36	161	1.20 (0.77-1.85)
Missing	28	81		26	66		26	74	
P for trend			0.07			0.76			0.75
P for heterogeneity			0.46			0.08			0.21

NOTE: Adjusted for age (categorical), study, race, sex, education level, pack-year (continuous), alcohol duration (continuous), duration of smoking pipe (continuous), and duration of smoking cigar (continuous).

*Random-effects estimates.

†The Seattle study was not included in the analysis for duration and cumulative consumption of marijuana. The Tampa and Seattle studies were not included in the analysis on frequency of marijuana consumption.

‡No laryngeal cases in Seattle (the number of controls for laryngeal cancer is different because the Seattle study is not included in the laryngeal cancer analysis).

5 joint-years of marijuana (*P* trend = 0.07). Dose-response relationships for frequency, duration, or cumulative consumption of marijuana use were not observed with HNC risk among never tobacco users.

In the analysis restricted to never alcohol users (345 cases and 997 controls; Table 5), the Seattle study was not included because all marijuana smokers were also alcohol drinkers. The Latin America study was also not included because no cases and only one control smoked marijuana without drinking alcohol. We observed almost no association between ever marijuana smoking and HNC risk (OR, 1.33; 95% CI, 0.77-2.12). However, we observed an increased risk of HNC associated with smoking marijuana for more than 20 years (OR, 3.12; 95% CI, 1.17-8.36), with a dose-response trend suggested (*P* = 0.05) and an increased risk associated with cumulative consumption of more than 5 joint-years (OR, 3.26; 95% CI, 1.32-8.06).

In the analysis restricted to never alcohol and never tobacco users, only the Houston and the Los Angeles studies had information on marijuana smoking for both cases and controls (149 cases and 407 controls). The OR for ever marijuana smoking was 1.06 (95% CI, 0.47-2.38). Association with frequency and duration of marijuana smoking could not be assessed in this group due to the limited numbers of subjects (only 10 cases and 33 controls used marijuana and were never tobacco users and never alcohol drinkers).

Stratification by sex, region (North America, Latin America), age (<50, ≥50), control type (hospital based or population based), or study period (before 2000 or after 2000) did not result in differences in the OR for ever marijuana smoking across the different strata.

For the ORs for ever marijuana use, additional adjustment for ever tobacco chewing (OR, 0.88; 95% CI, 0.62-1.23; Tampa, Houston, Los Angeles, and Seattle studies), ever use of snuff (OR, 0.85; 95% CI, 0.53-1.14; Los Angeles, Houston, and Seattle studies), passive smoking exposure (OR, 0.89; 95% CI, 0.49-1.61; Houston, Los Angeles, and Latin America studies), body mass index (OR, 0.84; 95% CI, 0.59-1.21; Houston, Los Angeles, Tampa, and Latin America studies), and family history of HNC (OR, 0.85; 95% CI, 0.59-1.21; Houston, Los Angeles, Tampa, and Latin America studies) did not change the

results. The results for the frequency and duration of marijuana smoking also remained unchanged with these adjustments.

Discussion

In our pooled analysis, we did not observe an association between marijuana smoking and the risk of HNC. Similarly, we did not observe an association among never tobacco users. Among never alcohol users, we observed an increased risk of HNC for smoking marijuana for more than 20 years; although we adjusted for tobacco use, we cannot rule out the possibility of residual confounding by tobacco.

We also did not observe an association between HNC risk and marijuana smoking when restricting the analysis to never tobacco and never alcohol users, but these results were based on only two studies, with low statistical precision. Tobacco smoking and alcohol drinking were associated with marijuana use among controls and cases. The controls in our study who were ever tobacco smokers had a higher proportion of ever marijuana use (16%) compared with the controls who were never tobacco smokers (12%). Controls who were ever drinkers had a higher prevalence of ever marijuana use (19%) compared with controls who were never drinkers (5%). However, the mean pack-years of tobacco smoking and frequency of alcohol drinking (in drinks per day) was greater among the never marijuana users than ever marijuana users among controls. The associations are further complicated by the strong combined effect of tobacco and alcohol on the risk of HNC.

Although the direction of the bias in our estimates is difficult to predict, bias due to measurement error must be present and bias due to differential selection or residual confounding cannot be ruled out. Human papillomavirus (HPV) has been suggested to be a risk factor for HNC and more specifically for oropharyngeal cancer (13). We were not able to account for this risk factor, but we observed an association between oropharyngeal cancer and marijuana smoking that was not confirmed by a dose-response relation. Recently, Gillison et al. (14) showed a strong association between marijuana smoking and HPV-16–positive SCC of the head and neck (HNSCC). They suggested that cannabinoids might promote the development of a HPV-16–positive HNSCC through decreased immune function. Although other exposures such as sexual history, tobacco, and alcohol were adjusted, the association could reflect residual confounding by these exposures. These alternative hypotheses could be explored by collecting data on both HPV and potential confounders of the association.

Although pooling data across several studies provided a larger number of HNC cases and controls than previous studies, there were several limitations inherent in pooled analyses. Our major concern was the heterogeneity across

Table 5. Marijuana smoking and the risk of HNC by tobacco and alcohol status

	Never tobacco users*,†			Never alcohol users‡		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total	353	1,017		345	997	
Marijuana smoking						
Never	295	797	1.00 (reference)	311	915	1.00 (reference)
Ever	57	220	0.93 (0.63-1.37)	34	79	1.27 (0.77-2.12)
Missing	1	0		0	3	
P for heterogeneity			0.21			0.06
Frequency of marijuana smoking (times per day)						
Never	295	797	1.00 (reference)	311	915	1.00 (reference)
0-1	52	205	0.93 (0.62-1.39)	26	68	1.30 (0.74-2.28)
>1	5	15	0.92 (0.31-2.68)	8	11	1.18 (0.43-3.19)
Missing	1	0		0	3	
P for trend			0.72			0.42
P for heterogeneity			0.06			0.22
Duration of marijuana smoking (in years)						
Never	295	797	1.00 (reference)	311	915	1.00 (reference)
>0-5	31	113	0.99 (0.62-1.57)	12	45	0.86 (0.42-1.77)
>5-10	9	47	0.69 (0.32-1.51)	6	11	1.22 (0.41-3.61)
>10-20	6	35	0.60 (0.24-1.50)	6	13	1.38 (0.47-4.04)
>20	11	25	1.60 (0.73-3.52)	10	10	3.12 (1.17-8.36)
Missing	1	0		0	3	
P for trend			0.99			0.05
P for heterogeneity			0.53			0.18
Cumulative exposure (joint-year)						
Never	295	797	1.00 (reference)	311	915	1.00 (reference)
>0-2	41	176	0.87 (0.57-1.33)	16	59	0.99 (0.52-1.88)
>2-5	5	18	0.89 (0.31-2.53)	3	10	0.58 (0.15-2.26)
>5	11	26	1.34 (0.62-2.92)	15	10	3.25 (1.31-8.02)
Missing	1	0		0	3	
P for trend			0.80			0.07
P for heterogeneity			0.17			0.23

*OR adjusted for age (categorical), sex, race, study, education level, and alcohol duration (continuous). Does not include Tampa and Latin America studies.
†Never tobacco users are never users of cigarette, pipe, cigar, chew, and snuff. Does not include Tampa and Latin America studies.
‡OR adjusted for age (categorical), sex, race, study, education level, pack-year (continuous), duration of smoking pipe (continuous), and duration of smoking cigar (continuous). Does not include Seattle and Latin America studies.

studies, especially due to differences in the definition of ever marijuana smoking and differences in social acceptance of marijuana smoking. Differences in the social acceptance of smoking marijuana may lead to differential misclassification across countries or regions. Marijuana is illegal in all of the countries included in this analysis, but to very different degrees, and it is not clear whether cases and controls may differ in the way they report their marijuana consumption. Heterogeneity was detected for the associations of frequency and joint-years of marijuana smoking with the risk of HNC.

From the definition of marijuana smoking, three of the studies could detect individuals who smoked even one joint in a lifetime, whereas the two other studies used definitions that attempted to capture regular marijuana smoking (once per week over 6 months or once per day over 1 year). The inclusion of moderate marijuana smokers in the reference category might have diluted the true association. For a common definition for ever marijuana smoking, we applied the highest cutoff (once per day for 1 year) across studies and did not observe an association between ever smoking and the risk of HNC.

The pattern of marijuana smoking is different compared with other smoking products. Whereas tobacco use is clearly addictive, with a high frequency and level of exposure needed to avoid withdrawal symptoms (15), marijuana smoking is often recreational, with the purpose of attaining an effect of euphoria that is reached with low levels of frequency and duration (16). Thus, despite the large size of our population, we lacked sufficient numbers of individuals who had smoked more than 5 joints per day and for more than 20 years, limiting our ability to assess the risk of HNC among heavy marijuana smokers.

Another possible reason that we did not observe an association between HNC risk and marijuana smoking is that aside from the Los Angeles study, there was a low proportion of marijuana smokers. The individual studies did not have enough statistical precision to detect or exclude an OR of 1.2 for HNC risk. Our estimates for HNC risk do not exclude the possibility of a modest OR for ever marijuana smokers. We also did not have adequate data to distinguish possible differences in effect due to different forms of smoking (joints, pipes, and water pipes). Furthermore, we had no data on variation in the weight or potency of ''joints'' across countries.

Marijuana smoke contains carcinogens similar to those in cigarette smoke (3, 17, 18). Some studies suggested that the tar contained in the smoke of marijuana is higher than that of cigarette (4, 17). On the other hand, Hall and MacPhee (19) reported that there is little mechanistic evidence that Δ^9-tetrahydrocannabinol (THC), the main psychoactive molecule of cannabis, or other cannabinoids have mutagenic or carcinogenic effects. Several studies have even suggested an anticarcinogenic effect of cannabis. According to Blazquez et al. (20), cannabinoids might inhibit vascular endothelial growth factor pathway by reducing the expression of 10 genes related directly or indirectly to the vascular endothelial growth factor pathway in mouse gliomas and thus reduce angiogenesis. Melamede (21) suggested that cannabinoids might also down-regulate immunologically generated free radical production. Thus, the carcinogenic effect of tar could be reduced by the anticancer mechanisms involving Δ^9-THC. Additionally, if cannabinoids promote the development of a HPV-16–positive HNSCC, as reported by Gillison et al., perhaps the association is relevant only in certain subgroups of HNC patients. It may be possible that the suppression of some aspects of immune function leads to a weaker response to the HPV infection, which leads to increased HNC risk. These mechanisms might explain the absence of an association between marijuana smoking and HNC risk overall.

In conclusion, we did not find evidence of a positive association between marijuana smoking and the risk of HNC. In an attempt to exclude the possibility of residual confounding from major risk factors, we restricted our analysis to never tobacco users and never alcohol users but still did not detect associations. Nonetheless, because the prevalence of frequent marijuana smoking was low in most of the contributing studies, we lacked precision to rule out a moderately increased risk, particularly among subgroups lacking exposure to tobacco and alcohol.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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