Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study

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Abstract

Background: **Despite several lines of evidence suggesting the biological plausibility of marijuana being carcinogenic, epidemiologic findings are inconsistent. We conducted a population-based case-control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers in Los Angeles.**

Methods: **Our study included 1,212 incident cancer cases and 1,040 cancer-free controls matched to cases on age, gender, and neighborhood. Subjects were interviewed with a standardized questionnaire. The cumulative use of marijuana was expressed in joint-years, where 1 joint-year is equivalent to smoking one joint per day for 1 year.**

Results: **Although using marijuana for ≥30 joint-years was positively associated in the crude analyses with each cancer type (except pharyngeal cancer), no positive associations were observed when adjusting for several confounders including cigarette smoking. The adjusted odds ratio estimate (and 95% confidence limits) for ≥60 versus 0 joint-years was 1.1 (0.56, 2.1) for oral cancer, 0.84 (0.28, 2.5) for laryngeal cancer, and 0.62 (0.32, 1.2) for lung cancer; the adjusted odds ratio estimate for ≥30 versus 0 joint-years was 0.57 (0.20, 1.6) for pharyngeal cancer, and 0.53 (0.22, 1.3) for esophageal cancer. No association was consistently monotonic across exposure categories, and restriction to subjects who never smoked cigarettes yielded similar findings.**

Conclusions: **Our results may have been affected by selection bias or error in measuring lifetime exposure and confounder histories; but they suggest that the association of these cancers with marijuana, even long-term or heavy use, is not strong and may be below practically detectable limits.** (Cancer Epidemiol Biomarkers Prev 2006;15(10):1829–34)

Introduction

Several lines of evidence, including the presence of known carcinogens and cocarcinogens in marijuana smoke, as well as results from cellular, tissue, animal, and human studies, suggest that marijuana smoking may predispose to cancer, particularly respiratory tract cancers (1). In a recent epidemiologic review of the marijuana-cancer association, we concluded that sufficient studies were not available to adequately evaluate the effect of marijuana on cancer risk (2). Two cohort studies and 14 case-control studies were reviewed. In the cohort studies, increased risks of lung or other tobacco-related cancers were not observed among persons who had used marijuana at least six times in their lifetimes, but increased risks of prostate and cervical cancers among tobacco nonsmokers, as well as adult-onset glioma among both tobacco smokers and nonsmokers, were observed (3, 4). The cutoff for marijuana use may have been too low for cancer risk to be detected, and confounding by life-style risk factors could not be ruled out for the cervical and prostate cancer findings.

The 14 case-control studies included 4 studies of head and neck cancers (5-8), 2 studies of lung cancer (9, 10), 2 studies of non-Hodgkin's lymphoma (11, 12), 1 study of anal cancer (13), 1 study of penile cancer (14), 1 study of bladder cancer (15), and several studies of childhood cancers with assessment of parental exposures (16-19). In a hospital-based study, Zhang et al. (8) reported an association of marijuana use with head and neck cancers, with dose-response relations observed for both frequency and duration of use. In contrast, in a larger population-based case-control study, Rosenblatt et al. (7) reported no association between oral cancer and marijuana use. In two smaller case-control studies of young subjects (≤45 years), no association was observed between regular cannabis use and oral cancer (5, 6).

The two lung cancer studies were conducted in North Africa, where marijuana is mixed with tobacco (9, 10). Although an 8-fold increase in risk was observed in the study in Tunisia, this finding could easily be due solely to tobacco effects (9). The investigators who conducted the case-control studies on penile and anal cancers did not detect any associations with marijuana use (13, 14). Two studies on non-Hodgkin's lymphoma exhibited null to inverse associations with lifetime marijuana use, but residual confounding could not be ruled out (11, 12). Results from the small study of bladder cancer suggested a positive association with marijuana use (15). Parental marijuana use during gestation was associated with increased risks of childhood leukemia, astrocytoma, and rhabdomyosarcoma, but dose-response relations were not assessed (16-20).

Limitations of previous studies include possible confounding due to cigarette smoking and other risk factors, error in

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measuring marijuana use and potential confounders, and the small number of cancer cases with a history of long-term or heavy use of marijuana. The latter limitation is due to the fact that regular marijuana use did not become common in the U.S. until the late 1960s and early 1970s, and that trend was mostly restricted to persons born after 1945 (21, 22). To deal with these problems, we conducted a large population-based case-control study of lung and upper aerodigestive tract (UAT) cancers among middle aged adults who are likely to have been exposed to appreciable amounts of marijuana, and we made a concerted effort to collect detailed information on the lifetime use of marijuana, tobacco, and alcohol use.

Materials and Methods

Study Design and Population. All subjects in this study were: (*a*) residents of Los Angeles County at the time of diagnosis for cases or at the time of recruitment for controls; (*b*) were 18 to 65 years of age during the study period, 1999 to 2004; and (*c*) spoke either English or Spanish, or had translators available at home. Subjects were not paid for their participation in this study.

Histologically confirmed new cases of lung and UAT cancers were identified by the rapid ascertainment system of the Cancer Surveillance Program for Los Angeles County, which is administered by the Keck School of Medicine and the Norris Comprehensive Cancer Center at the University of Southern California. The time from diagnosis to interview was <6 months for 89% of the study cases. The University of Southern California Cancer Surveillance Program is the population-based cancer registry for Los Angeles County, which has been collecting basic clinical and demographic information on all invasive cancers (except non-melanoma skin cancer) diagnosed among residents of Los Angeles County since 1972. Over 95% of cancer reports are histologically verified; the remainder are verified by magnetic resonance imaging, computed tomography scan or other diagnostic methods. Cases of lung and UAT cancers were excluded if they had a previous diagnosis of these malignancies; this information was determined from Cancer Surveillance Program records and verified from case self-reports in their interviews.

Controls did not have a history of lung or UAT cancers, and they were individually matched to cases on age decade, gender, and residential neighborhood. Specially trained field workers canvassed the neighborhood of each enrolled case and selected a sequence of 30 to 40 households according to a set algorithm. The field worker then attempted to identify eligible matches in the sequence of households by knocking on doors or, if no one answered, by leaving a letter describing the study, requesting information on eligibility, and inviting eligible persons to participate. If no response was obtained from selected households, second and third letters were sent as needed. If no eligible and willing match was identified, the field worker returned to the neighborhood and selected new households in an expanded sequence. The first eligible match in the sequence who was willing to participate was enrolled in the study and interviewed in the same manner as the case.

Among eligible cases that were identified by the Cancer Surveillance Program, participation rates were 39% for lung cancer, 54% for oral cancer, 45% for pharyngeal cancer, 42% for laryngeal cancer, and 35% for esophageal cancer. Among eligible lung cancer cases, the reasons for nonparticipation were refusal (16%), death (25%), inability to establish contact (14%), ill health (5%), and refused permission by the case's physician (1%). Among eligible UAT cancer cases, the reasons for nonparticipation were refusal (21%), death (10%), inability to establish contact (18%), and ill health (4%). Study cases and nonparticipating eligible cases did not differ appreciably with respect to age and gender, but African-Americans were 13% less likely to participate than were the other racial/ethnic groups. Among contacted eligible controls, the participation rate was 72%, and the reasons for nonparticipation were refusal (19%) and inability to establish contact (8%). Eligible females were 5% more likely to participate as controls than were eligible males.

Our analysis includes 611 incident cases of lung cancer (ICD-O2 C33.9-34.9), 303 oral cancers (C01.9-C09.9), 100 pharyngeal cancers (C10.0-C14.0, C30.0-C31.1), 90 laryngeal cancers (C32.0-C32.9), 108 esophageal cancers (C15.1-16.0), and 1,040 cancer-free population controls. Among cases of oral, pharyngeal, and laryngeal cancers, 465 (94%) were squamous cell carcinomas and 28 (5%) were other histologies. Among cases of lung cancer, 297 (49%) were adenocarcinomas, 115 (19%) were large cell carcinomas, 95 (15%) were squamous cell carcinomas, 75 (12%) were small cell carcinomas, and 29 (5%) were other histologies. Among cases of esophageal cancers, 74 (69%) were adenocarcinomas, 32 (30%) were squamous cell carcinomas, and 2 (2%) were other histologies. These histologic distributions of lung and esophageal cancers reflect the increasing proportion of adenocarcinomas and the decreasing proportion of squamous cell carcinomas that have been occurring in the U.S. (23) and Los Angeles County (24). Furthermore, we found very little difference in participation rates among different histologic types of the same cancer site.

Data Collection. Subjects were interviewed face-to-face with standardized questionnaires by specially trained interviewers. The protocol was approved by the Institutional Review Boards of University of California, Los Angeles and University of Southern California. Informed consent was obtained from all subjects, who were assured that all collected data, including illegal drug use, would remain confidential and that the investigators may not be compelled to provide such confidential information to anyone not connected with this study, including governments and courts (through a Confidentiality Certificate, No. DA-99-88, obtained from the National Institute of Drug Abuse). Subjects were first asked whether they ever smoked marijuana (excluding hashish). If they answered yes, they were asked detailed questions about their lifetime frequency, duration, type, and amount of use by age or year. Changes in marijuana use between periods of relative stability were recorded. Subjects were then asked separately about their use of hashish or hash oil by age or year. The interviews also requested information on the use of other drugs, including tobacco (cigarettes, cigars, pipes, and chewing tobacco) and alcohol, sociodemographic factors, diet, occupational history, environmental factors including exposure to environmental smoke, medical history (selected chronic diseases), and family history of cancer.

Variables were created for the lifetime use of marijuana (including hashish), cigarettes, and alcohol before cancer diagnosis for cases and comparable times for their matched controls. Cumulative marijuana use was expressed in joint-years, where 1 joint-year is equivalent to smoking one joint or one pipeful of hashish per day for 1 year; cumulative cigarette smoking was expressed in pack-years, in which 1 pack-year is equivalent to smoking one pack of cigarettes per day for 1 year; and cumulative alcohol use was expressed in drink-years, where 1 drink-year is equivalent to consuming one alcoholic drink per day for 1 year.

Statistical Methods. To increase precision and power over standard matched analyses, we used unconditional logistic regression models, including covariates for age and gender (the matching variables), which allowed us to compare cases of each cancer type with all controls (25). In the analysis of each cancer type, controls were excluded if they were more than 3 years younger than the youngest case or more than 3 years older than the oldest case. The association between marijuana use and each cancer type was obtained by treating marijuana

use as a set of four or five indicator variables (using never-users as the reference group; see Table 1) and by treating marijuana use as a continuous variable. To minimize leveraging from outliers in the analysis of continuous marijuana use, we excluded all subjects reporting >200 joint-years. Odds ratios (OR) and 95% confidence limits (CL) were estimated with and without adjustment for potential confounders. In addition to age and gender (included in adjusted model 1), we also adjusted for race/ethnicity (non-Hispanic White, African-American, Hispanic, other), educational level (five categories as shown in Table 1), and alcohol consumption (continuous in drink-years; model 2), plus cigarette smoking (ever/never and continuous in pack-years; model 3). To minimize age confounding and to account for age-matching, age was stratified into 15 fine categories (<34, 35-36, 37-38, 39-40, 41-42, 43-44, 45-46, 47-48, 49-50, 51-52, 53-54, 55-56, 57-58, and 59-62).

Because complete control for measured confounders such as tobacco use depends on modeling assumptions, we also estimated marijuana-cancer associations among subjects who reported that they never smoked cigarettes. Given the sparseness of data with the reduced sample size, we were not able to use as many categories of marijuana use in these analyses. To assess nonmultiplicative interactions of marijuana use with cigarette smoking and alcohol consumption, we fit logistic models with product terms for each of these interactions, treating the three predictors as continuous variables. Data analyses were done with SAS 8.0 software, and all reported P values are based on two-sided tests.

Results

The distribution of selected demographic factors and the three lifetime consumption variables are shown for each type of cancer and the controls in Table 1. Most subjects were 45 years of age or older, although laryngeal and esophageal cancer cases were older than subjects in the other groups. The proportion of males was 50% among lung cancer cases, 60% among controls, and >65% among the other case groups. The majority of all groups, except for cases of pharyngeal and laryngeal cancers were non-Hispanic Whites. As expected, cases of lung and UAT cancers were more likely than controls to have smoked cigarettes and to have used alcohol heavily. Marijuana use over 10 joint-years seemed to be more common among cases, especially oral and laryngeal cancers, than among controls. Among controls, 54% had used marijuana in their lifetimes, and 11% had used marijuana for ≥10 joint-years (equivalent to 3,650 or more joints). Also among controls, joint-years of marijuana use was positively associated with pack-years of cigarette smoking and drink-years of alcohol use, but inversely associated with years of education.

Crude and adjusted associations with each type of cancer in the total sample are shown in Table 2. In the crude analyses, marijuana use was positively associated with oral and

Table 1. Distribution of demographic and consumption variables for each type of cancer and controls, by category of each variable (percentages may not sum to 100 due to rounding)

Variable (category)	No. of cancer cases (%)					No. of controls (%)
	Oral	Pharynx	Larynx	Esophageal	Lung	
Total no. of subjects	303	100	90	108	611	1,040
Age (y)						
≤34	16 (5)	10 (10)	3 (3)	3 (3)	4 (1)	51 (5)
35 to ≤44	41 (14)	17 (17)	9 (10)	10 (9)	57 (9)	171 (16)
45 to ≤54	146 (48)	39 (39)	37 (41)	45 (42)	301 (49)	499 (48)
55+	100 (33)	34 (34)	41 (46)	50 (46)	249 (41)	319 (31)
Sex						
Male	233 (77)	67 (67)	71 (79)	83 (77)	303 (50)	623 (60)
Female	70 (23)	33 (33)	19 (21)	25 (23)	308 (50)	417 (40)
Race-ethnicity						
Non-Hispanic White	192 (63)	37 (38)	45 (50)	67 (62)	359 (59)	634 (61)
African-American	32 (11)	10 (10)	20 (22)	7 (7)	96 (16)	102 (10)
Hispanic	51 (17)	19 (19)	17 (19)	22 (20)	70 (11)	204 (20)
Other	28 (9)	32 (33)	8 (9)	12 (11)	85 (14)	99 (10)
Years of schooling (y)						
<12	56 (18)	23 (23)	27 (30)	20 (19)	107 (18)	116 (11)
12	67 (22)	23 (23)	23 (26)	34 (31)	158 (26)	184 (18)
13-15	79 (26)	28 (28)	24 (27)	25 (23)	186 (30)	272 (26)
16	60 (20)	16 (16)	10 (11)	17 (16)	89 (15)	209 (20)
>16	41 (14)	10 (10)	6 (7)	12 (11)	71 (12)	258 (25)
Pack-years of tobacco use*						
0	103 (34)	43 (43)	13 (14)	23 (21)	110 (18)	492 (47)
>0-20	74 (24)	22 (22)	22 (24)	29 (27)	102 (17)	353 (34)
>20-40	70 (23)	21 (21)	24 (27)	31 (29)	202 (33)	136 (13)
>40	56 (18)	14 (14)	31 (34)	25 (23)	197 (32)	58 (6)
Drink-years of alcohol use †						
0	57 (19)	33 (33)	11 (12)	16 (15)	170 (28)	264 (25)
>0-50	145 (48)	37 (37)	35 (39)	59 (55)	304 (50)	633 (61)
>50-100	34 (11)	14 (14)	12 (14)	15 (14)	59 (10)	70 (7)
>100	66 (22)	16 (16)	31 (35)	18 (17)	77 (13)	69 (7)
Joint-years of marijuana use ‡						
0	115 (38)	60 (60)	39 (43)	50 (47)	299 (49)	476 (46)
>0 to <1	91 (30)	21 (21)	24 (27)	30 (28)	161 (26)	322 (31)
1 to <10	40 (13)	8 (8)	7 (8)	13 (12)	65 (11)	124 (12)
10 to <30	20 (7)	5 (5)	8 (9)	5 (5)	32 (5)	57 (6)
30 to <60	12 (4)	2 (2)	5 (6)	6 (6)	20 (3)	23 (2)
≥60	24 (8)	4 (4)	7 (8)	3 (3)	33 (5)	35 (3)

*One pack-year of tobacco use is equivalent to smoking one pack of cigarettes per day for 1 year (i.e., 365 packs or 7,300 cigarettes).
†One drink-year of alcohol use is equivalent to having one alcoholic drink per day for 1 year (i.e., 365 drinks).
‡One joint-year of marijuana use is equivalent to smoking one joint per day for 1 year (i.e., 365 joints).

Table 2. Association (estimated OR and 95% CL) between cumulative marijuana use and cancer incidence, by type of cancer, amount of marijuana use, and covariate adjustment

Cancer type (marijuana use)	Cases, *N*	Controls, *N*	Crude OR (95% CL)	Adjusted OR (95% CL)		
				Model 1	Model 2	Model 3
Oral cancer						
50 joint-years*	297	1,023	1.7 (1.3, 2.2)	1.5 (1.1, 2.0)	1.2 (0.86, 1.6)	1.1 (0.80, 1.5)
P for trend*			0.0002	0.0064	0.33	0.53
Never	115	473	1	1	1	1
>0 to <1 joint-years	91	321	1.2 (0.86, 1.6)	1.1 (0.82, 1.6)	1.1 (0.75, 1.5)	1.1 (0.74, 1.5)
1 to <10 joint-years	40	124	1.3 (0.88, 2.0)	1.2 (0.81, 1.9)	1.0 (0.65, 1.7)	1.1 (0.65, 1.7)
10 to <30 joint-years	20	57	1.4 (0.83, 2.5)	1.3 (0.71, 2.2)	0.90 (0.48, 1.7)	0.92 (0.48, 1.7)
30 to <60 joint-years	12	23	2.1 (1.0, 4.4)	1.7 (0.80, 3.6)	1.1 (0.49, 2.4)	0.88 (0.38, 2.0)
≥60 joint-years	24	35	2.8 (1.6, 4.9)	2.3 (1.3, 4.0)	1.2 (0.61, 2.2)	1.1 (0.56, 2.1)
Pharyngeal cancer						
50 joint-years*	99	1,023	1.0 (0.55, 1.8)	0.96 (0.51, 1.8)	0.68 (0.33, 1.4)	0.75 (0.37, 1.5)
P for trend*			0.98	0.89	0.28	0.42
Never	60	473	1	1	1	1
>0 to <1 joint-years	21	321	0.52 (0.31, 0.87)	0.51 (0.30, 0.87)	0.63 (0.35, 1.1)	0.67 (0.37, 1.2)
1 to <10 joint-years	8	124	0.51 (0.24, 1.1)	0.54 (0.25, 1.2)	0.66 (0.28, 1.5)	0.71 (0.30, 1.7)
10 to <30 joint-years	5	57	0.69 (0.27, 1.8)	0.70 (0.26, 1.9)	0.38 (0.10, 1.4)	0.39 (0.10, 1.5)
≥30 joint-years	6	58	0.82 (0.34, 2.0)	0.73 (0.29, 1.8)	0.53 (0.19, 1.5)	0.57 (0.20, 1.6)
Laryngeal cancer						
50 joint-years*	87	1,026	1.6 (1.0, 2.5)	1.6 (1.0, 2.6)	1.0 (0.55, 1.9)	0.93 (0.50, 1.7)
P for trend*			0.043	0.052	0.99	0.81
Never	39	475	1	1	1	1
>0 to <1 joint-years	24	322	0.91 (0.54, 1.5)	0.94 (0.54, 1.6)	1.0 (0.56, 2.0)	0.81 (0.42, 1.6)
1 to <10 joint-years	7	124	0.69 (0.30, 1.6)	0.70 (0.30, 1.6)	0.58 (0.22, 1.5)	0.42 (0.15, 1.2)
10 to <30 joint-years	8	57	1.7 (0.76, 3.8)	1.7 (0.73, 4.0)	1.3 (0.51, 3.4)	0.91 (0.33, 2.5)
30 to <60 joint-years	5	23	2.6 (0.96, 7.4)	2.9 (0.98, 8.5)	1.3 (0.34, 4.7)	0.71 (0.19, 2.7)
≥60 joint-years	7	35	2.4 (1.0, 5.8)	2.4 (0.95, 6.0)	1.1 (0.37, 3.5)	0.84 (0.28, 2.5)
Esophageal cancer						
50 joint-years*	107	1,019	1.2 (0.75, 2.0)	1.2 (0.70, 2.0)	0.94 (0.52, 1.7)	0.83 (0.44, 1.5)
P for trend*			0.41	0.54	0.85	0.55
Never	50	472	1	1	1	1
>0 to <1 joint-years	30	318	0.89 (0.55, 1.4)	0.92 (0.56, 1.5)	0.84 (0.50, 1.4)	0.71 (0.41, 1.2)
1 to <10 joint-years	13	124	0.99 (0.52, 1.9)	0.97 (0.50, 1.9)	0.91 (0.44, 1.9)	0.77 (0.36, 1.6)
10 to <30 joint-years	5	57	0.83 (0.32, 2.2)	0.73 (0.27, 2.0)	0.57 (0.20, 1.6)	0.44 (0.15, 1.3)
≥30 joint-years	9	58	1.5 (0.69, 3.1)	1.3 (0.57, 2.8)	0.79 (0.34, 1.9)	0.53 (0.22, 1.3)
Lung cancer						
50 joint-years*	606	1,016	1.4 (1.1, 1.8)	1.7 (1.3, 2.3)	1.4 (1.0, 1.9)	1.0 (0.74, 1.4)
P for trend*			0.013	<0.0001	0.026	0.89
Never	299	470	1	1	1	1
>0 to <1 joint-years	161	317	0.80 (0.63, 1.0)	0.88 (0.68, 1.1)	0.87 (0.66, 1.1)	0.63 (0.46, 0.87)
1 to <10 joint-years	65	124	0.82 (0.59, 1.2)	1.0 (0.72, 1.5)	1.0 (0.70, 1.5)	0.71 (0.46, 1.1)
10 to <30 joint-years	32	57	0.88 (0.56, 1.4)	1.1 (0.71, 1.8)	0.89 (0.53, 1.5)	0.56 (0.31, 1.0)
30 to <60 joint-years	20	23	1.4 (0.74, 2.5)	2.0 (1.0, 3.8)	1.5 (0.75, 2.9)	0.82 (0.38, 1.7)
≥60 joint-years	33	35	1.5 (0.90, 2.4)	2.2 (1.3, 3.7)	1.5 (0.86, 2.6)	0.62 (0.32, 1.2)

NOTE: Crude estimates are unadjusted for covariates. Model 1 is adjusted for age (15 categories) and gender. Model 2 is adjusted for age (15 categories), gender, race/ethnicity (4 categories), education (5 categories), and drink-years. Model 3 is adjusted for age (15 categories), gender, race/ethnicity (4 categories), education (5 categories), drink-years, tobacco use (ever/never), and pack-years.

*Treating cumulative marijuana use as a continuous variable; the estimated OR is for a difference of 50 joint-years. To minimize leveraging from outliers, these regressions exclude subjects reporting >200 joint-years of marijuana use.

laryngeal cancers and weakly associated with esophageal and lung cancers. For example, the estimated crude OR for ≥60 versus 0 joint-years was 2.8 (95% CL, 1.6, 4.9) for oral cancer and 2.4 (95% CL, 1.0, 5.8) for laryngeal cancer. When adjusting for potential confounders, especially cigarette smoking, however, positive associations were no longer observed. Adjusting for all covariates (model 3 in Table 2), the estimated ORs for all non-reference categories of marijuana use were <1 for all outcomes except oral cancer, but there were no consistent monotonic associations. The adjusted OR for ≥60 versus 0 joint-years was 1.1 (95% CL, 0.56, 2.1) for oral cancer, 0.84 (95% CL, 0.28, 2.5) for laryngeal cancer, and 0.62 (95% CL, 0.32, 1.2) for lung cancer; the adjusted OR for ≥30 versus 0 joint-years was 0.57 (95% CL, 0.20, 1.6) for pharyngeal cancer and 0.53 (95% CL, 0.22, 1.3) for esophageal cancer. By treating marijuana use as a continuous variable, the estimated ORs corresponding to 50 joint-years are qualitatively consistent with the categorical results, although inverse associations are less apparent in the analyses of the continuous exposure (Table 2).

Although there were not enough UAT cancers to conduct adjusted subanalyses by histologic type, the results for lung cancer did not vary appreciably by histologic type; the estimated ORs remained <1 for all non-reference categories of marijuana use. None of the findings presented in Table 2 changed appreciably when adjusting for other potential confounders measured in this study, including the consumption of fruits and vegetables, income, marital status, passive smoking, and history of other chronic respiratory conditions.

The results of fitting models to never-users of cigarettes are shown in Table 3. Although we could not examine cancer associations with marijuana use over 10 joint-years, the results are qualitatively similar to those in Table 2. The only suggestion of a positive association was obtained for oral cancer (OR for >10 versus 0 joint-years, 1.8; 95% CL, 0.69, 4.7). The estimates in this table, however, are not very precise.

The combined effects of marijuana use with cigarette smoking and alcohol use were assessed by adding product terms to logistic model 3, treating these three variables as continuous. We detected no departure from multiplicative associations between marijuana and cigarette smoking or alcohol use, but all the results were very imprecise.

Furthermore, there was no evidence of a positive association between marijuana and cancer among those with heavy use of tobacco or alcohol.

Discussion

A major limitation of previous studies was the relative lack of subjects with use >10 joint-years, which limited their power to detect effects. In contrast, we had ample numbers of such users for oral and lung cancers. Nonetheless, and contrary to our expectations, we found no positive associations between marijuana use and lung or UAT cancers. Although we observed positive dose-response relations of marijuana use to oral and laryngeal cancers in the crude analyses, the trend was no longer observed when adjusting for potential confounders, especially cigarette smoking. In fact, we observed ORs <1 for all cancers except for oral cancer, and a consistent monotonic association was not apparent for any outcome. Similar findings were found when the analyses were restricted to subjects who never smoked cigarettes. The 95% confidence intervals for the adjusted ORs did not extend far above 1 (e.g., were under 2 for marijuana and lung cancer), which suggests that associations of marijuana use with the study cancers are not strong and may be below detectable limits for this type of study.

Despite several lines of evidence suggesting the biological plausibility of marijuana use being carcinogenic (1), it is possible that marijuana use does not increase cancer risk, as suggested in the recent commentary by Melamede (26). Although the adjusted ORs <1 may be chance findings, they were observed for all non-reference exposure categories with all outcomes except oral cancer. Although purely speculative, it is possible that such inverse associations may reflect a protective effect of marijuana. There is recent evidence from cell culture systems and animal models that 9-tetrahydrocannabinol, the principal psychoactive ingredient in marijuana, and other cannabinoids may inhibit the growth of some tumors by modulating key signaling pathways leading to growth arrest and cell death, as well as by inhibiting tumor angiogenesis (27-29). These antitumoral associations have been observed for several types of malignancies including brain, prostate, thyroid, lung, and breast.

Nonetheless, such inhibitory effects in some preclinical models do not necessarily imply that exposure to marijuana smoke can prevent cancer occurrence in humans. In contrast to the latter findings, moreover, 9-tetrahydrocannabinol has been shown to augment lung cancer growth in an immunocompetent mouse model due to its potent effect on immunosuppression (30).

Because consistent dose-response associations were not observed for ever-users of marijuana, it seems plausible that the inverse associations were due to chance or bias. Given the modest participation rates among eligible cancer cases identified by the cancer registry, selection bias may have occurred if marijuana use was associated with participation to a different extent for cases and controls. A downward bias in OR estimation would be expected if nonparticipation were selectively greater in exposed cases or unexposed controls, and the pattern we observed is most easily explained by the latter selection bias. We have no way of determining the direction or magnitude of selection bias, however; and the possibility simply adds to our uncertainty about the direction as well as the magnitude of effects.

Another major source of bias is error in measuring the lifetime use of marijuana. Although we devoted considerable attention and time to collecting detailed histories and we assured subjects of the confidentiality of the information they were giving, marijuana use is illegal and socially disapproved in the U.S. Thus, some subjects may have been reluctant to disclose marijuana habits to our interviewers, and this reluctance may have differed between cases and controls. In California, however, marijuana has long been only a minor infraction, and it has been legal for medical use since l996.

Of more concern, subject recall of how much marijuana they smoked many years ago was certainly imperfect. Consequently, we expected that underreporting of past marijuana use might be problematic. Our findings, however, do not seem indicative of serious underreporting. Rather, our estimates of lifetime frequency of usage among controls are consistent with findings from both the national and California samples of the National Survey on Drug Use and Health (31, 32). Furthermore, other researchers have concluded that self-reports of past marijuana use to be reasonably reliable (33, 34). Finally, if there were differential underreporting, we would have expected more reluctance to report among controls than cases, which would have elevated the estimates; instead, we found inverse associations.

Table 3. Association (estimated OR and 95% CL) between cumulative marijuana use and cancer incidence among subjects who never used cigarettes, by type of cancer, amount of marijuana use, and covariate adjustment

Cancer type (marijuana use)	Cases, *N*	Controls, *N*	Crude OR (95% CL)	Adjusted OR (95% CL)	
				Model 1	Model 2
Oral cancer					
Never	57	294	1	1	1
>0 to <1 joint-years	25	138	0.93 (0.56, 1.6)	0.86 (0.51, 1.5)	0.93 (0.53, 1.6)
1 to <10 joint-years	11	34	1.7 (0.80, 3.5)	1.5 (0.68, 3.1)	1.5 (0.68, 3.5)
≥10 joint-years	9	21	2.2 (0.96, 5.1)	2.0 (0.82, 4.7)	1.8 (0.69, 4.7)
Pharyngeal cancer					
Never	30	294	1	1	1
Ever	13	193	0.66 (0.34, 1.3)	0.61 (0.30, 1.2)	0.92 (0.41, 2.1)
Laryngeal cancer					
Never	7	296	1	1	1
Ever	6	193	1.3 (0.44, 4.0)	0.97 (0.31, 3.0)	1.2 (0.26, 5.5)
Esophageal cancer					
Never	14	293	1	1	1
Ever	9	192	0.98 (0.42, 2.3)	0.92 (0.37, 2.2)	0.79 (0.30, 2.1)
Lung cancer					
Never	91	291	1	1	1
>0 to <1 joint-years	10	136	0.24 (0.12, 0.47)	0.26 (0.13, 0.53)	0.44 (0.21, 0.92)
≥1 joint-years	9	55	0.52 (0.25, 1.1)	0.63 (0.29, 1.4)	1.1 (0.48, 2.6)

NOTE: Crude estimates are unadjusted for covariates. Model 1 was adjusted for age (four categories: ≤45, 46-50, 51-55, and 56-62) and gender. Model 2 was adjusted for age (four categories), gender, race/ethnicity (four categories), education (five categories), and drink-years.

Additional error in measuring cigarette smoking and alcohol consumption may also have affected our OR estimates because these variables seem to be important confounders for lung and UAT cancers. Although the net bias due to the errors could be substantial in either direction, our adjustments tended to decrease the observed marijuana-cancer associations, suggesting that if the errors are non-differential and independent of, or positively related to, marijuana reporting errors, more accurate measurements would further decrease the observed associations. Thus, it seems implausible that errors in confounder measurement would account for the weak inverse associations that we found. On the other hand, it is easily possible that errors in marijuana use assessment obscured the associations of marijuana with cancer.

If we focus on the upper 95% CL as an indication of the most harm that marijuana smoking may confer on cancer risk, perhaps marijuana use in the 10-joint-year range is at most a moderate risk factor that increases risk by 50% to 100%. Nonetheless, we cannot be sure that confounding has been fully controlled; and we have no data on selection effects, measurement errors, or their correlations. Thus, we have a greater degree of uncertainty about the effects of marijuana use on cancer risk than the confidence intervals reflect (35-38). These limitations may be insurmountable in studying marijuana use and cancer. Loss due to severe illness or death and refusals could be partially addressed by more rapid identification of cases, more aggressive recruitment of subjects (including payment for participation), and use of proxy respondents; but it seems unlikely that these efforts could eliminate the sources of bias, and they might produce new problems. It also seems unrealistic to expect that accurate information on errors in measurement of lifetime marijuana use will be obtainable. Furthermore, attempts to obtain reliability data (e.g., by applying more extensive questionnaires to subsamples) may face highly selective participation, as well as measurement errors. Cohort studies would be able to better address these concerns, but they would not have a large enough number of cases with heavy use to detect (let alone precisely estimate) associations.

It thus may be that some innovation will be needed in order to accurately estimate the effects of marijuana use on cancer risk. For example, it might be possible to augment data collected in a large cohort study by selecting additional cases and controls from a larger source population that includes the cohort (in essence, nesting the cohort within a large case-control study, the reverse of the usual nesting). In this design, the cohort would serve as a validation subsample to estimate selection biases and measurement errors.

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