

Marijuana use and cancer incidence (California, United States)

Stephen Sidney, Charles P. Quesenberry, Jr., Gary D. Friedman,
and Irene S. Tekawa

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The purpose of this retrospective cohort study was to examine the relationship of marijuana use to cancer incidence. The study population consisted of 64,855 examinees in the Kaiser Permanente multiphasic health checkup in San Francisco and Oakland (California, United States), between 1979-85, aged 15 to 49 years, who completed self-administered questionnaires about smoking habits, including marijuana use. Follow-up for cancer incidence was conducted through 1993 (mean length 8.6 years). Compared with nonusers/experimenters (lifetime use of less than seven times), ever- and current use of marijuana were not associated with increased risk of cancer of all sites (relative risk [RR] = 0.9, 95 percent confidence interval [CI] = 0.7-1.2 for ever-use in men; RR = 1.0, CI = 0.8-1.1 in women) in analyses adjusted for sociodemographic factors, cigarette smoking, and alcohol use. Marijuana use also was not associated with tobacco-related cancers or with cancer of the following sites: colorectal, lung, melanoma, prostate, breast, cervix. Among nonsmokers of tobacco cigarettes, ever having used marijuana was associated with increased risk of prostate cancer (RR = 3.1, CI = 1.0-9.5) and nearly significantly increased risk of cervical cancer (RR = 1.4, CI = 1.0-2.1). We conclude that, in this relatively young study cohort, marijuana use and cancer were not associated in overall analyses, but that associations in nonsmokers of tobacco cigarettes suggested that marijuana use might affect certain site-specific cancer risks. *Cancer Causes and Control* 1997, 8, 722-728

Key words: Cancer incidence, marijuana, retrospective cohort study, United States.

Introduction

Marijuana use is by far more prevalent than the use of any other illegal drug in the United States. It has been estimated that nearly one-third of the US population aged 12 and older has used marijuana.¹ The most common route of administration is smoking. Since marijuana smoke contains many of the same chemicals as tobacco smoke, in addition to containing 60 cannabinoid compounds, it is plausible to hypothesize that it may be carcinogenic.² However, marijuana has not been established as a risk factor for any cancer, although it may play

a role in the development of lung cancer³⁻⁵ and of head and neck cancers.⁵⁻⁹ The uncertainty in establishing marijuana as a cancer risk factor may be due, in part, to the difficulty in separating the effects of marijuana from the effects of tobacco cigarettes, since in many instances the marijuana smoker also smokes tobacco cigarettes. Even though a marijuana cigarette may be smoked in a more intense manner (greater puff volume and length of inhalation)¹⁰ than a tobacco cigarette, the total quantity of marijuana smoked by a user during his/her lifetime is

Authors are with the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California, USA. Address correspondence to Dr Sidney, Kaiser Permanente Division of Research, 3505 Broadway, Oakland, California 94611-5714, USA. This research was supported by Grant no. R01 DA06609 from the US National Institute on Drug Abuse. Dr Friedman is supported in part by Grant no. R35 CA49761 from the US National Cancer Institute. Data collection regarding alcohol use was supported by a grant from The Alcoholic Beverage Medical Research Foundation (Baltimore, MD, USA).

generally a tiny fraction of the quantity smoked by a tobacco cigarette user.

We report here the findings of a study of the relationship of marijuana use to cancer incidence in a cohort of nearly 65,000 members of a large, prepaid health plan. This study is important because relatively little research has been reported regarding the relationship of marijuana use to human cancer, and we are unaware of any other cohort studies which have examined this issue. We hypothesized that marijuana use would be associated with increased risk of tobacco-related cancers, but that it might be difficult to detect this risk because of the coexistence of tobacco cigarette smoking in marijuana smokers. In previously published work,¹¹ we did not find an association between marijuana use and cancer mortality.

Materials and methods

Study population

The study cohort is composed of 64,855 Kaiser Permanente Medical Care Program (KPMCP) members, aged 15 to 49 years (mean 33 years), who voluntarily completed self-administered research questionnaires between mid-1979 through 1985 regarding tobacco, marijuana, and alcohol use in the context of a multiphasic health checkup (MHC) conducted in the San Francisco (until 1980) and Oakland Kaiser Permanente facilities in California (US). Written assurance was provided at the beginning of the questionnaires that all answers would be kept confidential, and that the questionnaire would not become part of the medical record or sent to the member's doctor. Follow-up was carried out from the date of the MHC to date of the earliest of the following: cancer diagnosis ($n = 1,421$); death ($n = 495$); diagnosis of HIV positivity or AIDS ($n = 384$); membership termination ($n = 34,887$); or 31 December 1993 ($n = 27,668$). The mean length of follow-up was 8.6 years.

Source of follow-up data

Incident cancers through 1993 were determined from computerized databases of confirmed cancer cases maintained by the Northern California Cancer Center (prior to 1988) and from the Kaiser Permanente Northern California Regional Cancer Registry (1988-93). Cancer cases were categorized according to ICD-9 codes.¹² Cancer sites categorized as smoking-related included upper aerodigestive (including esophagus), lung, pancreas, kidney, and bladder, as specified by the International Agency for Research on Cancer (IARC) in 1984.¹³ We did not include cervical cancer and acute leukemia in the grouping of smoking-related cancers, although evidence has accumulated linking smoking to cancer of these sites.^{14,15} HIV/AIDS cases were ascertained from the Northern

California Kaiser Permanente Medical Care Program HIV/AIDS database. We excluded 92 cancer cases that occurred subsequent to or within one year prior to the date of HIV/AIDS diagnosis, distributed as follows: 68 Kaposi's sarcoma; 16 lymphatic cancers; eight other sites.

Mortality was ascertained through 1993 by computer-matching names and other demographic data with the California death file using the California Automated Mortality Linkage and Information System (CAMLIS).¹⁶ In a test subset of 4,695 MHC examinees, this method was found to produce more false-negative results (11 percent *cf* six percent of known dead classified as alive) and fewer false-positive results (0.07 percent *cf* 1.2 percent of known alive classified as dead) compared with utilization of the National Death Index in ascertainment of mortality.¹⁶ Membership status was determined for each year by examination of computerized files maintained by the Northern California Kaiser Permanente Medical Care Program.

Determination of marijuana use

Current marijuana smoking was defined by respondent's admission to smoking currently and more than six times ever. Former marijuana smoking was defined by denial of current smoking but admission to having smoked more than six times ever. Nonsmoking was defined as never having smoked. Experimenters were defined as those admitting to having ever smoked from one to six times. Ever-smokers included current and former users but excluded experimenters. Duration of use (number of years) and frequency of use ('less than once a month,' 'about once or twice a month,' 'about once or twice a week,' and 'almost every day') were assessed in ever-users. Data were not collected in former users regarding the length of time since they last used marijuana.

Determination of tobacco cigarette use and alcohol use

Persons were classified as current, former, or never-smokers of tobacco cigarettes on the basis of their questionnaire responses.¹⁷ Current and former smokers were also questioned about frequency (number of cigarettes per day) and duration (years) of smoking. Alcohol consumption was categorized as current use, former use, and nonuse. Current drinkers were questioned about how many drinks they usually had during the past year: 'nine or more per day,' 'six to eight per day,' 'three to five per day,' 'one or two per day,' 'less than one per day, but more than one per month,' and 'less than one per month (special occasions only).'

Analytic methods

The analyses were planned to compare the risk of cancer associated with ever-use of marijuana and with current use of marijuana relative to never or experimental use.

Statistical analyses were performed using SAS programs.¹⁸ Age-adjusted incidence rates were calculated by the direct method using 10-year age groupings with the 1990 US population as the standard. Cox proportional hazards models were used to examine the joint effect of sociodemographic characteristics, marijuana use, tobacco, and alcohol use on the risk of cancer, from which estimates of relative risks (RR) and associated 95 percent confidence intervals (CI) were obtained.¹⁹ Two-way interactions between marijuana and tobacco use and between marijuana and alcohol were tested by including cross-product terms in the proportional hazards models. The interaction terms were statistically significant in a few of the models (tobacco and ever-use of marijuana for colorectal cancer in women and melanoma in men; alcohol and both ever- and current use of marijuana for prostate cancer in men; alcohol and both ever- and current use of marijuana for breast cancer in women). However, the RR estimates associated with tobacco or alcohol use within any given level of marijuana use in these models had wide CIs and lack of dose-response, so that only the main effects are reported in this paper. To obtain estimates of the overall risk associated with marijuana use, adjusted for tobacco cigarette use, tobacco cigarette use was categorized as a three-level variable (*i.e.*, nonuser, former user, current user).

Results

Sociodemographic characteristics (Table 1)

Current users, former users, experimenters, and nonusers, respectively, comprised 22 percent, 20 percent, 20 percent, and 38 percent of the cohort. The percentage of ever-users was highest in the 20 to 29 year age group. Ever-use of marijuana was more common in men than in women, and more common in Whites followed by Blacks, Hispanics, and Asians.

Tobacco cigarette use

The distribution of marijuana use (ever *cf* nonusers/experimenter) and tobacco cigarette smoking (ever *cf* nonsmoker) are shown in Table 2. The prevalence of a history of tobacco-cigarette smoking was 54 percent higher in ever-users of marijuana (59.9 percent) than in nonusers/experimenters (38.8 percent). A substantial proportion of marijuana users were nonsmokers of tobacco cigarettes (40.1 percent of ever-users of marijuana [10,710 of 26,733]).

Distribution of cancer sites

Overall, there were 379 incident cancers in men, and 1,042 incident cancers in women. We performed analyses for cancers of all sites, tobacco-related cancers, and individual

Table 1. Sociodemographic characteristics of a cohort of Kaiser Permanente Medical Care Program members ($n = 64,855$) by marijuana use status, June 1979 through December 1985

Status at multiphasic health checkup	Never	Experimenter	Former	Current
Age (yrs)				
15-19	902	558	508	757
20-29	5,489	3,864	4,734	5,970
30-39	8,929	5,320	5,751	5,759
40-49	9,647	3,413	1,707	1,547
Gender				
Male	9,072	5,271	6,075	7,502
Female	15,895	7,884	6,625	6,531
Race				
White	9,894	7,316	8,372	8,743
Black	7,654	3,770	2,838	3,974
Asian	5,085	1,062	649	399
Hispanic	1,525	615	476	528
Other/unknown	809	392	365	389
Education				
≤ High school	5,837	2,420	1,887	2,518
Technical/business school/ some college	8,706	4,760	4,458	5,435
College graduate/ post graduate	9,941	5,703	6,034	5,850
Unknown	483	272	321	230
Total	24,967	13,155	12,700	14,033

sites with 30 or more gender-specific incident cancers (colorectal, lung, and melanoma for both genders; prostate for men, and breast and cervix for women). The counts for all these groupings and sites by marijuana and tobacco-cigarette use status are shown in Tables 3 and 4.

Table 2. Distribution of study population by gender and by ever-use of marijuana and tobacco cigarettes, Kaiser Permanente Medical Care Program

Marijuana/cigarette smoking history		Men	Women
Marijuana use	Tobacco cigarette use	No.	No.
Never	Never	8,170	15,360
Never	Ever	6,173	8,419
Ever	Never	5,593	5,117
Ever	Ever	7,984	8,039
Total		27,920	36,935

Marijuana and tobacco cigarette use in relation to cancer incidence

As expected, tobacco cigarette use, regardless of marijuana use status, was associated with increased risks of tobacco-related cancer ranging from 2.7 to 3.8 relative to nonuse of marijuana and tobacco cigarettes in models adjusted for age, race/ethnicity, education, and alcohol use (Tables 3 and 4); RRs for lung cancer associated with tobacco cigarette use ranged from 9.2 to 11.2. Ever-use of marijuana by nonsmokers of tobacco cigarettes was associated with increased risk in men of prostate cancer (RR = 3.1, CI = 1.0-9.5) and with a nearly significant increased risk in women of cervical cancer (RR = 1.4, CI = 1.0-2.1) relative to nonuse of marijuana and tobacco cigarettes. Additional adjustment for marital status did not appreciably alter the estimates of RRs for cancer of these sites, nor was it statistically significantly associated with these cancer sites. We also examined the association of marijuana use with invasive cervical cancer, comprising 11 percent (33 of 302) of all cervical cancers. Ever-use of marijuana in nonsmokers of tobacco cigarettes was asso-

Table 3. Counts, age-adjusted rates, and relative risks (RR) of all cancers, tobacco-related cancers, and cancers of specific sites by marijuana and cigarette smoking status in men, Kaiser Permanente Medical Care Program

Site of cancer	Marijuana, cigarette smoking history	Number of cases	Rate ^a	RR ^b	(CI) ^c
All sites	Never, never	109	149	1.0	—
	Never, ever	138	169	1.1	(0.9-1.5)
	Ever, never	36	186	0.8	(0.5-1.2)
	Ever, ever	96	165	1.1	(0.8-1.5)
Tobacco-related	Never, never	12	19	1.0	—
	Never, ever	56	68	3.1	(1.6-5.8)
	Ever, never	3	7	0.8	(0.2-2.9)
	Ever, ever	28	39	2.8	(1.4-5.6)
Colorectal	Never, never	16	16	1.0	—
	Never, ever	15	18	0.8	(0.4-1.6)
	Ever, never	4	7	0.7	(0.2-2.1)
	Ever, ever	10	29	0.9	(0.4-1.9)
Lung	Never, never	2	3	1.0	—
	Never, ever	32	39	10.3	(2.4-43.7)
	Ever, never	0	—	—	—
	Ever, ever	14	26	9.2	(2.0-42.0)
Melanoma	Never, never	23	27	1.0	—
	Never, ever	10	9	0.5	(0.2-1.0)
	Ever, never	6	11	0.5	(0.2-1.3)
	Ever, ever	19	25	1.1	(0.6-2.0)
Prostate	Never, never	9	16	1.0	—
	Never, ever	21	28	2.0	(0.9-4.5)
	Ever, never	5	95	3.1	(1.0-9.5)
	Ever, ever	7	31	1.7	(0.6-4.9)

^a Per 100,000 person-years, age adjusted to 1990 US population.

^b Adjusted for age, race, education, and alcohol use.

^c CI = 95% confidence interval.

Table 4. Counts, age-adjusted rates, and relative risks (RR) of all cancers, tobacco-related cancers, and cancers of specific sites by marijuana and cigarette smoking status in women, Kaiser Permanente Medical Care Program

Site of cancer	Marijuana, cigarette smoking history	Number of cases	Rate ^a	RR ^b	(CI) ^c
All sites	Never, never	408	260	1.0	—
	Never, ever	353	393	1.3	(1.1-1.5)
	Ever, never	93	403	1.1	(0.8-1.3)
	Ever, ever	188	408	1.2	(1.0-1.4)
Tobacco-related	Never, never	18	12	1.0	—
	Never, ever	55	54	3.8	(2.1-6.7)
	Ever, never	0	—	—	—
	Ever, ever	10	47	2.7	(1.2-6.3)
Colorectal	Never, never	27	18	1.0	—
	Never, ever	28	26	1.4	(0.8-2.4)
	Ever, never	1	2	0.3	(0.0-2.5)
	Ever, ever	6	8	0.9	(0.4-2.3)
Lung	Never, never	5	4	1.0	—
	Never, ever	36	35	9.8	(3.6-26.5)
	Ever, never	0	—	—	—
	Ever, ever	8	44	11.2	(3.3-37.7)
Melanoma	Never, never	23	11	1.0	—
	Never, ever	18	18	1.1	(0.6-2.0)
	Ever, never	8	71	1.0	(0.4-2.3)
	Ever, ever	16	19	1.2	(0.6-2.5)
Breast	Never, never	171	101	1.0	—
	Never, ever	113	117	0.9	(0.7-1.2)
	Ever, never	22	115	0.8	(0.5-1.3)
	Ever, ever	54	138	1.0	(0.8-1.5)
Cervix	Never, never	92	62	1.0	—
	Never, ever	80	118	1.7	(1.2-2.3)
	Ever, never	48	119	1.4	(1.0-2.1)
	Ever, ever	82	125	1.6	(1.2-2.2)

^a Per 100,000 person-years, age adjusted to 1990 US population.

^b Adjusted for age, race, education, and alcohol use.

^c CI = 95% confidence interval.

ciated with a nonsignificant increased risk of invasive cervical cancer (RR = 2.4, CI = 0.8-6.7). The overall risks of cancer associated with ever-use of marijuana are shown in Table 5, adjusted for tobacco cigarette smoking status (non-, former, current) as well as the other variables noted earlier. Ever use of marijuana was not associated in men or in women with increased or decreased risk of any cancer grouping or individual site. The results of analyses of cancer incidence excluding the 222 (15.6 percent of total cancers) which developed within the first two years of follow-up was similar to the overall results, suggesting that the overall results were not affected by symptoms caused by cancer prior to its diagnosis that affected the decision to use marijuana.

The findings in regard to current marijuana use were similar to those for ever-use of marijuana. Current marijuana use also was associated with increased risk of prostate cancer (RR = 4.7, CI = 1.4-15.5) and a nearly

Table 5. Risk of cancer in ever-users of marijuana relative to nonusers/experimenters adjusted for cigarette smoking status and other variables,^a Kaiser Permanente Medical Care Program

Site of cancer	Men		Women	
	RR ^b	(CI) ^c	RR ^b	(CI) ^c
All sites	0.9	(0.7-1.2)	1.0	(0.8-1.1)
Tobacco-related	0.9	(0.6-1.4)	0.7	(0.3-1.4)
Colorectal	0.9	(0.5-1.8)	0.6	(0.2-1.3)
Lung	0.9	(0.5-1.7)	1.1	(0.5-2.6)
Melanoma	1.2	(0.7-2.1)	1.1	(0.6-1.9)
Prostate	1.3	(0.6-2.6)	—	—
Breast	—	—	1.0	(0.8-1.3)
Cervix	—	—	1.1	(0.9-1.5)

^a Adjusted for age, race, education, alcohol use, and tobacco cigarette smoking.

^b RR = relative risk.

^c CI = 95% confidence interval.

significant increased risk of cervical cancer (RR = 1.6, CI = 1.0-2.5).

We examined the association of duration (years) and frequency of marijuana use for cancer-site groupings and for individual sites with 10 or more gender-specific incident cancers among ever-users of marijuana. Duration of use was not associated with the risk of any cancer site or grouping of cancers. For prostate cancer, a tendency toward an association of frequency of marijuana use with increased risk was evident, with usage one or more times per week (56.3 percent of male ever-users) associated with a nonsignificant twofold increase in the risk of prostate cancer relative to nonusers/experimenters. However, the addition of frequency of use did not improve the fit of any of the models for prostate cancer or for cancer of any other site or grouping of cancers.

Discussion

The main findings were the lack of association of marijuana use with overall cancer incidence and with the incidence of all tobacco-related cancers combined. Marijuana use was associated with an increased risk of prostate cancer in men who were nonsmokers of tobacco cigarettes, and a nearly significant risk of cervical cancer in women who were current marijuana smokers and nonsmokers of tobacco cigarettes.

The association between marijuana use and prostate cancer found in this study raises the question of potential hormonal mediation. There is a significant body of evidence suggesting that androgens are important in prostate carcinogenesis, including the following: (i) androgens are required for the normal growth and maintenance of the prostate;²⁰ (ii) testosterone has been shown to induce prostate cancer in laboratory rodents;²¹ and (iii) prostate cancer rarely occurs in eunuchs, and antiandrogen therapy or ablation results in regression of prostate cancer.²² Studies examining the relationship of serum testosterone to prostate cancer in humans have not shown consistent results.^{23,24} An early study showing that plasma testosterone levels in men were decreased in chronic marijuana users²⁵ has not been supported by most of the numerous subsequent studies regarding this issue.²⁶ Sexual activity measures have been inconsistently associated with prostate cancer,²⁷ although they are associated with psychoactive drug use.²⁸ It is notable that the prostate cancer cases represented in this study are relatively young compared with those occurring in the general population, since the maximum age reached by this cohort during follow-up was 63 years.

Cigarette smoking has been shown to be a risk factor for cervical cancer in many studies.¹⁵ The association of marijuana use with cervical cancer in nonsmokers might reflect confounding by sexual activity, since number of

sexual partners is a risk factor for cervical cancer²⁹ and is associated with psychoactive drug use.²⁸

The major limitations of this study include reliance on self-report for ascertainment of marijuana-use status; inability to study change in marijuana-use status during follow-up; and lack of lengthy follow-up into the geriatric age range, as noted earlier. We do not believe that under-reporting of marijuana use is likely to have been a significant problem because data collection on marijuana use was completed before the acceleration of the 'War on Drugs' in the late 1980s, during a period of time when the environment surrounding marijuana use was more accepting. Additionally, marijuana use rates in the study cohort were similar to those reported during the same time period by the National Household Survey on Drug Abuse, the most authoritative source of statistics on illegal drug use in the US.³⁰ Lack of longitudinal data regarding an exposure is a common feature of many cohort studies. We believe that it is unlikely that ever-use of marijuana would have increased substantially over time, because a relatively small proportion of the cohort are likely to have initiated marijuana use during follow-up which occurred in a period marked by a significant decline in self-reported marijuana use in the US.¹

In conclusion, this study did not show any significant associations between marijuana use and cancer in overall analyses, but showed associations suggesting increased risk of prostate and cervical cancer in marijuana users who were nonsmokers of tobacco cigarettes. We do not consider any of the findings to be conclusive, and as with all epidemiologic work, we strongly suggest that marijuana use and cancer be studied in other settings.

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