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Epidemiologic review of marijuana use and cancer risk

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Abstract

Marijuana is the most commonly used illegal drug in the United States and is considered by young adults to be the illicit drug with the least risk. On the other hand, marijuana smoke contains several of the same carcinogens and co-carcinogens as the tar from tobacco, raising concerns that smoking of marijuana may be a risk factor for tobacco-related cancers. We reviewed two cohort studies and 14 case–control studies with assessment of the association of marijuana use and cancer risk. In the cohort studies, increased risks of lung or colorectal cancer due to marijuana smoking were not observed, but increased risks of prostate and cervical cancers among non–tobacco smokers, as well as adult-onset glioma among tobacco and non–tobacco smokers, were observed. The 14 case–control studies included four studies on head and neck cancers, two studies on lung cancer, two studies on non-Hodgkin's lymphoma, one study on anal cancer, one study on penile cancer, and four studies on childhood cancers with assessment of parental exposures. Zhang and colleagues reported that marijuana use may increase risk of head and neck cancers in a hospital-based case–control study in the United States, with dose-response relations for both frequency and duration of use. However, Rosenblatt and co-workers reported no association between oral cancer and marijuana use in a population-based case–control study. An eightfold increase in risk among marijuana users was observed in a lung cancer study in Tunisia. However, there was no assessment of the dose response, and marijuana may have been mixed with tobacco. Parental marijuana use during gestation was associated with increased risks of childhood leukemia, astrocytoma, and rhabdomyosarcoma, but dose-response relations were not assessed. In summary, sufficient studies are not available to adequately evaluate marijuana impact on cancer risk. Several limitations of previous studies include possible underreporting where marijuana use is illegal, small sample sizes, and too few heavy marijuana users in the study sample. Recommendations for future studies are to (1) focus on tobacco-related cancer sites; (2) obtain detailed marijuana exposure assessment, including frequency, duration, and amount of personal use as well as mode of use (smoked in a cigarette, pipe, or bong; taken orally); (3) adjust for tobacco smoking and conduct analyses on nonusers of tobacco; and (4) conduct larger studies, meta-analyses, or pooled analyses to maximize statistical precision and investigate sources of differences in results. Despite the challenges, elucidation of the association between marijuana use and cancer risk is important in weighing the benefits and risks of medical marijuana use and to clarify the impact of marijuana use on public health.

Keywords: Cannabis; Marijuana smoking; Neoplasms; Epidemiology; Review (publication type)

1. Introduction

Marijuana (cannabis) is the most commonly used illegal drug in the United States, and it is considered by young adults to be the illicit drug with the least risk (Johnston et al., 2003, 2004). Several lines of evidence support the suggestion that marijuana smoking may be a risk factor for aerodigestive tract cancers:

1. Marijuana smoke contains several of the same carcinogens and co-carcinogens as those in tobacco smoke, including vinyl chlorides, phenols, nitrosamines, reactive oxygen species, and various polycyclic aromatic hydrocarbons (PAHs) (Hoffmann et al., 1975).
2. Benzo[*a*]pyrene, a procarcinogenic PAH, is present in marijuana tar at a higher concentration than in tobacco tar (Hoffmann et al., 1975).
3. Relative to tobacco smoking, marijuana smoking may involve inhalation of approximately three times the amount of tar and the retention of one third more of

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the inhaled tar in the respiratory tract (Wu et al., 1988).

4. Smoking a few marijuana cigarettes a day has been reported to have similar effects, as observed on histopathologic evaluation of the tracheobronchial epithelium, as those observed with daily smoking of more than 20 tobacco cigarettes (Fligiel et al., 1997; Gong et al., 1987).
5. Evaluation of bronchial mucosal biopsy specimens obtained from marijuana smokers without any clinically apparent disease showed more abnormalities than were observed for non–marijuana smokers in molecular markers of dysregulated growth, such as Ki-67 (a proliferation marker), epidermal growth factor receptor, and DNA ploidy (marker of genetic instability) (Barsky et al., 1998).

Other research has focused on the potential therapeutic aspects of marijuana for patients with cancer or with chronic diseases such as multiple sclerosis. For patients with cancer, marijuana has been studied for palliative effects, such as appetite stimulation and relief of pain and nausea and vomiting, as well as for potential antitumor effects such as tumor growth inhibition (Guzman, 2003). The U.S. Food and Drug Administration (FDA) has approved two capsule drugs related to marijuana, dronabinol (Marinol) and nabilone (Cesamet), for treatment of nausea and vomiting due to cancer chemotherapy (Guzman, 2003). Marijuana smoking for medical use is not approved by the FDA, although smoking marijuana for medical purposes has been legalized in several states in the United States.

It is critical to assess whether marijuana use may contribute to cancer causation in human beings because many individuals assume it to be a harmless drug. Because of its use for medical purposes, the notion that it is safe is further propagated. Although smoking of marijuana is presumably the most common form of use (Duffus, 1997), marijuana can also be taken orally, either directly or mixed with food. Data on the prevalence of marijuana use by method of intake do not seem to be widely available. It will be important to examine whether there are differences in cancer risk depending on the way in which marijuana is used. In this article, we review the published epidemiologic studies on marijuana use and cancer and make recommendations for future research directions.

2. Epidemiologic studies

We used the keywords ‘‘marijuana,’’ ‘‘cannabis,’’ and ‘‘cancer’’ on PubMed/Medline and identified epidemiologic studies on marijuana use and cancer risk, published up to November 2004. We also reviewed the literature citation of each of the publications identified. Epidemiologic studies for which investigators assessed marijuana use and provided risk estimates for marijuana exposure were included in our review. Study design, subject recruitment methods, and risk estimates reported for these studies are presented in Table 1 for cohort studies and Table 2 for case–control studies.

Two cohort studies, in which investigators assessed marijuana smoking as a possible risk factor for cancer, were both retrospective and both based on the same population of Kaiser Permanente subscribers in Northern California, from approximately the same study period (Efird et al., 2004; Sidney et al., 1997). In the first cohort study, current and ever-marijuana use, defined as use of marijuana six or more times over a lifetime, was not associated with risks of cancer overall, tobacco-related cancers (cancers of the upper aerodigestive tract, lung, pancreas, kidney, and bladder), or other cancer sites studied for men or women, after adjustment for age, race, education, alcohol use, and cigarette smoking (Sidney et al., 1997). Among non–tobacco smokers, ever marijuana smokers had increased risks for prostate cancer [relative risk (RR) = 3.1, 95% confidence interval (CI) = 1.0-9.5] and cervical cancer (RR = 1.4, 95% CI = 1.0-2.1). No cases of lung cancer were identified among men and women who used marijuana but did not smoke tobacco, and in only three men in the cohort of marijuana smokers who did not smoke tobacco did tobacco-related cancers develop. Perhaps this cohort did not capture long-term or regular/heavy marijuana smokers, or the cut-off for ever-marijuana use at six or more times per lifetime was too low for cancer risk to be increased. Confounding by lifestyle risk factors or residual socioeconomic confounding may be responsible for the cervical and prostate cancer findings.

In the second cohort study, Efird et al. (2004) found a moderately increased risk of malignant primary adult-onset glioma for ever-marijuana smokers (RR = 1.9, 95% CI = 0.9-4.0) after adjustment for sex, race, education, smoking status, alcohol consumption, and coffee intake. We presume that ever use was defined, as in the first study, as use of marijuana at least six or more times in a lifetime (Sidney et al., 1997). Risk factors for glioma such as ionizing radiation (Savitz & Trichopoulous, 2002) were not accounted for as potential confounders.

Fourteen case–control studies on marijuana smoking and cancer risk have been published to date, including six studies on tobacco-related cancers (Hsairi et al., 1993; Llewellyn et al., 2004a, 2004b; Rosenblatt et al., 2004; Sasco et al., 2002; Zhang et al., 1999), four studies on other cancers (Daling et al., 1987; Holly et al., 1999; Maden et al., 1993; Nelson et al., 1997), and four studies on childhood cancers with assessment of parental exposures (Grufferman et al., 1993; Kuijten et al., 1990; Robison et al., 1989; Wen et al., 2000).

When one considers the epidemiologic data obtained on marijuana smoking and tobacco-related cancers, tobacco use is the most important factor to consider as a potential confounder. It has been reported that tobacco smoking is

Table 1
Cohort studies on the association of marijuana use and cancer

Study location	Cohort description	Exposure assessment	Cancer site	Exposure categories	No. of cases/deaths	RR (95% CI)	Adjustment for potential confounders	Comments	Source
California, USA	Cohort of 64,855 Kaiser Permanente subscribers who received health check-ups between 1979 and 1985, aged 15–49 years, follow up to 1999 through cancer registry and death records.	Self-administered questionnaires	All sites, and selected sites	**Ever and current use**	**Men, overall**		Age, race, education, alcohol use, tobacco cigarette smoking	Definition of ever use was ≥6 times use over lifetime.	a
				All sites	–	0.9 (0.7-1.2)			
				Tobacco-related cancer[1]	–	0.9 (0.6-1.4)			
				Colorectal cancer	–	0.9 (0.5-1.8)			
				Lung cancer	–	0.9 (0.5-1.7)			
				Melanoma	–	1.2 (0.7-2.1)		Dose-response relations for duration (years) and frequency (times per week or month) were not observed.	
				Prostate cancer	–	1.3 (0.6-2.6)			
					Women, overall				
				All sites	–	1.0 (0.8-1.1)			
				Tobacco-related cancer[1]	–	0.7 (0.3-1.4)			
				Colorectal cancer	–	0.6 (0.2-1.3)			
				Lung cancer	–	1.1 (0.5-2.6)			
				Melanoma	–	1.1 (0.6-1.9)			
				Breast cancer	–	1.0 (0.8-1.3)			
				Cervical cancer	–	1.1 (0.9-1.5)			
				Ever and current use	**Men, non–tobacco smokers**		Age, race, education, alcohol use		
				All sites	36	0.8 (0.5-1.2)			
				Tobacco-related cancer[1]	3	0.8 (0.2-2.9)			
				Colorectal cancer	4	0.7 (0.2-2.1)			
				Melanoma	6	0.5 (0.2-1.3)			
				Prostate cancer	5	3.1 (1.0-9.5)			
					Women, non–tobacco smokers				
				All sites	93	1.1 (0.8-1.3)			
				Tobacco-related cancer[1]	0	—			
				Colorectal cancer	1	0.3 (0.0-2.5)			
				Melanoma	8	1.0 (0.4-2.3)			
				Breast cancer	22	0.8 (0.5-1.3)			
				Cervical cancer	48	1.4 (1.0-2.1)			
California, USA	Cohort of 105,005 Kaiser Permanente subscribers who received health check-ups between 1979 and 1985, aged ≥25 years, follow up to 1999 through cancer registry.	Self-administered questionnaires	Malignant primary glioma	Never	60	1.0	Smoking status (cigarettes, cigars, pipes), sex, race, alcohol, education, coffee intake		b
				Ever	9	1.9 (0.9-4.0)			
				Frequency					
				<1 per month	1	0.6 (0.1-4.4)			
				≥1 per month	8	2.8 (1.3-6.2)			
				Unknown	24	1.3 (0.8-2.2)			
				P for trend		.08			

Adapted/summarized from

[a]*Cancer Causes and Control, 8*, 1997, pp. 722–728, Marijuana use and cancer incidence (California, United States), S. Sidney, C. P. Quesenberry, Jr., G. D. Friedman, and I. S. Tekawa, part of tbls. 3, 4, and 5, pp. 725–726, copyright 1997, with kind permission of Springer Science and Business Media.

[b]*Journal of Neuro-Oncology, 68*, 2004, pp. 57–69, The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors, J. T. Efird, G. D. Friedman, S. Sidney, A. Klatsky, L. A. Habel, N. V. Udaltsova, S. Van Den Eeden, and L. M. Nelson, part of tbl. 2, p. 60, copyright 2004, with kind permission of Springer Science and Business Media.

[1]Cancers of the upper aerodigestive tract, lung, pancreas, kidney, and bladder.

– Number of cases not presented; — not available; CI = confidence interval; RR = relative risk.

Table 2
Case–control studies on the association of marijuana use and cancer

Study location/ period	Cancer site	Characteristic of cases	Characteristic of controls	Exposure assessment	Exposure categories	OR (95% CI)	Adjustment for potential confounders	Comments	Source
Tobacco-related cancers									
New York, USA/ 1992–1994	Head and neck (ICD-9 140-150, 160-161)	173 SCC untreated cases from hospital, histologically confirmed. 63.1% male. Response rate = 90.1%.	176 blood donors without history of cancer, frequency matched on age and sex. 63.1% male. Response rate = 89.8%.	Questionnaire completed by subject	**Ever use**	2.6 (1.1-6.6)	Age, sex, race, education, alcohol use (<100 drinks per month, ≥100 drinks permonth), packyears of cigarette smoking (continuous), passive smoking	Association stronger for subjects ≤55 years of age.	a
					Times/day				
					0	1.00			
					1	4.0 (0.9-17.2)			
					>1	5.4 (0.9-33)			
					P for trend	.0214			
					Years of use				
					0	1.00			
					1–5	3.9 (0.99-15.0)			
					>5	4.9 (1.07-22.3)			
					P for trend	.0134			
Washington state, USA/ 1985–1995	Oral (tongue, gums, floor of mouth, tonsils, oropharynx, other intraoral sites)	407 carcinoma in situ and SCC cases, 18–65 years of age, identified from cancer registry. 70.8% male. Response rate = 54.5% for 1985–1989, 63.3% for 1990–1995.	615 subjects from random-digit dialing, frequency matched on age and sex. 71.5% male. Response rate = 63% for 1985–1989, 61% for 1990–1995.	Face-to-face interviews with a structured questionnaire	**Ever use**	0.9 (0.6-1.3)	Birth year, sex, education, alcohol consumption, packyears of cigarette smoking, study	Data are from two studies: one conducted 1985–1989 and one conducted 1990–1995.	b
					Times used/ week				
					Never	1.00			
					<1 year use	1.0 (0.6-1.8)			
					<1 time/week	0.8 (0.5-1.4)			
					1–7 times/week	0.8 (0.4-1.6)			
					>7 times/week	0.5 (0.2-1.6)			
					Years of use				
					Never	1.00			
					<1	0.8 (0.4-1.2)			
					1	0.2 (0.1-0.7)			
					2–5	1.3 (0.6-2.6)			
					6–15	0.7 (0.4-1.4)			
					>15	1.2 (0.6-2.2)			
United Kingdom/ 1990–1997	Oral, oropharynx (ICD-10 C00-06, C09-10)	116 SCC of oral cavity and oropharynx, ≤45 years of age, identified from cancer registry. 56.0% male. Response rate = 59%.	207 patients without cancer, matched individually to case by age, sex, residence. 54% male. Response rate not available.	Questionnaire completed by subject	**Cannabis smoker**		Age, sex, residence, alcohol, and cigarette smoking	Dose-response assessment not reported.	c
					Overall	1.0 (0.5-2.2)			
					Men	0.9 (0.4-2.2)			
					Women	1.7 (0.4-7.0)			
United Kingdom/ 1999–2001	Oral, oropharynx (ICD-10 C00-06, C09-10)	53 SCC of oral cavity and oropharynx, ≤45 years of age, identified from cancer registry. 52.8% male. Participation rate = 80%.	91 patients without cancer, matched individually to case by age, sex, residence. 51.1% male. Response rate not available.	Questionnaire completed by subject	**Cannabis smoker**		Age, sex, residence, alcohol, and cigarette smoking	Dose-response assessment not reported.	d
					Overall	0.3 (0.1-1.8)			
					Men	0.3 (0.1-3.9)			
					Women	0.7 (0.1-184.9)			
Tunisia/ 1988–1989	Lung	110 cases diagnosed in a hospital, 70.0% have histologic confirmation. 97.3% male.	110 residents in Tunisia, matched individually on age, sex, and average number of cigarettes per day.	Face-to-face interviews with questionnaire	**Cannabis use**	8.2 (1.3-15.5)	Age, sex, number of cigarettes per day (0, 1–10, 11–20, >20), water pipe use, and snuff use	"Cannabis use" was not defined. Assessment of dose-response relations not reported.	e

Casablanca, Morocco/ 1996–1998	Lung	118 incident cases diagnosed at a hospital. 96.6% male. Response rate for combined group of cases and controls = 90%.	235 patients matched on age, sex, and residence (two per case). 96.6% male. Response rate for combined group of cases and controls = 90%.	Interview by physician with a structured questionnaire, face-to-face	**Hashish/kiff and snuff use** None Hashish/kiff Snuff Hashish/kiff & snuff	 1.00 1.99 (0.63-6.30) 1.06 (0.33-3.47) 5.64 (1.55-20.54)	Age, sex, residence, tobacco smoking status	Definition of ever use and data on frequency or duration not available. Kiff includes tobacco.	f
Other cancers									
Washington, USA & Canada/ 1978–1985	Anal	148 cases identified from cancer registry, <70 years of age, of all histologic types, including in situ and invasive lesions. 39.2% male. Interviews conducted for 71.2% of eligible cases identified.	166 colon cancer cases identified from cancer registry, matched individually on age, sex, year of diagnosis, and geographic area. 38.6% male. Interviews available for 67.3% of eligible subjects.	Face-to-face interviews with questionnaire	**Ever use**	0.8 (0.2-4.0)	Age, residence, cigarette smoking (never, formerly, currently), geographic area	Dose-response relations not assessed.	g
Washington, USA & Canada/ 1979–1990	Penile (ICD 187.1–187.4)	110 cases identified from cancer registry, ≤74 years of age, including SCC and in situ. Response rate = 50.2%.	355 subjects from random-digit dialing, frequency matched on age, reference year. Response rate = 70.3%.	Face-to-face interviews with questionnaire	**Ever use**	1.5 (0.7-2.3)	Age, alcohol consumption, cigarette smoking (never, formerly, currently), number of sexual partners		h
					Frequency Never ≤50 times >50 times	 1.0 1.7 (0.8-3.9) 1.0 (0.3-3.6)	Age, alcohol consumption, number of sexual partners		
California, USA/ 1989–1992	Non-Hodgkin's lymphoma	378 identified from cancer registry, 18–75 years of age, residents of Los Angeles, English/ Spanish speaker, HIV seronegative. 48.9% male. Overall percentage with non-Hodgkin's lymphoma interviewed = ~36.7.	378 subjects matched individually on age, sex, race/ethnicity, neighborhood of residence, and interview language. 48.9% male.	Face-to-face interviews with questionnaire	**Lifetime use - Men** No use Any use 1–5 times 6–900 times ≥901 times	 1.00 0.86 (0.50-1.48) 0.68 (0.34-1.38) 0.93 (0.46-1.88) 1.09 (0.48-2.48)	Age, sex, race/ ethnicity, neighborhood of residence, and interview language		i
California, USA/ 1988–1995	Non-Hodgkin's lymphoma	1,281 cases identified from Northern California cancer registry, 21–74 years of age. 45.2% women. 54.7% heterosexual men. Overall percentage with non-Hodgkin's lymphoma interviewed = ~56.7.	2,095 subjects from random-digit dialing, frequency matched on age, sex, and residence. 78% of eligible controls completed interviews.	Face-to-face interviews with structured questionnaire	**No. of times used** **Women** Never <40 40–999 ≥1,000 **Men** Never <40 40–999 ≥1,000	 1.00 0.56 (0.40-0.77) 0.58 (0.35-0.97) 0.71 (0.34-1.5) 1.00 0.64 (0.49-0.84) 0.52 (0.37-0.73) 0.49 (0.31-0.78)	Age		j

(*continued on next page*)

Table 2 (*continued*)

Study location/ period	Cancer site	Characteristic of cases	Characteristic of controls	Exposure assessment	Exposure categories	OR (95% CI)	Adjustment for potential confounders	Comments	Source
Childhood cancers, assessing parental exposures									
Multicenter, USA & Canada/ 1980–1984	Childhood acute nonlympho-blastic leukemia	204 cases identified from registry of Children's Cancer Study Group, diagnosed at <18 years of age. Response rate = 77.9%.	204 subjects from random-digit dialing, matched individually on date of birth, race, and telephone area code and exchange. Response rate = 78%.	Telephone interviews of mothers and fathers of subjects, with structured question-naire.	**Maternal use** of mind-altering drugs during or in the year before the pregnancy (9 of 11 cases of use of marijuana only)	11.0 (1.42-85.20)	Date of birth, race, residence, and telephone area code	Authors reported that adjustment for mother's age, education, tobacco use, and alcohol did not result in reduction in risk, nor loss of statistical significance.	k
					Paternal use	1.47 ($P = .32$)			
Multicenter, USA, Canada, & Australia/ 1983–1993	Childhood leukemia	1,805 cases of acute lymphoblastic leukemia, 528 of acute myeloid leukemia, ≤8 months of age, selected from registry files of Children's Cancer Study Group.	2,723 subjects from random-digit dialing, matched individually on year of birth and telephone area code and exchange number.	Telephone interviews of mothers and fathers of subjects, with structured questionnaire.	**Ever marijuana use** by father	1.5 ($P < .05$)	Year of birth, telephone area code and exchange number	Dose-response assessment not available.	l
Pennsylvania, New Jersey, and Delaware, USA/1980–1986	Childhood astrocytoma	163 cases identified from 8 hospital tumor registries. Diagnosed at <15 years of age. 56% male. Response rate = 80%.	163 subjects from random-digit dialing, matched individually on birth date, race, and telephone exchange.	Telephone interviews of mothers and fathers of subjects, with structured questionnaire.	**Gestational marijuana exposure**	2.8 (0.9-9.9)	Age, race, and residence	Dose-response relations not assessed. Data on paternal use not presented.	m
Multicenter, USA/1982–1988	Childhood rhabdomy-osarcoma	322 cases identified from registry of Children's Cancer Study Group. Diagnosed from 0 to 20 years of age. 67% male. Response rate = 79.8%.	322 subjects from random-digit dialing, matched individually on age, sex, and race. 67% male.	Telephone interviews of mothers and fathers of subjects, with structured question-naire.	**Marijuana use** **Maternal**	3.0 (1.4-6.5)	Age, sex, race, birthmarks on child, bleeding/ cramping during pregnancy, and prematurity of child	Marijuana use for year preceding child's birth was assessed. Factors associated with rhabdomyosarcoma in data were adjusted for.	n
					Paternal	2.0 (1.3-3.3)			

Adapted/summarized from

[a]Z.-F. Zhang, H. Morgenstern, M. R. Spitz, D. P. Tashkin, G.-P. Yu, J. R. Marshall, T. C. Hsu, and S. P. Schantz, Marijuana use and increased risk of squamous cell carcinoma of the head and neck, *Cancer Epidemiology, Biomarkers & Prevention 8*, pp. 1071–1078, copyright 1999, American Association for Cancer Research.

[b]K. A. Rosenblatt, J. R. Daling, C. Chen, K. J. Sherman, and S. M. Schwartz, Marijuana use and risk of oral squamous cell carcinoma, *Cancer Research 64*, pp. 4049–4054, copyright 2004, with permission of the American Association for Cancer Research.

[c]*Oral Oncology 40*, C. D. Llewellyn, K. Linklater, J. Bell, N. W. Johnson, and S. Warnakulasuriya, An analysis of risk factors for oral cancer in young people: a case-control study, pp. 304–313, copyright 2004, with permission from Elsevier Ltd.

[d]C. D. Llewellyn, N. W. Johnson, and K. A. A. S. Warnakulasuriya, Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case–control study in Southern England, *Journal of Oral Pathology & Medicine 33*, pp. 525–532, copyright 2004, with permission of Blackwell Publishing.

[e]M. Hsairi, N. Achour, B. Zouari, H. Ben Romdhane, A. Achour, M. Maalej, & T. Nacef, [Etiologic factors in primary bronchial carcinoma in Tunisia], *La Tunise medicale 71*, pp. 265–268, copyright 1993, with permission from Societe Tunisienne Des Sciences Medical.

associated with marijuana smoking (Rigotti et al., 2000), and detailed adjustment for tobacco use may be necessary to avoid spurious associations of cancers with marijuana use. Moreover, alcohol use has also been associated with marijuana use (Johnston et al., 2004). Thus, detailed adjustment for alcohol use would be necessary when one examines alcohol-related cancers. Of the six studies on tobacco-related cancers, tobacco smoking was adjusted for in the two studies on lung cancer (Hsairi et al., 1993; Sasco et al., 2002), and both tobacco smoking and alcohol consumption were adjusted for in the four studies on head and neck cancers (Llewellyn et al., 2004a, 2004b; Rosenblatt et al., 2004; Zhang et al., 1999).

The association between marijuana use and head and neck cancers was investigated in a hospital-based case–control study, including 173 cases and 176 control subjects (Zhang et al., 1999). A 2.6-fold increase in head and neck squamous cell carcinoma (SCC) risk was reported for ever use of marijuana (95% CI = 1.1-6.6), with dose-response trends observed for both frequency (times per day) and duration (years) of marijuana use. In contrast, a population-based case–control study of 407 carcinomas in situ and SCC cases of the oral cavity and 615 control subjects (Rosenblatt et al., 2004) revealed no association with marijuana use [odds ratio (OR) = 0.9, 95% CI = 0.6-1.3] and no dose-response trends for frequency (times per week) or duration (years) of marijuana use. Marijuana was examined as a potential risk factor for SCC of the oral cavity and oropharynx in two other studies in the United Kingdom among younger subjects (≤45 years of age) from the same population in different study periods (Llewellyn et al., 2004a, 2004b). Regular cannabis smokers did not have elevated risks of oral cancer after adjustment for age, sex, residence, alcohol consumption, and cigarette smoking in either study. The sample size was relatively small in these two analyses (53 and 116 cases), and regular cannabis use was not defined with a specific frequency or duration (Llewellyn et al., 2003).

The discrepant results among the head and neck cancer studies may be due, in part, to differences in biases, as well as to random variation. The two studies, one by Zhang et al. (1999) and one by Rosenblatt et al. (2004), that included detailed marijuana exposure assessment have different limitations. The study by Rosenblatt et al. (2004) was population-based, with 407 cases and 615 control subjects, whereas the study by Zhang et al. (1999) was hospital-based, with only 173 cases and 176 control subjects. Rosenblatt et al. (2004) proposed that the discrepant results in the two studies may be attributed to the low prevalence of marijuana use among the blood donor control subjects in the study by Zhang et al. (1999), who may have had healthier lifestyle behaviors than the general population. They have estimated that the expected number of marijuana smokers among control subjects was higher than the observed number of marijuana smokers among control subjects. Although blood donors at the cancer center where

[f]*Cancer Causes and Control, 13*, 2002, pp. 609–616, A case–control study of lung cancer in Casablanca, Morocco, A. J. Sasco, R. M. Merrill, I. Dari, V. Benhaïm-Luzon, F. Carriot, C. I. Cann, and M. Bartal, part of tbl. 2, p. 612, copyright 2002, with kind permission of Springer Science and Business Media.

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[n]*Cancer Causes and Control, 4*, 1993, pp. 217–224, Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children, S. Grufferman, A. G. Schwartz, F. B. Ruymann, and H. M. Maurer, part of tbls. 2 and 3, pp. 219–220, copyright 1993, with kind permission of Springer Science and Business Media.

CI = Confidence interval; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*; OR = odds ratio; SCC = squamous cell carcinoma.

the study took place were required to be between the ages of 17 and 75 years, to weigh at least 110 pounds, and to be in ''good health,'' there is the possibility that they were donating blood for a relative and shared some lifestyle factors with the patient with cancer. Therefore, the possible direction of bias owing to having blood donor control subjects would not necessarily be away from the null and is, in fact, difficult to predict. Rosenblatt et al. (2004) also suggested that their own null results might be due to the low proportion of heavy or chronic marijuana users in their study population, which might indeed reduce the contrast if an additional assumption of higher risks among heavier users is made. On the other hand, the low proportion of heavier users might increase random variation and could just as well produce an overestimate.

Both studies are subject to underreporting of marijuana use because such use is illegal in the United States. The study by Rosenblatt et al. (2004) may be more susceptible to such underreporting, because the interviews were conducted face-to-face, whereas, in the study by Zhang et al. (1999), subjects completed questionnaires. Differences in the proportion of eligible subjects participating in the study were also apparent between the two studies. Zhang et al. (1999) had response rates of 90% among cases and control subjects. Rosenblatt et al. (2004) had combined data from two studies in the same population from different study periods, and they reported case response rates of 55% and 63% and control subject response rates of 63% and 61%. If, as often occurs, nonparticipants tended to be control subjects with high-risk lifestyle behaviors, including marijuana use, the study by Rosenblatt et al. (2004) may be more vulnerable to bias away from the null. However, no association was found.

The two lung cancer studies with assessment of marijuana use as a possible risk factor were conducted in North Africa. Hsairi et al. (1993) reported a highly elevated OR for ever use of cannabis in a case–control study in Tunisia, including 110 lung cancer cases and 110 control subjects (OR = 8.2, 95% CI = 1.3-15.5). Dose-response relations for frequency and duration of marijuana use were not assessed. The amount of marijuana and tobacco used among these subjects would be of great interest to know because marijuana is thought to be used in larger amounts, and together with tobacco, in this region. Sasco et al. (2002) studied hashish and kiff use in Morocco in a case–control study, including 118 lung cancer cases and 235 control subjects. Kiff (or kif), prevalent in Northern Morocco, is a preparation of powder from the dried flower of the female *Cannabis sativa* plant mixed with tobacco (Nahas et al., 1975). They reported an increased risk of lung cancer for subjects who used hashish/kiff and snuff (OR = 5.64, 95% CI = 1.55-20.54), but results were less clear for subjects who used hashish/kiff without snuff (OR = 1.99, 95% CI = 0.63-6.30) and subjects who used snuff only (OR = 1.06, 95% CI = 0.33-3.47). A possible explanation for the observed association may be that this category captured subjects who used hashish/kiff and snuff at higher durations and frequencies. Because kiff includes tobacco, the independent effect of marijuana cannot be assessed in this study.

Investigators have examined marijuana use and anal cancer (Daling et al., 1987), penile cancer (Maden et al., 1993), and non-Hodgkin's lymphoma (Holly et al., 1999; Nelson et al., 1997). The main hypothesis of interest for the study on anal carcinoma (Hsairi et al., 1993) was whether sexual practices and sexually transmitted diseases were risk factors for anal cancer. The case group included 148 patients with anal carcinoma, whereas the control group included 166 patients who had colon cancer. Patients with colorectal cancer are unlikely to be representative of the population at risk that gave rise to the anal cancer cases and thus may not be a valid control group, because tobacco smoking and possibly marijuana smoking could be a risk factor for colorectal cancer (International Agency for Research on Cancer, 2004). In any event, the results were almost uninformative (OR = 0.8, 95% CI = 0.2-4.0). In the study on penile cancer, with 110 cases and 355 population-based control subjects, Maden et al. (1993) primarily assessed factors, such as sexual activity, medical conditions, human papillomavirus, and tobacco smoking. The OR for ever-marijuana use was 1.5 (95% CI = 0.7-2.3), adjusted for age, alcohol consumption, cigarette smoking, and number of sexual partners. This result may be due to residual confounding by socioeconomic status/lifestyle factors or random error.

Two studies on non-Hodgkin's lymphoma, one with 378 case–control subject pairs (Nelson et al., 1997) and one with 1,281 cases and 2,095 control subjects (Holly et al., 1999), exhibited null to inverse associations with lifetime marijuana use. In the larger study, the ORs for use of marijuana ≥1,000 times in a lifetime were 0.49 (95% CI = 0.31-0.78) for men and 0.71 (95% CI = 0.34-1.5) for women, adjusted for age. However, inverse associations were also observed for higher number of sexual partners and for use of other illicit substances, such as cocaine/crack, speed, and LSD. These results raise the suspicion that the study is biased downward in general, perhaps because of higher underreporting by cases relative to control subjects. An inverse association was observed in a multivariate model, including several factors associated with non-Hodgkin's lymphoma in the study such as the number of sexual partners, but the possibility of residual confounding cannot be excluded.

Parental marijuana use during the gestational period has been associated with childhood cancers, including leukemia (Robison et al., 1989; Wen et al., 2000), astrocytoma (Kuijten et al., 1990), and rhabdomyosarcoma (Grufferman et al., 1993). However, the number of exposed cases in all these studies is small, resulting in unstable estimates. In all studies, structured telephone interviews of mothers and fathers of children with cancer, as well as of matched control subjects identified through random digit dialing,

were used. Robison et al. (1989) reported an OR of 11.0 for ''maternal mind-altering drug use'' (mostly marijuana use) during the gestational period and acute nonlymphoblastic leukemia, but the 95% CI was wide (1.42-85.2). For paternal use, the OR was 1.47 ($P = .32$). Wen et al. (2000) reported an OR of 1.5 for paternal marijuana use and childhood leukemia. No confidence interval was given, but a P value of $<.05$ was reported. Kuijten et al. (1990) did not report on paternal use with childhood astrocytoma but reported an OR of 2.8 (95% CI = 0.9-9.9) for maternal use and childhood astrocytoma. Finally, Grufferman et al. (1993) reported ORs for rhabdomyosarcoma of 3.0 (95% CI = 1.4-6.5) for maternal use and 2.0 (95% CI = 1.3-3.3) for paternal use. It is not clear how much these positive reports arose from selection of significant associations among many combinations of drugs and cancers, or from publication bias, and, if real, how much they represent confounding by other drug use. Moreover, recall bias could have led to the case parents overreporting exposure to marijuana.

The studies published on parental tobacco smoking and childhood cancers (involuntary smoking from the child's perspective) were assessed by the International Agency for Research on Cancer, and it was concluded that the results were inconsistent and the studies were likely to be affected by bias (International Agency for Research on Cancer, 2004). In a meta-analysis on maternal tobacco smoking during pregnancy and childhood cancers, Boffetta et al. (2000) reported a small increase in overall cancer risk (RR = 1.10, 95% CI = 1.03-1.19), but not in specific cancers such as leukemia. The RR of lung cancer for active tobacco smoking ranged from 15 to 30, and the corresponding RR of lung cancer for passive tobacco smoking was moderate (<1.50) (Vineis et al., 2004). Because the RR of leukemia due to active tobacco smoking was on the order of 1.5 to 2.0 (Vineis et al., 2004), the corresponding RR of leukemia for passive tobacco smoking would be modest at best. Therefore, one might expect that an increase in childhood leukemia risk, if any, owing to involuntary marijuana smoking would be very small and difficult to detect, unless there are strong leukemogens other than benzene that might exist in marijuana smoke.

3. Discussion

It is difficult to assess the association between marijuana use and cancer risk in epidemiologic studies. Measurement must rely on questionnaires, subject recall, and subject honesty regarding a drug that is illegal and associated with strong potential confounders, such as tobacco and excessive alcohol use, which, themselves, must be assessed from questionnaires and subject recall and are not socially approved behaviors. Therefore, differential exposure and confounder measurement error would be reasonable to expect, especially (but not only) in case–control studies.

From the standpoint of pathophysiology, there is every reason to expect some adverse effect of marijuana use on aerodigestive tract cancers. Nonetheless, results of cohort studies have not revealed an increased risk of tobacco-related cancers among marijuana smokers, possibly because few users smoke enough marijuana to elevate their risk to a detectable level. Case–control studies face a similar lack of power owing to rarity of heavy marijuana use. Nonetheless, in some, but not all, associations with tobacco-related cancers have been detected. Findings of four studies of parental marijuana use during the gestational period have revealed its association with increased risk of childhood cancers, but the results are highly unstable, are not consistent by cancer type across studies, and may reflect poorly controlled confounding by other drug use (including tobacco or alcohol) or multiple comparisons.

To evaluate associations between marijuana use and cancer, more data are needed. In addition, data should include accurate measurements of use of tobacco, alcohol, and other drugs; should be analyzed in a way to minimize potential confounding and allow for dose-response analysis; and should be collected in a way that maximizes accurate subject reporting. Marijuana use is illegal in almost every country in the world, but a few countries (e.g., The Netherlands, Belgium, and some Swiss cantons and Canadian provinces) have adopted zero or near-zero enforcement and thus may present opportunities for more valid studies. The prevalence of marijuana use differs by birth cohort, being highest in the United States for individuals born in the 1950s onward, although heavy chronic use remains uncommon. Thus, when one takes into account the long latent period for the development of clinically detectable cancer, the published studies thus far may not have captured cancer cases in these birth cohorts that had long-term marijuana use.

4. Recommendations

We have five recommendations for future studies:

1. The research focus should be primarily on possible disease outcomes of active tobacco smoking. Because marijuana smoke contains several of the same carcinogens as those in tobacco smoke, ideal cancer sites to focus on include cancers of the lung and head and neck.
2. Detailed marijuana exposure assessment should be obtained. Dose-response relations need to be analyzed for frequency (times per day or per week), duration (years), and cumulative exposure of marijuana use. Because the unit of marijuana used is not uniform or standard in comparison with that of cigarettes, the potency and amount of marijuana used each time need to be explored. Studies need to be designed to assess how the marijuana was taken—that is, whether it was eaten or smoked and if smoked, how smoked

(e.g., joints, pipes, water pipes)—and whether any and how much used was of hashish (a concentrated product) as opposed to raw cannabis. Other important factors include ages at start and end of marijuana use and depth and duration of inhalation because longer breathhold times have been shown to be associated with greater respiratory deposition of marijuana tar (Tashkin et al., 1991).

3. For tobacco-related cancers, risk estimates must be adjusted at least for tobacco use (e.g., total packyears of smoking and years since quitting), and, whenever possible, analyses among non–tobacco smokers may be informative. For regions in which marijuana is often prepared as a mixture with tobacco (e.g., kiff in North Africa), it will be important to differentiate between marijuana taken alone and marijuana mixed with tobacco or other substances. In addition, the possible interaction effects of marijuana and tobacco on cancer risk should be assessed, particularly because marijuana use is associated with a higher prevalence of regular tobacco smoking (Johnston et al., 2003).
4. Analyses need to present data for chronic users, because simply merging everyone into an ''ever-used'' category will submerge relatively infrequent long-term regular users (for whom a detectable effect could be expected) among a much larger number of people who used marijuana briefly or rarely. Gathering enough chronic users requires large numbers of subjects. Although larger case–control studies on tobacco-related cancers are ongoing, additional approaches to increasing statistical precision would be to conduct meta-analyses and pooled analyses. The convenience of meta-analyses is that the original data do not have to be collected, and a summary effect estimate can be calculated from published results. However, meta-analysis does not allow one to use uniform category definitions across studies. At present, it would not be possible to conduct an informative meta-analysis on marijuana use and cancer. Pooled analysis is preferable to a meta-analysis because a more detailed analysis can be conducted. However, it requires more time and effort to collect original data from various studies. To assess marijuana use as a risk factor among non–tobacco smokers, a pooled approach may be ideal because non–tobacco smokers are rare among patients with aerodigestive tract cancer. Meta-analyses are subject to publication bias if positive associations are more likely to be published and appropriate data for the analyses are identified through publications.
5. Careful selection of the geographic location for the study may aid in addressing some of the difficulties encountered in marijuana and cancer studies. Although it may be difficult to find an ideal location and the study would still be subject to potential biases, perhaps these suggestions can be used as guidelines:
   - Conduct the study in a country or region in which marijuana use is not illegal to help minimize underreporting and misclassification bias.
   - Recruit a study population with high exposure to marijuana use to facilitate the assessment of a range of exposure categories.
   - Minimize confounding by tobacco smoking by selecting a study population with low tobacco smoking prevalence.

Although it is challenging to study the potential association between marijuana use and cancer risk, it is a worthwhile effort. The evaluation would contribute invaluable data in weighing the benefits and risks of medical marijuana use. It would also add to the understanding of the impact of marijuana use on public health.

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