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An epidemiologic review of marijuana and cancer: an update

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Abstract

Marijuana use is legal in two states and additional states are considering legalization. Approximately 18 million Americans are current marijuana users. There is currently no consensus on whether marijuana use is associated with cancer risk. Our objective is to review the epidemiologic studies on this possible association. We identified 34 epidemiologic studies on upper aerodigestive tract cancers (n=11), lung cancer (n=6), testicular cancer (n=3), childhood cancers (n=6), all cancers (n=1), anal cancer (n=1), penile cancer (n=1), non-Hodgkin's lymphoma (n=2), malignant primary gliomas(n=1), bladder cancer (n=1), and Kaposi's sarcoma (n=1). Studies on head and neck cancer reported increased and decreased risks, possibly because there is no association, or because risks differ by HPV status or geographic differences. The lung cancer studies largely appear not to support an association with marijuana use, possibly because of the smaller amounts of marijuana regularly smoked compared to tobacco. Three testicular cancer case-control studies reported increased risks with marijuana use (summary odds ratios 1.56 (95%CI=1.09-2.23) for higher frequency; 1.50 (95%=1.08-2.09) for ≥10 years). For other cancer sites, there is still insufficient data to make any conclusions. Considering that marijuana use may change due to legalization, well-designed studies on marijuana use and cancer are warranted.

Introduction

In July 2014, the New York Times Newspaper Editorial Board called for marijuana to be legalized in the United States (1). Regarding potential health issues that marijuana may cause, a New York Times article cited a New England Journal of Medicine review and mentioned that the link with lung cancer was unclear and if there is any increased risk, it is

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lower than that of cigarette smoking (2). The New England Journal of Medicine article that was cited reported that the association between marijuana use and cancer could not be ruled out (3). Certainly the potential benefits of medical marijuana use must be considered and weighed against the harms, but the potential role of marijuana smoking in causing cancer needs to be carefully reviewed.

In 2012, Colorado and Washington legalized marijuana use for adults age 21 years or older (4). Medical marijuana is legal in 23 states and the District of Columbia with laws that have been changing over the time period between 1996 and 2014 (5). The states which permit medical marijuana include Alaska, Arizona, California, Colorado, Connecticut, District of Columbia, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont, and Washington (5). Nevertheless in more than half of the states, it is still illegal for people to use, buy, sell, possess, cultivate, and transport marijuana. Also, it is illegal to sell marijuana to those under 21 by law. However, fourteen additional states are currently considering legalization of marijuana (6).

In 2012, 18.7% of young adults (ages 18-25 years), 7.2% of children 12-17 years of age and 5.3% of adults ≥ age 26 years used marijuana in the past month, and 40.3% of past-month marijuana users (5.4 million) used it daily or nearly daily. Moreover, since 2002, and especially after 2007, near-daily use of marijuana in persons 12 years of age and older has increased steadily (7) at the same time that perceived risk from marijuana has declined (8). Among American adults, approximately 18 million people (7.6%) were current marijuana users (9) in contrast to an estimated 42.1 million (18.1%) current cigarette smokers (10). In 2012, there were approximately 6,600 new marijuana users each day (7). The increasing trends in marijuana use prevalence over the past several years, along with the declining perceptions of health risks from marijuana and greater availability of marijuana in states where it has been legalized for medical or recreational use, suggest that it is likely (albeit not certain) that the prevalence of marijuana use will continue to increase.

In 2005, we published an epidemiologic review of marijuana use and cancer risk, including articles published up to November 2004 (11). The 2005 review included two cohort studies and 14 case-control studies, with an assessment that there were not sufficient studies available to adequately evaluate the impact of marijuana on cancer risk. The limitations in previous studies included possible underreporting where marijuana use is illegal, small sample sizes, and too few heavy marijauna users in the study. In this current review, our objective is to provide an updated review including these previously reviewed studies as well as additional articles published. We will evaluate whether there is evidence to support an association between marijuana use and cancer risk, or support the lack of association.

Materials and Methods

We used the keywords “marijuana,” “cannabis,” and “cancer” on PubMed/Medline and identified epidemiologic studies on marijuana use and cancer risk, published up to August 2014. We also reviewed the literature citation of each of the publications identified. Epidemiologic studies for which investigators assessed marijuana use and provided risk

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estimates for marijuana exposure were included in our review. Study design, subject recruitment methods, and risk estimates reported for these studies are presented in the tables, ordered by publication date. For each study, we chose the best estimates from the publication to present in the tables, such as RR or OR among never-smokers and RR or OR adjusted for potential confounders, including tobacco smoking. We also show the cancer risk estimates by frequency and/or duration if those estimates were available, prioritizing cumulative exposure estimates (joint-years), if available.

We conducted a meta-analysis when at least three combinable ORs were available and the exposure variable was comparable. The three studies on marijuana use and testicular cancer met this criteria since the exposure categories were fairly comparable for combining estimates. For head and neck cancer, a meta-analysis was not warranted considering that subgroups by HPV status and geographic region appeared to be important for the marijuana and cancer association (i.e. combining estimates is not appropriate). For lung cancer, a meta-analysis was not warranted since most studies did not report any association and a large consortium pooled analysis had recently been published. For childhood cancers, the cancers covered by the studies were very heterogeneous, thus a meta-analysis was not warranted. Summary ORs were estimated with the statistical program STATA, version 12.1, by inverse-variance weighting, using a random-effects model that included a term for heterogeneity among the studies. Tests for heterogeneity among the studies were conducted for each analysis.

Results

Four cohort studies and 30 case-control studies were identified for investigations of marijuana use and cancer risk. They included 11 studies on upper aerodigestive cancers (12-22), 6 studies on lung cancer (16, 23-27), three studies on testicular germ cell tumors (28-30), 6 studies on childhood cancers (31-36), one study on all cancers(37), one study on anal cancer (38), one study on penile cancer (39), two studies on non-Hodgkin's lymphoma (40)(41), one study on malignant primary gliomas(42), one study on bladder cancer (43), and one study on Kaposi's sarcoma (44).

Upper aerodigestive tract cancer (Table 1)

A hospital-based case-control study of 173 cases and 176 controls in New York reported a 2.6-fold increase (95%CI=1.1-6.6) in head and neck cancer risk due to marijuana use (12). Dose-response trends were observed for both frequency (times per day) and duration (years) of marijuana use in this study. In contrast, a population-based study in Washington of 407 cases and 615 controls reported no association between marijuana use and oral cavity cancer risk (13). Two small studies in the UK (116 and 53 cases) reported no association between oral and oropharyngeal cancer risk and cannabis smoking, and did not report on any dose-response trends (14,15).

In the Los Angeles population-based case-control study, no increased risk of head and neck cancers oral cavity (n=303), pharynx (n=100), larynx (n=90)) or esophageal cancer (n=108) was observed among ever-users of marijuana after adjusting for age, gender, race/ethnicity, educational level, alcohol consumption, and tobacco cigarette smoking (16). No association

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between marijuana use among never-tobacco cigarette smokers and head and neck cancer was observed; however, the risk estimates were not very precise. The limitations of the study were potential recall bias, downward bias in OR estimation due to nonparticipation greater in exposed cases than in unexposed controls, and potential underreporting of past marijuana use. The strengths of the study included the population-based study design, collecting the data with assurance to the study subjects that all information provided would be kept confidential, and estimating risk among never-tobacco smokers to minimize the potential effect of residual confounding by tobacco smoking.

In a case-control study in New Zealand, Aldington et al. reported no association between ever use of cannabis and head and neck cancer risk, and no dose-response relation for joint-years of cannabis use after adjusting for age, sex, ethnicity, alcohol consumption, income, packyears of cigarette smoking (17). The study included 75 cases age <55 years old and 319 controls matched by age and district health boards in New Zealand from 2001 to 2005. The limitations of this study included the small sample size and inclusion of many head and neck cancer sites with various etiologies (ex. nasopharyngeal cancer, nasal cavity cancer). Strengths of this study included the population-based design and the focus on a cohort of subjects who were likely to have higher marijuana prevalence (<55 years old in the study).

Gillison et al. reported on a strong association between marijuana use and HPV-16-positive head and neck cancer risk after adjusting for race, tobacco smoking, alcohol drinking, number of teeth lost, frequency of tooth brushing, and number of oral sex partners in a hospital-based case-control study (18). Dose-response relations for number of joints usually smoked per month and for years of marijuana smoking were observed. This study included 240 cases and 322 controls matched by age and sex to each HPV-16-positive and HPV-16-negative case subject recruited at the Johns Hopkins Hospital from 2000 to 2006. Limitations of this study were potential recall bias, possible misclassification of tumor HPV status, potential confounding by use of other substances, and that the general population may not have been represented by the control population. This is one of the few studies, on the other hand, that has explored marijuana use for head and neck cancer, stratified on HPV infection status, which is a strong risk factor for oropharyngeal cancers.

In the International Head and Neck Cancer Epidemiology (INHANCE) consortium pooled data analysis including 3 hospital-based case-control studies and 2 population-based case-control studies, Berthiller et al did not observe any associations between smoking marijuana and the risk of head and neck cancer after adjusting for age, sex, race, study, education level, and alcohol duration (19). This pooled analysis included the Los Angeles study (493 cases and 1,040 controls)(16) and the Seattle study (407 cases and 615 controls)(13). The other studies included in the pooled analysis did not publish their results separately. Investigation of the frequency of marijuana smoking (times per day) or duration (years) did not show any dose-response relations. The pooled analysis included 4,029 cases and 5,015 controls from North America and South America. Associations were not detected in an analysis restricted to never tobacco users. The limitations of this study included potential recall bias since all the studies were case-control in design, fairly low prevalence of marijuana use in the study population and possible differential misclassification of the exposure across countries or region due to different reporting of marijuana consumption. The strengths of this study

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included a large sample size, fairly high response rates, and adjustment on the same set of factors which would not be possible in a meta-analysis. The key strength is the reporting of estimates among never tobacco users and never alcohol users, which is difficult in individual studies due to limited sample sizes since the majority of head and neck cancer patients are tobacco smokers and drinkers.

Liang et al observed a decreased risk of head and neck squamous cell cancer with marijuana use in a population-based case-control study of 434 cases and 547 controls matched to cases on age, gender, and town of residence in Boston from 1999 to 2003 (20). Odds ratios were adjusted for age, gender, race, education, family history of cancer, HPV-16 serology, smoking (pack-years), and average drinks of alcohol per week. Dose-response relations were observed for frequency, duration, cumulative exposure, years since last marijuana use and age at start of marijuana use and the risk of head and neck cancer. The limitations of this study include potential recall bias, possible residual confounding when adjusting on tobacco and no differentiation between the subsites for head and neck cancers. Strengths of this study include adjustment and stratification on HPV 16 antibody status, tobacco and alcohol and identification of dose-response trends.

In another INHANCE pooled data analysis, focusing on 1,921 oropharyngeal cases and 356 oral tongue cases and 7,639 controls, Marks et al. observed a possible increased risk in oropharyngeal cancer and a possible decreased risk in oral tongue cancer due to marijuana use with dose-response trends for both frequency and duration. The analysis included 9 case-control studies from Baltimore, Seattle (407 cases and 615 controls)(13), Latin America, Boston (434 cases and 547 controls)(20), Los Angeles (493 cases and 1,040 controls)(16), and North Carolina, that recruited subjects from 1985 to 2013 (21). The previous INHANCE report (19) had included 5 of these case-control studies; thus 765 of the 1,921 oropharyngeal cancer cases and 211 of the 356 oral tongue cases had been included in the previous analysis. The odds ratio estimates were adjusted for age, sex, race, education level, ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking, and alcohol-year. When restricted to never tobacco users and never alcohol drinkers, the estimates for individual exposure categories were not significant, however the trend for cumulative exposure was significant, and the risk estimate for > 10 joint-years was 3.94 (0.59–26.3). The OR for marijuana use adjusting on HPV status in the select studies with HPV data available suggested no association overall, although a decreased risk was observed for individuals who were HPV 16 negative. Limitations of this study were potential recall bias, and different measurements of marijuana across the studies. Strengths of this study were the large sample size due to the data pooling efforts, and stratified analysis by tobacco and alcohol, and adjustment and stratification on HPV where possible.

In the case-control study of nasopharyngeal cancer, Feng et al reported an increased risk between cannabis consumption of 2000 times or more in a lifetime, and nasopharyngeal cancer risk in men after adjusting forage, SES (socioeconomic status), dietary factors and cigarette smoking frequency (22). However, smoking cannabis alone did not appear to confer an increased risk of nasopharyngeal cancer (OR=0.97, 95%CI=0.37-5.52). This study included 636 cases and 615 controls in North Africa recruited between 2002 to 2005. Limitations of this study include potential recall bias, potential bias due to the inclusion of

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prevalent cases, using hospital controls, possible underestimation of cannabis consumption, the nearly universal reporting of tobacco cigarette smoking among cannabis users and inability to disentangle effects of cannabis when mixed with tobacco and smoked in the form of a kif. Strengths of this study included the large sample size, adjustment for cigarette smoking and the dose-response observed for frequency and lifetime cannabis use.

Lung cancer (Table 2)

The 6 lung cancer studies were conducted in Los Angeles (16), Northern Africa (23, 24), New Zealand (25), Sweden (26) and in multiple locations for a pooled analysis (27). Hsairi et al reported that cannabis use increased the risk of lung cancer by 8.2 fold (95%CI=1.3-15.5)(23) in a case-control study of 110 cases and 100 controls in Tunisia. Dose-response relations were not assessed in this study to our knowledge. Adjustments were made for age, sex, cigarettes smoked per day, water pipe use, and snuff use. Tobacco is mixed with marijuana in this region, thus disentangling the effects of marijuana is difficult.

In the Los Angeles population-based case-control study of 611 lung cancer cases, dose-response relations were not observed between marijuana use and lung cancer after adjusting for age, gender, race/ethnicity, educational level, alcohol consumption, and cigarette smoking (16). In the analysis restricted to never cigarette smokers, the odds ratios did not suggest an association between marijuana use and lung cancer. Strengths and limitations of this study were discussed above.

Berthiller et al (24) pooled data from three separate hospital-based case-control studies including 430 cases and 755 controls from Tunisia (45), Morocco (46), and Algeria, and reported an increased risk of lung cancer for ever marijuana use. Dose-response relations were not observed for frequency or duration alone, but a dose-response was observed for cumulative joint-year exposure to cannabis. Limitations of the study include different questions used to assess marijuana use across the three studies, difficulty in separating out tobacco since all cannabis users were tobacco smokers and in this region tobacco is mixed in with the cannabis. Strengths of the study include the increased sample size due to the data pooling approach, careful adjustment for tobacco use, and dose-response relations observed for cumulative exposure. The Voirin et al study in Tunisia (45) and Sasco et al. study in Morocco (46) will not be reviewed separately since the entire data was included in the pooled analysis, and the analytic approach and results were very similar to the pooled study it contributed to.

In the New Zealand case-control study of lung cancer, Aldington et al reported an increased risk of lung cancer in young adults <55 years) due to heavy cannabis use (>10.5 joint-yrs) after adjusting for age, sex ethnicity, a family history of lung cancer, pack-years of cigarette smoking (25). Dose-response relations were observed for joint-years of cannabis use. The study of lung cancer included 79 cases and 324 controls matched in 5-years age groups in New Zealand between 2001-2005. The limitations of the study were a fairly small sample size (only 4 controls and 14 cases in the subgroup with (>10.5 joint-yrs of cannabis use) resulting in imprecise estimates of risk in this subgroup, and potential recall bias. The strengths of the study included the population-based design, and dose-response identified for cumulative joint-years of cannabis exposure.

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The cohort study on lung cancer included 48,321 young men aged 18-20 years old during military conscription in Sweden from 1969 to 2009 (26). Ever cannabis smoking was not clearly associated with lung cancer risk. The authors noted that a clear dose-response relationship was not present after adjusting for tobacco smoking, level of alcohol consumption, respiratory conditions, and conscripts' SES in 1970. An increased lung cancer risk was observed for men who smoked cannabis more than 50 times by the time of conscription (26). Limitations of this study include self-report of cannabis smoking at conscription which was not anonymized and may lead to underreporting. Other limitations include lack of detailed information of use on patterns of cannabis or tobacco before conscription and after conscription, misclassification biases of unmeasured post-conscription changes in marijuana or tobacco use, and potential residual confounding due to tobacco smoking since 91% of the cannabis smokers were also tobacco smokers. They were not able to adjust for true lifetime use of tobacco including use during the 40-year follow-up period, but adjusted only for tobacco use up to the time of conscription at ages 18-20 years in this study. The authors noted that it is also possible that tobacco was mixed with cannabis, although the habits and culture at the time (1969-70) are unclear. The strengths of this study were the cohort design, large sample size of the cohort, and having a long follow-up period of 40 years.

In a pooled data analysis of lung cancer including of 6 case-control studies, Zhang et al reported that there were no dose-response relationships observed between cannabis smoking and lung cancer after adjusting for age, sex, highest education, and study, reporting on never-tobacco smokers (27). This pooled analysis included 2,159 cases and 2,985 controls from studies conducted in Los Angeles (16), New York, Florida, Canada, the United Kingdom, and New Zealand (25). The Los Angeles (611 cases/1,040 controls) and New Zealand (79 cases and 324 controls) studies reviewed here were included in this pooled analysis. The four other studies included in the pooled analysis did not publish their results on marijuana use, to our knowledge. The limitations of this study were potential recall bias and the heterogeneity of marijuana exposure assessment across the studies. The strengths of this study consisted of the large sample size due to data pooling efforts, and the investigation of lung cancer risk among never-tobacco smokers.

Testicular cancer (Table 3)

In a population-based case-control study of testicular cancer, Daling et al. observed an association between ever marijuana use and testicular cancer after adjusting for age, reference year, alcohol use, current smoking, and history of cryptorchidism (28). Increased testicular cancer risk were observed in categories of frequency and duration of marijuana use for current marijuana users, although dose-response relations were not obvious. The study included 369 cases aged 18 to 44 years old and 979 age-matched controls who resided in the same 3 countries in the U.S. from 1999 to 2006. The limitations of this study consisted of potential recall bias due to self-report of use of marijuana and a small number of categories of marijuana use. The strengths of this study were that this is the largest testicular cancer study published to date and had a population-based design.

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Trabert et al. reported that there was an increased risk of testicular cancer with daily marijuana use after adjusting for age, race, alcohol use, cigarette smoking, and history of cryptorchidism (29). The study included 187 cases and 148 controls from Texas, Louisiana, Arkansas, and Oklahoma from 1990 to 1996. The limitations of this study were potential recall bias, inability to evaluate current use with data because only less <10% of their study population reported current marijuana use and difficulty interpreting the temporal relationship between marijuana and testicular germ cell tumors.

Lacson et al observed an increased risk of testicular cancer with marijuana use after adjusting for cocaine use, amyl nitrite use, cryptorchidism, religiosity, and education (30). This study included 163 cases and 292 controls matched on age, race/ethnicity, and neighborhood in Los Angeles country from 1986 to 1991. Higher testicular cancer risk was observed in the lower frequency and duration categories, although the differences were not statistically significant. Limitations of this study were potential recall bias, and a small number of categories for the frequency of use of marijuana. Strengths of this study were that the categories used in the other two testicular cancer studies were similar and thus more easily comparable.

We conducted a meta-analysis of these 3 studies (Table 4) and observed no association with ever use of marijuana and testicular cancer risk. However, for the upper category of frequency of marijuana use, a 1.56-fold (95%CI=1.09-2.23) increase in testicular cancer risk was observed. Similarly, for 10 or more years of marijuana smoking a 1.5-fold (95%CI=1.08-2.09) increase in testicular cancer risk was observed.

Childhood cancers (Table 5)

Five of the six studies on childhood cancers and marijuana use were based on the Children's Cancer Study group. Parental marijuana use during the gestational period was associated with childhood leukemia(31, 32), astrocytoma (33) and rhabdomyosarcoma(34). These studies shared limitations such as small numbers of exposed cases, possible exposure misclassification due to the potential recall bias, and no dose-response assessments. Strengths consisted of large sample size and information on use of specific recreational drugs within specific time periods relative to pregnancy and birth.

In the case-control study of childhood acute myeloid leukemia, Trivers et al. observed no association of childhood AML with parental marijuana use (35). This study included 638 cases who were age <18 years old and 610 controls matched on age and resident location in Washington State from 1999 to 2006. Although paternal ever marijuana use appeared to be associated with the risk of childhood acute myeloid leukemia, assessment of specific time periods relative to the pregnancy and birth did not support an association. Furthermore, frequency of maternal marijuana use was not associated with leukemia risk.

In the case-control study of childhood neuroblastoma, Bluhm et al. did not observe an association of an increased risk of childhood neuroblastoma after adjusting for household income in the year of birth and age at diagnosis in three categories and other drugs used (36). An increased risk of neuroblastoma was observed for maternal marijuana use in the first trimester, with four-fold increases in risk for the categories of frequency of use. The

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study of childhood neuroblastoma included 538 cases and 504 controls matched on age in North America from 1992 to 1994.

Other cancers (Table 6)

A large cohort study of 64,855 individuals in California, marijuana use was not associated with cancer risk nor with tobacco-related cancers, after adjustment for age, race, education, alcohol use and cigarette smoking (37). In the subgroup analysis of never-tobacco smokers, marijuana use was associated with an increased risk of prostate cancer and cervical cancer. Dose-response relations with frequency and duration of marijuana use were not observed with cancer risk nor with the risk of specific cancer sites. Daling et al. reported on 148 anal cancer cases and reported no association with ever marijuana use when compared to 166 colon cancer cases (38). Penile cancer risk was also not associated with marijuana use according to a study of 110 cases and 355 controls (39).

The two case-control studies on Non-Hodgkin's lymphoma reported on null to possibly protective associations (40, 41). In the study including 1,281 cases and 2,095 controls from Northern California, a 50% reduction in risk for men was observed for a 1,000 or more times marijuana use and a 40% reduction in risk for women was observed for 40-999 times of marijuana use (41). However, protective associations were also observed for sexual behaviors and cocaine use; thus it is unclear whether the associations between marijuana use and lymphoma risk were due to residual confounding.

In another California cohort of 105,005 individuals, marijuana use at a frequency of one or more times per month appeared to increase the risk of malignant primary glioma (42) after adjustment for smoking status, sex, race, alcohol, education and coffee intake. Although the cohort design was a strength, the small number of cases (n=69) was a limitation in the study.

In the case-control study of transitional cell carcinoma of bladder, Chacko et al observed a significant association of transitional cell carcinoma and marijuana after adjusting for Agent Orange exposure, radiation exposure, and dye exposure, with dose-response relations (43). The study of transitional cell carcinoma included 52 cases age <60 years old and 168 controls in the U.S. The limitations of this study were small sample size, potential recall bias due to self-report and lack of adjustment on tobacco smoking which is an established risk factor for bladder cancer.

The Kaposi's sarcoma cohort study was a US multicenter study of natural treated histories of HIV-1 infection in men who have sex with men (44). The study was started in 1984 and had three recruitment periods with emphasis on enrolling more ethnically diverse men in the later periods: 1984-85, 1987-1991, and 2001-2003. Of the 1,335 white men included in the study, 401 Kaposi's sarcoma cases were identified and included in the analysis. Recent use of any of four drugs (marijuana, cocaine, poppers and amphetamine) was not associated with Kaposi's sarcoma risk, after adjusting for age, college education, study center, alcohol use, tobacco smoking, number of male sexual partners since the last study visit, lifetime number of sexual partners, receptive anal intercourse and condom use, antiretroviral therapy, CD4 cell count, and sexually transmitted infection score. Limitations of this study were the self-report of drugs, pre-specified categories for frequencies of marijuana use, and lack of

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consistent testing for HHV-8 from all participants which lead to many individuals being excluded from the analysis. Strengths of this study were large sample size, having a long follow-up period, the ability to examine the effect of substance use from different exposure periods, and adjusting for multiple potential confounders.

Discussion

The largest number of studies for a cancer site under investigation for the impact of marijuana use appears to involve head and neck cancer. There were a total of 8 case-control studies and 2 pooled analysis studies on head and neck cancer and marijuana use. One study reported an increased risk (12), five studies reported no association (13, 13-17), and one study reported a decreased risk of head and neck cancer (20). Of the five studies reporting no association, two of the studies were very small in sample size (<100 cases) and may have limited power to detect associations. Gillison et al reported no association between marijuana use and head and neck cancer for HPV-16 negative patients and an increased risk for HPV-16 positive patients (18). The pooled analyses have reported no overall association for head and neck cancer (19), but a possible increased risk with dose-response for oropharyngeal cancer and a decreased risk for oral tongue cancers (21). In the head and neck cancer pooled analysis (19) two of the published studies (13, 16) out of the five studies pooled were included, whereas the oropharyngeal/oral tongue pooled analysis included 3 published studies (13, 16, 20) out of the 9 studies pooled. The evidence is inconsistent but may be consistent with no association or with opposite directions of association depending on subgroups of populations. The three studies that investigated HPV and marijuana on the risk of head and neck cancer suggest that HPV may be a modifying factor between marijuana use and head and neck cancer risk (18, 20, 21).

For lung cancer, there are three published case-control studies (16, 23, 25), one cohort study (26) and two pooled analysis studies (24, 27). The North African studies are consistent in reporting increased risks of lung cancer (23, 24) with dose-response relations. However, tobacco is mixed with cannabis in the region, thus it is difficult to rule out residual confounding by tobacco smoking. The study in New Zealand (25) reported an increased risk with dose response for cumulative exposure, while the study in Los Angeles reported no association (16). Both of these studies were included in the lung cancer consortium pooled analysis which was recently published (27), and reported no overall association and no dose-response relations. The cohort study on lung cancer reported an increased risk for marijuana use with a dose-response for the number of times used in a lifetime, but “lifetime” use was assessed only up until the ages of 18-20 years with no information on subsequent use over the ≤40-year follow-up period and no dose-response for frequency. The lung cancer studies appear to be consistent with no association with marijuana, although affirming no association is inherently difficult.

Highest exposure categories as presented in studies on marijuana use and lung cancer ranged from “> 50 lifetime frequency” (i.e. approximately 1 joint/week for one year, or 1/7 joint-year) in one study, “> 1 or 2 joint-years” in two studies, to “> 10 joint-years” in two other studies. Even the 10 joint-years of cumulative lifetime use of marijuana would translate into only 0.5 pack-years of cigarette smoking, assuming similar carcinogenic potency and similar

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amount of tobacco used in joints and cigarettes*. In most studies on tobacco smoking and lung cancer such a cumulative exposure would be classified as never smoker. Further, assuming a relative risk of 1.2 for lung cancer for a cumulative cigarette smoking of 2-4 pack-years, and making the same assumptions as above, a similar relative risk of lung cancer would require 40-80 joint-years of marijuana use, a lifetime use hardly seen in any of the studies reviewed here.

That marijuana smoking may be a risk factor for the development of cancer is suggested by several lines of evidence. First, the tar phase of marijuana smoke contains at least similar amounts of some pro-carcinogenic polycyclic aromatic hydrocarbons (PAHs), including benz(α)pyrene and benzanthracene, to those of the tar obtained from the smoke of the same quantity of tobacco (47-49). Secondly, although marijuana is generally smoked in lower amounts than tobacco, the prolonged breathholding time during marijuana smoking and the reduced rod filtration due to more loosely packed marijuana leads to a 4-fold increase in the respiratory deposition of tar (which contains the carcinogenic PAHs) compared to the deposition of tar from the smoking of a comparable quantity of tobacco (50). This greater lung deposition from marijuana smoking, along with the higher concentration of some known carcinogens in marijuana smoke, is likely to magnify the level of exposure to carcinogens from each marijuana cigarette. Thirdly, delta-9 tetrahydrocannabinol (THC), the major psychoactive ingredient in marijuana, can interact with the aryl hydrocarbon receptor, activating transcription of cytochrome P4501A1 (51), which is involved in the biotransformation of PAHs into active carcinogens. Fourth, hamster lung explants exposed to marijuana smoke for up to 2 years exhibited abnormalities in cell growth and accelerated malignant transformation (52). Fifth, non-small cell lung cancer cell lines implanted into immunocompetent mice exhibited accelerated growth when the animals were injected intra-peritoneally with THC, a finding that was associated with THC-induced overproduction of immunosuppressive cytokines (IL-10 and TGF-β) and underproduction of immunostimulatory cytokines (IL-2 and INF-γ), consistent with a THC-related, cytokine-dependent inhibition of antitumor immunity (53). Sixth, endobronchial biopsies obtained from habitual smokers of marijuana without a history of tobacco smoking have demonstrated a number of histopathologic alterations, including squamous metaplasia, cellular atypia and increased nuclear/cytoplasmic ratio, that are considered to be pre-malignant (54, 55). Seventh, immunohistochemical assessment of these biopsies has shown significantly increased expression of molecular markers of pre-tumor progression, including EGRF (epidermal growth factor receptor) and Ki-67 (a nuclear proliferation protein) compared to nonsmokers (56).

In view of the above findings, a null association between marijuana use and lung cancer is somewhat surprising since marijuana smoke contains known carcinogens in amounts comparable to those found in tobacco smoke (49). While the generally smaller amounts of marijuana that are regularly smoked compared to tobacco might appear to explain the null association of marijuana with lung cancer, the absence of a dose-response relationship between marijuana use and lung cancer, in contrast to the strong dose-response relationship noted for tobacco (16), would argue against this explanation. A more likely explanation is a tumor-suppressant effect of THC and other cannabinoids evident in both cell culture systems and animal models of a variety of cancers, as reviewed by Bifulco et al. (57). These anti-

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tumoral effects (anti-mitogenic, pro-apoptotic and anti-angiogenetic) could possibly counteract the tumor-initiating or tumor-promoting effects of the carcinogens within the smoke of cannabis.

The three testicular cancer case-control studies were fairly consistent with one another in terms of an increased risk observed even for fairly moderate frequency and duration of use (28-30). It is perhaps surprising that testicular cancer would be associated with marijuana use, since tobacco smoking is not thought to be associated with testicular cancer risk. The three studies were conducted in various regions of the US and had similar definitions of marijuana use (asking study participants about ever marijuana use). The study periods recruited participants from 1986 to 2006 with only a few years overlap across the three studies, suggesting that the possible association has been consistent over the last few decades. Although the three studies investigated testicular cancer risk by frequency and duration of marijuana use, none showed strong dose-response relations. All three studies adjusted on age and cryptorchidism, both of which are established risk factors for testicular cancer. Although maternal gestational tobacco smoking was associated with cryptorchidism, it is unknown whether cryptorchidism is also associated with marijuana use, thus, it may not meet the second property of a confounder that the covariate is associated with the exposure. The proportion of testicular cancer patients with cryptorchidism is fairly low (<10%), thus it is unlikely to impact the estimates greatly even if it is not a confounder. Additionally, Daling et al conducted analyses with exclusions of cases and controls with cryptorchidism and presumably the estimates were not greatly affected. Two of the studies also adjusted on tobacco smoking and alcohol use (28, 29), while Lacson et al adjusted on education, religiosity, cocaine use, and amyl nitrate use (30). Tobacco smoking and alcohol drinking are not established risk factors for testicular cancer, and thus would not meet the first property of confounders that the covariate is a risk factor for the disease. It may be useful in future studies to report on adjustments of potential confounders in several combinations separately: 1) established risk factors for testicular cancer (age, cryptorchidism), and 2) factors strongly associated with marijuana use (tobacco smoking, alcohol drinking). Although cryptorchidism, tobacco smoking and alcohol drinking may not meet all three properties of a confounder, it would still be useful to show estimates adjusted for these factors to assure that unknown associations are not causing confounding.

For other cancers such as bladder cancer and childhood cancer, there are still insufficient data to make any conclusions on an association with marijuana. Although large-scale pooled analyses have been published recently for both head and neck cancer and lung cancer, there does not appear to be sufficient data to conclude whether there is an association or not with marijuana use. Considering that marijuana use may change due to the legalization efforts, large-scale well-designed studies on marijuana use and cancer may be warranted. The potential risks conferred by marijuana use, although it may be a moderate risk, needs to be clarified for the 18 million Americans who are currently using marijuana today.

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Future study recommendations

Some future study recommendations are as follows:

- **Collect specific information on the type of marijuana use.** The studies to date assumed marijuana was smoked, to our knowledge, and did not ask about how the marijuana was used. Marijuana is most commonly smoked (with or without tobacco depending on the geographic region), but can also be ingested with food.
- **Focus on never-tobacco smokers.** If possible never tobacco smokers are an ideal group to study association between marijuana smoking and smoking related cancers because the effect of marijuana use on cancer can be more easily disentangled from the effect of tobacco smoke on cancer risk. In another words, the potential independent effect of marijuana can be better characterized. The possibility of residual confounding in any associations observed will be minimized if the study population is restricted to never-smokers.
- **Adjust carefully for tobacco smoking.** If tobacco smokers are in the study population, the adjustment for tobacco smoke should include multiple variables such as tobacco smoking status (never, past, current), frequency, duration, and years since quitting. Adjustment on only tobacco smoking status (never, past, current) for example may leave residual confounding. If the cancer under study is not associated with tobacco smoking, adjustment for tobacco smoking is not necessary since it does not meet the three properties of confounders. However, as a conservative approach, it would be useful to report on estimates adjusted for tobacco smoking separately, even if the cancer under study is not a tobacco-related cancer.
- **Report on groups of subsites of head and neck cancers.** Sincethe results of previous studies suggest substantial heterogeneity in the risk estimates according to head and neck cancer subsites, risk estimates for marijuana use should be reported separately by subsite. Since head and neck cancer subsites have different etiology, e.g. oropharynx cancers be strongly related to HPV, and those HPV positive cancers perhaps may not be strongly related to tobacco and alcohol, risk conferred by marijuana use may also differ.
- **Stratification by HPV statusfor cancers of the oropharynx.** Previous studies also suggest that HPV status may be a potential modifier of the marijuana and oropharynageal cancer association, results should be stratified on HPV status when studying oropharyngeal cancer. Interactions should be assessed between HPV status and marijuana use with statistical tests.
- **Conduct a prospective cohort design.** The majority of previous studies have been case-control, which have the inherent limitation of potential recall bias. To minimize recall bias and study multiple cancer sites, a prospective cohort study design is preferably for future studies focusing on the association between marijuana use and cancer risk. Conducting the study in regions/states where

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marijuana use is legalized with a sizable proportion of long-term and heavy users would likely reduce reporting bias and increase the power of the study. Further, the cohort design would allow to investigate the full range of cancers potentially associated with marijuana use.

- **Continue data pooling efforts.** Though we conducted a meta-analysis for testicular cancer, the estimates were not adjusted for the same factors, thus a pooled analysis for testicular cancer would be very informative. Additionally, one of the studies had restricted the frequency and duration estimates to current users instead of both current and past users, thus the estimates were not entirely comparable. Fine tuning these types of analytical issues would be possible in a pooled analysis.
- **Additional analyses of studies on head and neck, and lung cancers.** Although large scale pooled analyses have been conducted for both head and neck, and lung cancers, additional efforts to elucidate some of the issues raised above (e.g. type of marijuana use), and if possible, additional analyses of HPV status for oropharyngeal cancer are be warranted.
- **The development of marijuana related biological markers in future epidemiological studies.** It is of importance to developand validate marijuana smoking related exposure markers including DNA adducts; exposure related early biological responses such as specific somatic mutations of tumor suppressor gene; genetic polymorphisms of metabolic, inflammation and DNA repair genes; and epigenetic markers including DNA methylation, microRNA, etc.

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Table 1

Epidemiologic studies on marijuana use and upper aerodigestive tract cancers

Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
New York, 1992-1994 Zhang et al. (12)	Oral cavity, salivary gland, nasopharynx, oropharynx, hypopharynx, larynx, esophagus	173 SCC untreated cases from hospital, histologically confirmed, Response rate: 90.1%	176 blood donors without history of cancer, frequency matched on age & sex, Response rate: 89.8%	Questionnaire filled by subject	**Ever use** **Frequency** 0 times/day 1 times/day >1 times/day p for trend **Duration** 0 years 1-5 years >5 years p for trend	2.6 (1.1-6.6) 1.00 4.0 (0.9-17.2) 5.4 (0.9-33) 0.0214 1.00 3.9 (0.99-15.0) 4.9 (1.07-22.3) 0.0134	• Adjusted for age, sex, race, education, alcohol use, packyears of cigarette smoking, passive smoking. • Association stronger for subjects ≤55 years. • Dose-response trends observed for both frequency (times per day) and duration (years) of marijuana use
Washington state, 1985-1995 Rosenblatt et al. (13)	Oral (tongue, gums, floor of mouth, tonsils, oropharynx, other intraoral sites)	407 carcinoma in situ and SCC cases, 18-65 years old, identified from the cancer registry, Response rate: 54.5% for 1985-1989, 63.3% for 1990-1995	615 subjects from random-digit dialing, frequency matched on age & sex, Response rate: 63% for 1985-1989, 61% for 1990-1995	Face-to-face interviews with a structured questionnaire,	**Ever use** **Frequency** Never <1 year use <1 times/week 1-7 times/week >7 times/week **Duration** Never <1 year 1 year 2 – 5 years	0.9 (0.6-1.3) 1.00 1.0 (0.6-1.8) 0.8 (0.5-1.4) 0.8 (0.4-1.6) 0.5 (0.2-1.6) 1.00 0.8 (0.4-1.2) 0.2 (0.1-0.7) 1.3 (0.6-2.6)	• Adjusted for birth year, sex, education, alcohol consumption, packyears of cigarette smoking, study. • Data are from 2 studies, one conducted in 1985-1989, the other in 1990-1995 • Included in the Berthiller et al pooled analysis

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
					Frequency		(19) and Marks et al. pooled analysis) and Marks et al. pooled analysis ( ) and Marks et al. pooled analysis (21)
					Never	1.00	
					<1 year use	1.0 (0.6-1.8)	
					<1 times/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)	
					Duration		
					Never	1.00	
					<1 year	0.8 (0.4-1.2)	
					1 year	0.2 (0.1-0.7)	
					2 – 5 years	1.3 (0.6-2.6)	
					6 – 15 years	0.7 (0.4-1.4)	
					>15 years	1.2 (0.6-2.2)	
UK, 1990-1997 Llewellyn et al. (14)	Oral, oropharynx	116 SCC of the oral cavity and oropharynx, ≤45 years old, identified from the cancer registry, Response rate: 59%	207 patients without cancer, matched individually to case by age, sex, residence, Response rate: not available.	Questionnaire filled by subject	**Ever use**		• Adjusted for age, sex, residence, alcohol and cigarette smoking • Dose-response assessment not reported.
					Overall	1.0 (0.5-2.2)	
					Men	0.9 (0.4-2.2)	
					Women	1.7 (0.4-7.0)	
UK, 1999-2001 Llewellyn et al.(15)	Oral, oropharynx	53 SCC of the oral cavity and oropharynx, ≤45 years old, identified from the cancer registry, Response rate: 80%	91 patients without cancer, matched individually to case by age, sex, residence, Response rate: not available.	Questionnaire filled by subject	**Ever use**		• Adjusted for age, sex, residence, alcohol and cigarette smoking • Dose-response assessment not reported.
					Overall	0.3 (0.1-1.8)	
					Men	0.3 (0.1-3.9)	
					Women	0.7 (0.1-184.9)	
Los Angeles, 1999- 2004	Head and neck cancer (oral cavity, pharynx, and larynx) and	303 oral cavity, 100 pharyngeal, 90 laryngeal cancer and 108 esophageal cancer cases	1,040 cancer-free controls matched to cases on age,	Questionniares by interviewers	**Oral cancer**	**Never smokers**	• Adjusted on age, gender, race/ethnicity, educational
					Never	1	

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
Hashibe et al. (16)	esophageal cancer(19)	from the cancer registry Response rates: Oral cancer: 54% Pharyngeal cancer: 45% Laryngeal cancer: 42% Esophageal cancer: 35%	gender, and neighborhood. LA residents age 18-65. Response rate: 72%		>0 to <1 joint-years	0.93 (0.53-1.6)	level, alcohol consumption • Estimates shown are for never-smokers • Included in the Berthiller et al pooled analysis (19) and Marks et al. pooled analysis (21)
					1 to <10 joint-years	1.5 (0.68-3.5)	
					≥10 joint-years	1.8 (0.69-4.7)	
					Pharyngeal cancer		
					Never	1	
					Ever	0.92 (0.41-2.10)	
					Laryngeal cancer		
					Never	1	
					Ever	1.2 (0.26-5.5)	
					Esophageal cancer		
					Never	1	
					Ever marijuana use	0.79 (0.30-2.1)	
New Zealand, 2001-2005 Aldington et al.(17)	Oral cavity, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavities	75 cases, <55 years old, from the New Zealand Cancer Registry and hospital databases, Response rate: 76%	319 controls from electoral roll, frequency matched by age, and district health boards, Response rate: 66%	Questionniares by interviewers	**Ever cannabis use**	1.0 (0.5-2.3)	• Adjusted on age, sex, ethnicity, alcohol consumption, income, packyears of cigarette smoking
					Joint-years		
					None	1.0	
					1st tertile (<1)	0.4 (0.1-2.2)	
					2nd tertile (1-8.3)	1.2 (0.3-4.2)	
					3rd tertile (<8.3)	1.6 (0.5-5.2)	
					p for trend	0.57	
Baltimore, MD, 2000-2006 Gillison et al. (18)	Head and Neck squamous cell carcinomas (oral cavity, paranasal sinus, pharynx, larynx, unknown primary head and neck)	240 cases from a hospital Response rate: 77%	Two control subjects (n=322) matched by age and sex to each HPV-16-positive and HPV-16-negative case subject from outpatient Response rate: 70%	Auto computer-assisted self-interview	**Joint-years**		• Adjusted on race, tobacco use, alcohol use, tooth loss, frequency of tooth brushing, and number of oral sex partners. • Dose-response relations observed for both frequency (joints/month; p for
					HPV-16 positive		
					0 joint-years	1.0	
					1-4 joint-years	2.0 (0.76-5.2)	
					5-14 joint-years	6.0 (1.2-29)	
					≥15 joint-years	6.4 (1.6-26)	
					p for trend	0.003	
					HPV-16 negative		
					0 joint-years	1.0	

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
					1-4 joint-years	1.0 (0.41-2.5)	trend=0.007) and duration (years; p for trend=0.011) among HPV-16-positive patients
					5-14 joint-years	1.7 (0.41-7.4)	
					≥15 joint-years	2.0 (0.50-7.8)	
					p for trend	0.29	
South America and United States, 1985-2006 Berthiller (19)	Head and neck cancer (oral cavity, pharynx, and larynx)	4,029 cases of head and neck cancers from five case-control studies within the INHANCE Consortium Response rates: Seattle, WA: 54%, 63% Tampa, FL: 98%, Los Angeles, CA: 49%, Houston, TX: 95%, Havana, Buenos: 95%	5,015 controls of head and neck cancers from five case-control studies within INHANCE Consortium Response rate: Seattle, WA: 63%, 61%, Tampa, FL: 90%, Los Angeles, CA: 68%, Houston, TX: 80%, Havana, Buenos: 86%	Pooled self-reported questionnaire data	**Joint-years**		• Age, sex, education, race/ethnicity, study center, pack-years, duration of smoking pipe, duration of smoking cigar, and duration of alcohol drinking in years • Dose-response trends were not observed for frequency or duration of marijuana use • Included the published Los Angeles study (16) and Seattle study (13)
					Oral cavity		
					Never	1.00	
					>0-2 joint-years	0.73 (0.50-1.08)	
					>2-5 joint-years	0.68 (0.32-1.46)	
					>5 joint-years	0.73(0.46-1.16)	
					P for trend	0.07	
					Pharynx		
					Never	1.00	
					>0-2 joint-years	1.15 (0.68-1.94)	
					>2-5 joint-years	1.29 (0.45-3.75)	
					>5 joint-years	1.03 (0.47-2.26)	
					P for trend	0.76	
					Larynx		
					Never	1.00	
					>0-2 joint-years	0.84 (0.52-1.36)	
					>2-5 joint-years	0.31 (0.09-1.07)	
					>5 joint-years	1.20 (0.77-1.85)	
					P for trend	0.75	
Boston, MA, 1999-2003 Liang et al. (20)	Head and neck squamous cell carcinoma	434 cases identified from clinics and departments at nine medical facilities in Greater Boston, MA. Age >18Response rate: 88%	547 controls matched to cases on age, gender, and town of residence, randomly	Self-administered questionnaire.	**Lifetime marijuana (times/week * years)**		• Adjusted for age, gender, race, education, HPV 16 serology, family history
					None	1.00	
					>0 to <5	0.63 (0.34-1.17)	

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
			selected from Massachusetts town books. Response rate: 47%		5 to <15 15 to <90 ≥90 p for trend **Never smokers** Ever marijuana use	0.36 (0.18-0.69) 0.53 (0.30-0.94) 0.78 (0.41-1.47) 0.03 0.48 (022-1.06)	of cancer, smoking pack-years, and average alcohol drinks per week. • Dose-reponse trends were observed for both frequency (times per week) and duration (years) of marijuana use and head and neck cancer risk • Decreased risk of head and neck cancer was observed among HPV-negative individuals, with dose-response observed for frequency (p trend =0.02) • Included in the Marks et al. pooled analysis (21)
Seattle, Latin America, Boston, Los Angeles, North Carolina, 1983-2013 Marks et al. (21)	Oropharyngeal and Oral Tongue Cancer	1,921 oropharyngeal cases and 356 oral tongue cases from 9 case-control studies within INHANCE Consortium Response rate: N/A	7,639 controls from 9 case-control studies within INHANCE Consortium Response rate: N/A	Pooled self-reported questionnaire data	**Joint-years** **Oropharyngeal** Never >0-1 joint-years 2-19 joint-years >10 joint-years P for trend	 1.0 1.12 (0.87-1.45) 1.34 (1.04-1.71) 1.14 (0.85-1.2) 0.055	• Adjusted for age, sex, race, education level, ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking, and alcohol-year.

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
					Oral tongue		• Dose-response relations for frequency (use per week) and duration (years) were observed for both oropharyngeal and oral tongue cancers(13, 16)
					Never	1.0	
					>0-1 joint-years	0.39 (0.18-0.88)	
					2-19 joint-years	0.64 (0.31-1.29)	
					>10 joint-years	0.31 (0.11-0.89)	
					P for trend	0.004	• For never tobacco users and never alcohol drinkers, the estimates for individual exposure categories were not significant, however the trend for cumulative exposure was significant, and the risk estimate for > 10 joint-years was 3.94 (0.59–26.3)
							• Included the published Seattle (13), Boston (20), Los Angeles (16) studies
North Africa, 2002- 2005 Feng et al (22)	Nasopharyngeal carcinoma (NPC)	636 cases identified from five hospitals by clinicians in the oncology and radiotherapy departments Response rate: N/A	615 controls from Algeria, Morocco and Tunisia. Matched by center, age, sex, and childhood household type (urban/rural)	Interviews	**Lifetime frequency in men**		• Adjusted for age, socioeconomic status, dietary factors and cigarettes smoked per day
					Never	1.00	
					<2000 times	1.86 (0.79-4.36)	
					>=2000 times	2.62 (1.00-6.86)	
					Never	1.00	

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
			Response rate: N/A		Smoking cannabis	0.97 (0.37-2.52)	
					Smoking cannabis with tobacco	1.94 (0.96-3.92)	

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Table 2

Epidemiologic studies on marijuana use and lung cancer

Studylocation,period, author, reference	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
Tunisia, 1988-1989 Ilsairi et al. (23)	110 cases diagnosed in a hospital, 70.0% have histological confirmation, 97.3% male. Response rate: N/A	110 residents in Tunisia, individually matched on age, sex and average number of cigarettes/ dayResponse rate: N/A	Face-to-face interviews with questionnaire	Cannabis use	8.2 (1.3-15.5)	• Adjusted for age, sex, number of cigarettes/day, water pipe use and snuff use • 'Cannabis use' was not defined. Assessment of dose-response relations not reported.
Los Angeles, CA, 1999- 2004 Hashibe et al. (16)	611 lung cancer cases from the cancer registry Response rate: 39%	1,040 cancer-free controls matched to cases on age, gender, and neighborhood. LA residents age 18-65. Response rate: 72%	Subjects were interviewed face-to-face with a standardized questionnaire	Never >=0 to 1 joint-years >=1 joint years	**Never smokers** 0.44 (0.21-0.92) 1.1 (0.48-2.6)	• Adjusted for age, gender, race/ ethnicity, educational level, and alcohol consumption. • Estimates shown are for never-smokers • Included in the Zhang et al. pooled analysis (27)
Tunisia, Morocco, Algeria, 1996-2004 Berthiller et al. (24)	430 cases from hospitals from 3 studies Response rate: N/A	755 hospital-based controls Response rate: N/A	Pooled self-reported questionnaire data	**Ever cannabis use** **Joint years** Never >0 to <2 joint-years ≥2 joint-years	2.4 (1.5-3.7) 1.00 1.76 (0.81-3.82) 3.44 (1.51-7.86)	• Adjusted on age, occupational exposure, country, years of tobacco smoking • Estimates by frequency and duration did not show any dose-response (not presented in paper) • Includes data from Voirin et al

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Studylocation,period, author, reference	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
				Joint years		
				Never	1.00	
				>0 to <2 joint-years	1.76 (0.81-3.82)	
				≥2 joint-years	3.44 (1.51-7.86)	
New Zealand, 2001-2005 Aldington et al. (25)	79 cases identified from the New Zealand Cancer Registry and hospital database. Age<55 years. Response rate: 77%	324 controls matched in 5-yr age groups and district health boards Response rate: 66%	Interviewer-administered questionnaires	**Cannabis use** **Joint-yrs** Nonsmoker First tertile (<1.39) Second tertile (1.39-10.5) Third tertile (>10.5)	 1.0 0.3 (0.1-1.7) 0.5 (0.1-2.0) 5.7 (1.5-21.6)	• Adjusted for age, sex ethnicity, pack-years of cigarette smoking and family history of lung cancer. • For ever joint-year increase, RR=1.08 (95%CI=1.02-1.15) • Included in the Zhang et al. pooled analysis (27)
Sweden, 1969- 2009, Callaghan et al. (26)	179 lung cancer cases	Cohort of 49,321 young men age 18-20 years old in military conscription	Self-reported questionnaires. The 1969-1970 conscription collected information about alcohol and drug use	**Ever Cannabis smoking** **Lifetime frequency** Never Once 2-4 times 5-10 times 11-50 times > 50 times	1.25 (0.84-1.87) 1.00 1.52 (0.77-3.01) 0.66 (0.27-1.62) 0.68 (0.21-2.16) 1.68 (0.77-3.66) 2.12 (1.08-4.14)	• Adjusted for cigarette smoking (frequency), alcohol consumption, respiratory conditions, socioeconomic status. • Duration of use was not available.
U.S., Canada, UK, and New Zealand, 2010 Zhang et al.(27)	2,159 cases from 6 case-control studies in the lung cancer (ILCCO) consortium Response rate: N/A	2,985 controls from 6 case-control studies in the lung cancer (ILCCO) Consortium Response rate: N/A	Pooled self-reported questionnaire data	**Never-tobacco smokers** Nonhabitual cannabis smoker Habitual **Joint-years** <1 joint-years 1 to <10 joint-years ≥10 joint-years **continuous joint-years**	 1.00 1.03 (0.51-2.08) 1.00 1.26 (0.57-2.75) 0.54 (0.12-2.55)	• Adjusted for age, sex, race, highest education, and study • Estimates presented are for never-tobacco smokers • Included the published studies from Los Angeles

(45)and Sasco et al. ( )and Sasco et al. (

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Study location,period, author, reference	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
				Nonhabitual cannabis smoker Habitual	1.00	(16), and New Zealand ( ), and New Zealand (
				Joint-years	1.03 (0.51-2.08)	
				<1 joint-years		
				1 to <10 joint-years	1.00	
				≥10 joint-years	1.26 (0.57-2.75)	
				continuous joint-years	1.04 (0.93-1.07)	
					1.00 (0.93-1.07)	

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Table 3

Epidemiologic studies on marijuana use and testicular cancer

Study location, period, author, reference	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
Washington State, 1999 – 2006, Daling et al. (28)	369 cases ages 18 to 44 years Response rate: 67.5%	979 age-matched controls who resided in the same 3 countries Response rate: 52.2%	Interviewer-administered questionnaires	**Frequency** Daily or >=1 d/per week Less than once/per week **Duration** <10 years ≥10 years	 2.0 (1.3-3.2) 1.4 (0.9-2.3) 1.8 (1.0-3.3) 1.6 (1.1-2.5)	• Adjusted for age, reference year, alcohol use, current smoking, history of cryptorchidism
Texas, Louisiana, Arkansas, or Oklahoma, 1990- 1996, Trabert et al. (29)	187 cases from hospital-based cased-control study at University of Texas M.D. Anderson Cancer Center. Age 18-50 Response rate: N/A	148 controls from hospital-based cased-control study at University of Texas M.D. Anderson Cancer Center Response rate: N/A	A self-administered questionnaire ascertaining demographics, lifestyle habits medical history, and diet.	**Frequency** Never <1/day Daily or >1/day **Duration** <10 years ≥10 years	 1.0 0.5 (0.3-0.9) 2.2 (1.0-5.1) 0.6 (0.3-1.0) 1.2 (0.6-2.8)	• Adjusted for age, race, alcohol use, cigarette smoking, and history of cryptorchidism
Los Angeles, 1986-1991 Lacson et al. (30)	163 cases identified in the Los Angeles Cancer Registry, age 18-35 Response rate: 81%	292 controls matched on age, race/ethnicity, and neighborhood Response rate: 78.7%.	An interview using structured questionnaires	**Frequency** <1 per week ≥1 per week **Duration** <10 years ≥10 years	 2.10 (1.09-4.03) 1.53 (0.73-3.24) 2.09 (1.09-3.98) 1.51 (0.66-3.47)	• Adjusted on cryptorchidism, education, religiosity, and reported use of cocaine, and amyl nitrite • Crude ORs did not show any associations • Duration among former users appeared to show the strongest associations with marijuana use

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Table 4

Meta-analysis of three studieson marijuana use and testicular cancer

	OR	(95%CI)	p for heterogeneity
Ever use	1.19	(0.72-1.95)	0.033
Frequency			
Never	1.00		
<1 day or week	1.28	(0.51-3.22)	<0.001
≥1 day or week	1.56	(1.09-2.23)	0.640
Duration			
Never	1.00		
<10 years	1.31	(0.60-2.84)	0.008
≥10 years	1.50	(1.08-2.09)	0.812

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Table 5

Epidemiologic studies on marijuana use and childhood cancers

Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
Multicenter, US & Canada, 1980-1984 Robison et al. (31)	Childhood acute nonlympho-blastic leukemia	204 cases, identified in registry of Children's Cancer Study Group, diagnosed at <18 years of age, Response rate: 77.9%	204 subjects from random digit dialing, individually matched on date of birth, race, telephone area code and exchange Response rate: 78%	Telephone interviews of mothers & fathers of subjects, with structured questionnaire	Maternal use of mind-altering drugs during or in the year before the pregnancy Paternal use	11.0 (1.42-85.20) 1.47, p=0.32	• Adjusted for date of birth, race, residence, telephone area code • 9 of 11 cases had maternal marijuana only • The authors reported that adjustment for mother's age, education, tobacco use, alcohol did not result in reduction in risk or loss of statistical significance.
Multicenter, US, Canada & Australia, 1983-1993 Wen et al. (32)	Childhood leukemia	1,805 acute lymphoblastic leukemia cases, 528 acute myeloid leukemia, age ≤18 months, selected from registration files of the Children's Cancer Study Group	2,723 subjects from random digit dialing, individually matched on year of birth, telephone area code, & exchange number	Telephone interviews of mothers & fathers of subjects, with structured questionnaire	Ever marijuana use by father	1.5 (p<0.05)	• Adjusted for year of birth, telephone area code, exchange number D • Dose-response assessment not available.
Pennsylvania, New Jersey, Delaware, US, 1980-1986 Kujiten et al. (33)	Childhood astrocytoma	163 cases, identified through 8 hospital tumor registries, diagnosed at <15 years, Response rate: 80%	163 subjects from random digit dialing, individually matched on birth date, race, telephone exchange.	Telephone interviews of mothers & fathers of subjects, with structured questionnaire	Gestational marijuana exposure	2.8 (0.9-9.9)	• Adjusted for age, race, residence Dose-response relations not assessed. • Data on paternal use not presented.
Multicenter, US, 1982-1988	Childhood rhabdo-myosarcoma	322 cases, identified in the registry of the	322 subjects from random	Telephone interviews of mothers & fathers	Maternal use of marijuana	3.0 (1.4-6.5)	• Adjusted for age, sex, race,

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
Grufferman et al. (34)		Children's Cancer Study Group, diagnosed at 0-20 years of age Response rate: 79.8%	digit dialing, individually matched on age, sex, race.	of subjects, with structured questionnaire	Paternal use	2.0 (1.3-3.3)	birthmarks on child, bleeding/cramping during pregnancy, prematurity of child • Factors associated with rhabdo-myosarcoma in data were adjusted for.
Multicenter, US and Canada, 1989-1993, Trivers et al. (35)	Childhood acute myeloid leukemia	638 cases age <18 identified from the Children's Cancer Group. Response rate: 83 %	610 matched controls. Matched to the cases on age, and residential location. Using a random digit dialing (RDD) procedure. Response rate: 79%	Telephone interviews of mothers & fathers of subjects, with structured questionnaire	**Maternal** Never Ever **Paternal** Never Ever	 1.00 1.00 0.89 (0.66-1.19) 1.37 (1.02-1.83)	• Adjusted for age at the index child's birth, parental education, household income, alcohol consumption and cigarette smoking before, during and after pregnancy, maternal history of fetal loss prior to the index pregnancy, and birth order. • Maternal and paternal marijuana use in specific time periods did not support an association. • Frequency of marijuana use was not associated (data not presented in publication)
Multicenter, North America, 1992-1994, Bluhm et al. (36)	Childhood neuroblastoma	Mothers of 538 children with neuroblastomas identified through the Children's Cancer Group and Pediatric Oncology Group. Age: birth to 19 years old. Response rate: 73%	504 age-matched control identified by random-digit dialing. Response rate: 72%	Maternal interview by trained interviewers using a standardized questionnaire	**Maternal** None Any **Frequency in first trimester** <1 pipeful per day 1 or more pipefuls per day	 1 1.37 (0.77-2.49) 4.16 (1.52-14.61) 4.42 (1.09-29.58)	• Adjusted on household income, age at diagnosis, other drugs used • Maternal marijuana use in specific time periods did not support an association, except

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Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
					None	1	
					Any	1.37 (0.77-2.49)	
					Frequency in first trimester	4.16 (1.52-14.61)	
					<1 pipeful per day	4.42 (1.09-29.58)	
					1 or more pipefuls per day		

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Table 6

Epidemiologic studies on marijuana use and other cancers

Study location, period, author, reference	Cancer site	Characteristics of cases	Characteristic of controls or cohort	Exposure assessment	Exposure categories	RR or OR (95% CI)	Adjustment for potential confounders and other notes
California, US 1979-1999 Sidney et al. (37)	All sites, and selected sites	1,421 cancers	Cohort of 64,855 Kaiser Permanente subscribers who received health checkups, aged 15-49 years, follow up through cancer registry and death records	Self-administered questionnaires	**Ever & current use**	**Men, non-tobacco smokers**	• Adjusted for age, race, education, and alcohol use • Estimates shown are for non-tobacco smokers • Definition of ever use was ≥6 times use over lifetime. • Dose-response relations for duration (years) and frequency (times/week or month) were not observed.
					All sites	0.8 (0.5-1.2)	
					Tobacco-related cancer[1]	0.8 (0.2-2.9)	
					Colorectal cancer	0.7 (0.2-2.1)	
					Melanoma	0.5 (0.2-1.3)	
					Prostate cancer	3.1 (1.0-9.5)	
						Women, non-tobacco smokers	
					All sites	1.1 (0.8-1.3)	
					Tobacco-related cancer [1]	---	
					Colorectal cancer	0.3 (0.0-2.5)	
					Melanoma	1.0 (0.4-2.3)	
					Breast cancer	0.8 (0.5-1.3)	
					Cervical cancer	1.4 (1.0-2.1)	
Washington, US & Canada, 1978-1985 Daling et al. (38)	Anal	148 cases identified through the cancer registry, <70 years of age, of all histologic types, including in situ and invasive lesions. Interviews conducted for 71.2% of eligible cases identified.	166 colon cancer cases identified through the cancer registry, individually matched on age, sex, year of diagnosis and geographic area. Interviews available for 67.3% of	Face-to-face interviews with questionnaire	**Ever use**	0.8 (0.2-4.0)	• Adjusted for age, residence, cigarette smoking (never, formerly, currently), geographic area • Dose-response relations not assessed.

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			eligible subjects. eligible subjects.				
Washington, US & Canada, 1979-1990 Maden et al. (39)	Penile	110 cases, identified through the cancer registry, ≤74 years old, including squamous carcinoma 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** **Frequency** Never ≤50 times >50 times	1.5 (0.7-2.3) 1.0 1.7 (0.8-3.9) 1.0 (0.3-3.6)	• Adjusted for age, alcohol consumption, cigarette smoking (never, former, current), no of sexual partners • Adjusted for age, alcohol consumption, no of sexual partners
California, US, 1989-1992 Nelson et al. (40)	Non-Hodgkin's lymphoma	378 cases identified through the cancer registry, 18-75 years old, residents of Los Angeles, English/ Spanish speaker, HIV seronegative. Overall % interviewed of NHL cases ∼36.7%.	378 subjects individually matched on age, sex, race/ ethnicity, neighborhood of residence, and interview language.	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)	• Adjusted for age, sex, race/ ethnicity, neighborhood of residence, and interview language.
California, US, 1988-1995 Holly et al. (41)	Non-Hodgkin's lymphoma	1,281 cases identified through the Northern California cancer registry, ages 21-74, Overall % interviewed of NHL cases ∼56.7 %.	2,095 subjects from random digit dialing, frequency matched on age, sex, residence. 78% of eligible controls completed interviews.	Face-to-face interviews with structured questionnaire	**No of times used** Never <40 40-999 ≥1000 **No of times used** Never <40 40-999 ≥1000	**Women** 1.00 0.56 (0.40-0.77) 0.58 (0.35-0.97) 0.71 (0.34-1.5) **Men** 1.00 0.64 (0.49-0.84) 0.52 (0.37-0.73) 0.49 (0.31-0.78)	• Adjusted for age • Estimates adjusted for age, education, sexual partners, vaccinations, medications, and other factors were significant for men, and for men and women combined
California, US	Malignant primary glioma	69 cases of glioma	Cohort of 105,005	Self-administered questionnaires	Ever use	1.9 (0.9-4.0)	• Adjusted for smoking

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1977-1999 Efird et al. (42)			Kaiser Permanente subscribers who received health checkup, aged ≥25 years, follow up through cancer registry		**Frequency** <1/month ≥1/month Unknown P for trend	 0.6 (0.1-4.4) 2.8 (1.3-6.2) 1.3 (0.8-2.2) 0.08	status (cigarettes, cigars, pipes), sex, race, alcohol, education, coffee intake
US, Chacko et al. (43)	Transitional cell carcinoma of bladder	52 cases age<60 with transitional cell carcinoma of bladder from hospitals. Response rate=88.5%	168 age-matched controls Response rate=69.2%	A self -administered questionnaire	**Marijuana** Ever smoked Current smoke Joint-years>40	 3.4 1.9 3.5	• Adjusted for agent orange exposure, radiation exposure, and dye exposure • Not adjusted for tobacco smoking • Confidence intervals were not reported in the publication, thoug the p for trend for increasing joint-years of marijuana was reported (p=0.01)
Chicago, IL, Baltimore, MD, Washington, DC, Pittsburgh, PA, and Los Angeles, CA, 1984-2003, Chao et al. (44)	Kaposi's Sarcoma	Cohort of 1,335 white men who have sex with men who were HIV positive or seroconverted before 2003, 401 Kaposi's sarcoma casesFollow-up rate: N/A		Interviewer-administered questionnaire	**Ever Marijuana use** **Frequency** None Monthly or less Weekly or more	1.25 (0.87-1.79) 1.00 1.15 (0.77-1.70) 1.52 (0.99-2.32)	• Adjusted for age, education, study center, alcohol use, tobacco smoking, number of male sexual partners, lifetime number of sexual partners, receptive anal intercourse and condom

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							use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro use, antiretro • Five year lag was applied for exposure • Duration of use was not available.
					Frequency		
					None	1.00	
					Monthly or less	1.15 (0.77-1.70)	
					Weekly or more	1.52 (0.99-2.32)	