Abstract
Introduction: Cannabis smoke contains carcinogens similar to tobacco, in addition to compounds with antitumor activity. Cannabis use reduces the risk of obesity and cannabinoids inhibit chronic inflammation, known causes of cancer. The net effect of Cannabis use on cancer risk is not known.

Objective: To examine the association between Cannabis use and cancer risk in the United States.

Methods: Identify and analyze published data on cancer risk in Cannabis users.

Results: A total of 55 data points, consisting of risk ratios of cancer in Cannabis users and nonusers, were identified from 34 studies. Of these, 5 did not contain data essential for inclusion in the meta-analysis. The remaining data showed a nonsignificant trend to an association with reduced risk (relative risk [RR] = 0.90, p > 0.06, N = 50) although heterogeneity is high (I² = 72.4%). Removal of data with high risk of selection bias (defined as those from North Africa and those that failed to adjust for tobacco) and data with high risk of performance bias (defined as those with fewer than 20 cases or controls among Cannabis users) resulted in an RR < 1.0 (RR = 0.86, p < 0.017, N = 24) and large effect size (Hedges g = 0.66), but did not decrease heterogeneity (I² = 74.9%). Of all cancer sites, only testicular cancer showed an RR value > 1, although this was not significant and had a negligible effect size (RR = 1.12, p = 0.3, Hedges g = 0.02). Following removal of testicular cancers the remaining data showed a decrease in risk (RR = 0.87, p < 0.025, N = 41). Cancers of the head and neck showed a negative association with cancer risk (RR = 0.83, p < 0.05), with a large effect size (Hedges g = 0.55), but high heterogeneity (I² = 79.2%). RR did not reach statistical significance in the remaining cancer site categories (lung, testicular, obesity-associated, other). The data are consistent with a negative association between Cannabis use and nontesticular cancer, but there is low confidence in this result due to high heterogeneity and a paucity of data for many cancer types.

Keywords: cancer risk; Cannabis; marijuana; meta-analysis; scoping review

Introduction
The impact of Cannabis use on cancer risk is of considerable interest. Cancer is a leading cause of death in the United States and around the world. In the United States alone, > 1.7 million diagnoses and 607,000 deaths are projected from cancer in 2019 (Ref.1) and cancer deaths were responsible for $94.4 billion in lost earnings in 2015 (Ref.2). The real costs are much higher than this, however, because even cancer patients who will make a full recovery face lengthy, expensive, and stressful treatment regimens.

The pharmacological activity of Cannabis is primarily due to the presence of phytocannabinoids, a group of lipid-soluble chemicals. These act by mimicking the cannabinoids produced by the endocannabinoid system (ECs), an important physiological signaling system. The cellular and physiological actions of cannabinoids arise from interaction with a variety of widely distributed receptor types, of which cannabinoid receptor type 1 (CB₁) and cannabinoid receptor type 2 have received the greatest attention.3
The ECs appears to be dysregulated by the modern American diet. In particular, emerging evidence suggests that an elevated dietary ratio of omega-6/omega-3 fatty acids may lead to excess production of the endocannabinoid signals N-arachidonoylthanolamide and 2-arachidonoylglycerol, leading to overstimulation of CB1 and contributing in turn to the emerging epidemic of obesity, metabolic syndrome, and associated diseases.\(^4\text{-}\text{6}\) CB1 is also stimulated by the exogenous cannabinoid Δ9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid in \textit{Cannabis}.

Paradoxically, however, acute stimulation of CB1 is associated with weight gain and antagonists of CB1 increase metabolic rates,\(^4\text{-}\text{6}\) yet \textit{Cannabis} users show decreased body mass index (BMI) relative to nonusers.\(^4\) This may be due to downregulation of CB1 in \textit{Cannabis} users, which would desensitize the ECs and counteract the impact of the modern American diet on weight gain.\(^4\)

\textit{Cannabis} has both protumor and antitumor actions. Which effect predominates in \textit{Cannabis} users? \textit{Cannabis} is emerging as a palliative option for cancer patients.\(^7\text{-}\text{14}\)

Medical \textit{Cannabis} use reduces opioid use,\(^8\text{-}\text{11}\) counteracting multiple side effects of chemotherapy, improves mood and outlook, and provides relief from insomnia.\(^12\text{-}\text{14}\) If \textit{Cannabis} causes cancer, these therapeutic benefits might be offset in cancer patients by stimulation of existing tumors or creation of new neoplasms. However, if \textit{Cannabis} reduces cancer risk, the case for inclusion of \textit{Cannabis} in therapeutic cancer care strategies is augmented. In addition, if moderate, adult \textit{Cannabis} use is found to reduce risk of cancer, a leading cause of death, this information must be included in estimates of its impact on public health.

\textbf{Tumorigenic activity of \textit{Cannabis}}

\textit{Cannabis} has several tumorigenic properties, manifested when smoked. \textit{Cannabis} smoke contains carcinogens similar to those in tobacco smoke, including tar and polycyclic aromatic hydrocarbons, and these may be at higher concentration than in tobacco smoke.\(^15\text{,}16\) Users who smoke \textit{Cannabis} heavily have histological changes, including inflammation, in the lungs and airways resembling those prestaging the initiation of tobacco-related lung cancer.\(^17\) Sharing of joints or pipes is hypothesized to increase risk of human papilloma virus exposure, a significant cause of oral and other cancers.\(^18\) Furthermore, although cannabinoids usually inhibit cancer cells \textit{in vitro} and in mouse models,\(^3\) they stimulate growth of some cancer cell lines in laboratory studies.\(^19\)

\textbf{Antitumor activity of \textit{Cannabis}}

Actions that reduce cancer risk include reduced risk of obesity and diabetes mellitus (DM), and inhibition of inflammation by cannabinoids. In addition, in laboratory studies, cannabinoids and other compounds in \textit{Cannabis} directly inhibit cancer initiation, growth, and spread at the cellular level.

\textbf{Decreased obesity rates in \textit{Cannabis} users.} Obesity increases the risk of cancer.\(^20\text{-}\text{26}\) Cancers of the breast, colon, and rectum, prostate, esophagus, stomach (cardia), pancreas, uterine corpus, gallbladder, kidney, liver, ovary, and thyroid, as well as multiple myeloma, are positively associated with obesity.\(^20\text{-}\text{26}\) In the United States, between 1982 and 2000, obesity caused about 20% and 14% of cancer deaths in women and men, respectively.\(^20\)

Note that obesity rates are substantially higher today than in 2000, and rates of obesity-related cancers are increasing even in young people as the obesity rate continues to rise.\(^23\)

The percentage of cancer deaths attributable to obesity are therefore likely to be much higher today than they were in 2003, when the study by Calle et al. was published,\(^20\) even as tobacco use and lung cancer are declining. However, using the numbers from Calle et al.,\(^20\) a minimum of 85,000 to 120,000 of the 607,000 cancer deaths projected for 2019 (Ref.\(^1\)) are caused by obesity. Similarly, an estimated 3.6% of all new cancer cases worldwide are caused by excess body fat.\(^26\)

A recent review determined that \textit{Cannabis} use is associated with reduced obesity risk (mean risk ratio = 0.68) and BMI (average decrease in BMI relative to nonusers = 6%).\(^4\) Like weight loss following bariatric surgery,\(^27\) reduced obesity rates in response to \textit{Cannabis} use may decrease cancer risk. \textit{Cannabis} use protects against nonalcoholic fatty liver disease,\(^28\) a disorder that is strongly associated with obesity and is an independent predictor of gastric and liver cancer, cancer types strongly associated with obesity.\(^24\text{,}25\) \textit{Cannabis} users may thus have lower risk of obesity-associated cancer types simply due to decreased risk of obesity.

\textbf{Decreased inflammation.} Chronic inflammation is associated strongly both with obesity and with the initiation and progression of cancer.\(^27\text{-}\text{30}\) A decrease in BMI of 7%, similar in magnitude to the observed 6% decrease in BMI associated with \textit{Cannabis} use,\(^4\) decreases proinflammatory and increases anti-inflammatory gene expression in visceral adipose tissue.\(^31\) Cytokines involved in inflammation play a significant role in
promoting cancer, and therefore, drugs such as nonsteroidal anti-inflammatory drugs decrease cancer risk.32 A number of cannabinoids have anti-inflammatory effects in laboratory studies, and cannabinoids are therefore of interest for development as a therapy option for chronic inflammation, currently an unmet medical need.33 Thus, Cannabis use may directly inhibit inflammation at the cellular level, and in addition, indirectly reduces inflammation by decreasing BMI and risk of obesity. Both actions should decrease cancer risk. This effect would be offset if inflammatory responses are desensitized with chronic use.4

Improved insulin sensitivity and decreased risk of DM. Cannabis use is associated with reduced risk of DM, reduced fasting insulin levels, and reduced insulin resistance.34–38 In contrast, DM and elevated insulin or C-peptide levels are associated with greater cancer risk, and faster growth and aggressiveness of colorectal, pancreatic, liver, postmenopausal breast, and endometrial cancers, and thus increased mortality from these cancers.39

Probiotic actions of cannabinoids on the gut microbiome. The gut microbial flora interacts closely with the EcS and plays an important role in metabolism.40 Changes in the intestinal microbial flora, including a shift in the ratio of Firmicutes:Bacteroidetes, are correlated with obesity. These changes are also associated with the initiation and progression of systemic inflammation, and increased risk of colorectal cancer.41 Cannabinoids oppose this gut dysbiosis.41 In mice fed a high-fat diet, chronic THC administration not only prevents obesity, but also prevents changes in the gut microbial flora from one characteristic of a lean phenotype to one associated with obesity and increased risk of colorectal cancer.41

Direct antitumor properties of Cannabis. Multiple chemicals in Cannabis, including psychoactive and nonpsychoactive cannabinoids as well as flavonoids, possess antitumor activity.42–45 Cannabinoids inhibit tumor initiation, metastasis, vascular adhesiveness, tissue invasiveness, and angiogenesis, while selectively stimulating apoptosis of cancer cells.3,42–44,46–56 They thus, by multiple mechanisms, inhibit all stages of cancer initiation, development, growth, and spread. As a result, in laboratory studies and animal models, cannabinoids destroy tumors while leaving surrounding cells unharmed.42–44 In laboratory studies, cannabinoids in-

Hypotheses

The impact of Cannabis use on cancer risk will depend on the relative magnitudes of the carcinogenic and antitumor effects, leading to three hypotheses:

1. the carcinogenic effects predominate, leading to greater cancer risk in users;
2. the carcinogenic and antitumor effects cancel each other leading to no net impact (null hypothesis);
3. the antitumor effects predominate, leading to reduced cancer risk in users.

Adding complexity, the balance between the opposing effects of carcinogens and antitumor compounds may differ among cancer types, and different tissues may be exposed to different concentration ratios of carcinogens and cannabinoids. Tissues of the mouth, pharynx, larynx, and lungs are directly exposed to carcinogens from smoke while other tissues are not. Furthermore, some cell types may be more sensitive to the carcinogenic or antitumor actions than others, and effects of Cannabis use on risk factors, such as obesity or inflammation, also influence the balance between these opposing actions.

Methods

Review of the literature on the effects of Cannabis use on cancer rates

Information sources. PubMed, MEDLINE, Web of Science, and Google scholar were screened for articles presenting data on risk ratios of cancer in Cannabis users and nonusers.

Search strategy. PubMed, MEDLINE, and Web of Science were searched using “(Cannabis or marijuana) AND (cancer) NOT (therapeutic or palliative), most recently in August 2019. Google scholar was also searched for references using the terms “Cannabis and cancer” and “Marijuana and cancer.” Titles were evaluated for relevance, and case studies and those addressing palliative or therapeutic care were rejected. Those potentially reporting risk ratios were selected for further analysis and data extraction. Review and data source articles were also examined for references.

Summary measures. The principal summary measure is the risk ratio of cancer in Cannabis users, relative to
### Table 1. Studies Identified in Literature Searches

| Reference                  | Study population                  | Study type    | Cancer type        | Adjustments                                                                 | Data used                                      |
|----------------------------|-----------------------------------|---------------|--------------------|------------------------------------------------------------------------------|-----------------------------------------------|
| Aldington et al.           | New Zealand                       | Case–control  | Head and neck      | Age, sex, ethnicity alcohol consumption, income, and pack-years of cigarette smoking | Ever vs. never user                           |
| Aldington et al.           | New Zealand                       | Case–control  | Lung               | Sociodemographic factors, tobacco smoking status, and pack-years              | Nonsmoker vs. smoker                         |
| Berthiller et al.          | North Africa                      | Case–control  | Lung               | Age, occupational exposure, country (in pooled analysis), and lifetime pack-years of tobacco smoking | Ever vs. never user                           |
| Berthiller et al.          | North and South America, Havana    | Case–control  | Oral, pharyngeal, laryngeal | Age, sex, race, education, family history of cancer, HPV-16, smoking, and average drinks of alcohol/week | Ever vs. never user                           |
| Callaghan et al.           | Sweden                            | Cohort        | Lung               | Age, race, education, alcohol use, and tobacco cigarette                      | Ever vs. never user                           |
| Callaghan et al.           | Sweden                            | Cohort        | Testicular         | Age, cryptorchidism, paternal history of testicular cancer, frequency of tobacco smoking, alcohol consumption | Ever vs. never user                           |
| Chacko et al.              | United States; VA hospitals        | Case–control  | Transitional cell of bladder | No adjustments                                                               | Ever vs. never user                           |
| Chao et al.                | United States                     | Cohort        | Kaposi’s sarcoma   | Age, education, study center, tobacco smoking, alcohol use, number of male sexual partners since last visit, lifetime sexual partners at time of enrollment, receptive anal intercourse and condom use, history of STIs, antiviral therapy, and CD4 counts | HIV, HHV-8 coinfected, weekly or more frequent use, recent use |
| Daling et al.              | Washington State, United States, B.C. Canada | Case–control  | Anal               | Age, residence, and cigarette smoking (never, former, or current)              | Ever vs. never user                           |
| Daling et al.              | Washington State, United States    | Case–control  | Testicular         | Age at reference, reference year, alcohol use, current smoking, and history of cryptorchidism | Ever vs. never user                           |
| Efird et al.               | California, United States          | Cohort        | Gloma              | Cigars, pipes, sex, race, alcohol, education, and coffee                       | Ever vs. never user                           |
| Feng et al.                | North Africa                      | Case–control  | Nasopharyngeal     | Age, SES measures, associated dietary factors, and cigarettes smoked per day | Ever vs. never user                           |
| Gillison et al.            | United States Johns Hopkins        | Case–control  | Head and neck squamous cell | Race; tobacco and alcohol use; number of teeth lost; frequency of tooth brushing; and number of oral sex partners | HPV-16 negative; current users vs. nonusers |
| Han et al.                 | United States                      | Case–control  | Lung               | Age, gender, race/ethnicity, education, health insurance, family income, tobacco use, duration of alcohol use, durations of nonmedical use of pain relievers, tranquilizers, stimulants, and sedatives | Never vs. < 1 year, 2–10 years, 11+ years. No ever vs. never provided. No case or control numbers provided. |
| Hashibe et al.             | United States California (Los Angeles) | Case–control  | Oral, pharyngeal, laryngeal, esophageal | Age, sex, education, alcohol, cigarette                                       | Weighted average across user groups, >0–60+ joint-years vs. nonuser |
| Holly et al.               | United States California           | Case–control  | Non-Hodgkins lymphoma | Age                                                                            | Used Cannabis > 1000 × (highest usage rate) |
| Hsairi et al.              | North Africa                       | Case–control  | Bronchial           | Age, sex, and cigarettes/day Cocaine use, amyl nitrite, cryptorchidism, religiosity, education | User vs. nonuser Ever vs. never user |
| Lacson et al.              | United States California           | Case–control  | Testicular         | Age and presence of diabetes in diabetes, change in BMI during cancer treatment, and presence of diabetes during cancer treatment | Ever vs. never user |
nonusers, in the form of adjusted odds ratio (AOR), relative risk (RR), and adjusted hazard ratio (AHR).

Selection of data to use in further analyses
Studies considered for this review included case–control and cohort studies that present risk ratio data (AORs, RR, or AHR), comparing rates of cancer in Cannabis users and nonusers.

Many studies presented multiple values for risk ratios for a single cancer type or site, including values for different user groups (duration of use, frequency of use, quantity of use, etc.) and adjustment for different confounders. The data selected for use in the analysis consisted of ever versus never use, current versus never use, or ever versus nonhabitual use categories, as available (Table 1).
The data from the most fully adjusted model were selected from each study. One study failed to provide a single value for overall user risk, but rather assigned data to distinct groups based on cumulative exposure (i.e., 0 to 1, 1 to <10, 10 to <30, 30 to <60, and ≥60 joint years). For these data, to determine the effects of average use, the values for each usage group were weighted by the number of cases in that group, then the weighted average across user groups was determined and used to provide a summary AOR. The references identified, study population, study type (case–control or cohort), cancer type, adjustments, and comparison type (i.e., ever use vs. never use, etc.) from each reference are summarized in Table 1.

Conversion of AOR data to RR data
Risk ratios from the various studies were reported as AOR, RR, or AHR. Odds ratios and RR are similar in value at risk ratios near one, but diverge as risk ratios diverge from one and are therefore not directly comparable. To provide a single measurement unit for analysis, AOR data were converted to RR following Zhang and Kai. HR data are considered equivalent to RR and were not converted.

Statistical analysis
Statistical analysis of the data was performed with the software program JASP using a Dersimonian–Laird random effects meta-analysis model.

Effect size was calculated as:

\[
\text{Effect size (ES)} = \ln \left( \frac{\text{userpos}}{\text{userneg}} \right) - \ln \left( \frac{\text{nonuserpos}}{\text{nonuserneg}} \right)
\]

Standard error was calculated as:

\[
\text{Standard error} = \sqrt{\left( \frac{1}{\text{userpos}} + \frac{1}{\text{userneg}} + \frac{1}{\text{nonuserpos}} + \frac{1}{\text{nonuserneg}} \right)}
\]

where userpos and userneg are number of cancer cases and cancer free in Cannabis users, and nonuserpos and nonuserneg are numbers of cancer cases and cancer free in nonusers.

Examination of heterogeneity in the data
Heterogeneity was examined by selectively removing specific blocks of data, including data with high risk of selection bias, high risk of performance bias, and data for specific cancer sites, and by examining data for each category of cancer type or site independently.

Examination of risk of publication bias
Publication bias was investigated by analyzing funnel plot asymmetry using rank correlation in JASP.

Examination of impact of risk of selection and performance bias on heterogeneity
The results of the literature search consist of a series of articles that present risk ratios for cancer in Cannabis users. These were screened to identify and remove data with high risk of selection and performance bias, as defined below.

Removal of data with high risk of selection bias. The goal of the study was to examine the data on the risk of cancer due to Cannabis use in the United States. Therefore, data that did not fit this population was determined to be at high risk of selection bias. In the context of this study, high risk of selection bias was defined as failure to adequately adjust for tobacco use. Elimination of studies with high risk of selection bias thus involved eliminating studies that failed to adjust for tobacco use, or those that compared user and nonuser populations that universally or predominantly use tobacco, due to the inability to adequately adjust for tobacco use in this scenario.

Data collected in North Africa were determined to be at high risk of selection bias, and were also removed, because North African Cannabis users consume Cannabis in the form of kiff or hashish, and mix Cannabis with tobacco. These delivery methods are rare in the United States and interfere with adjustment for tobacco as a confounding factor.

Removal of data with high risk of performance bias. Many of the measures used to evaluate risk of performance bias in meta-analyses are not applicable in the current data set, as these data arose from comparison of cancer rates among study populations rather than documentation of changes in response to treatment interventions. Sample size was therefore selected as the most obvious measure of the potential for performance bias. The impact of removal of small sample size data, reporting measures of risk based on 20 or fewer Cannabis-using cases or controls, was examined. For studies reporting risk ratios for
multiple cancer sites, data from each individual cancer site were assessed for number of cases and controls among Cannabis users, and those with fewer than 20 cases or controls were eliminated, while data for sites with more than 20 cases and controls were retained.

The Grubbs test\(^{93}\) was used to test, for outlier status, the highest and lowest values remaining in the data after removal of data with high risk of selection bias. No outliers were detected.

Examination of data from specific cancer sites
The data were separated into the following five cancer sites: (1) cancers of the head and neck (head and neck squamous cell carcinoma, laryngeal, nasal, nasopharyngeal, oral, pharyngeal, and sinonasal), (2) lung, (3) testicular, (4) obesity related (esophageal, colorectal, breast, prostate, cervical), and (5) other types (melanoma, anal, penile, bladder, glioma, and non-Hodgkin’s lymphoma, types that did not fit into the other categories). Each of these subsets was analyzed independently.

Analysis of data
Some studies reported risk ratios for multiple cancer sites (i.e., oral, pharyngeal, laryngeal, etc.). These were considered as independent data points in the analysis. AOR data were converted to RR before statistical analysis.\(^{91}\) Data were imported into the JASP meta-analysis software in the form of log RR. Means and confidence intervals (CIs) were obtained as log RR values from the meta-analysis software, then converted back to RR. Statistically significant differences in risk were accepted when 95% CIs excluded 1.0, or \(p < 0.05\) in the output of the meta-analysis software.

Heterogeneity was quantified as \(I^2\) (Ref.\(^{94}\)). Effect size was calculated as Hedges \(g\), with correction of bias for small samples for cancer sites with low \(N\) following Durlak.\(^{95}\)

Effect size was calculated as Hedges \(g\), defined as:

\[
Hedges\ g = \frac{mean\ 1 - mean\ 2}{pooled\ SD}
\]

Mean 1 is the mean log of RR data (logRR) of users, and mean 2 is 0 (logRR of nonusers, with RR defined as 1.0). Correction for small sample size was performed as:

\[
Hedges\ g\ corr = \left(1 - \frac{3}{N}\right) * Hedges\ g
\]

Exposure dependence
Eight articles provided data amenable to analysis of exposure-dependent effects.\(^{57\text{-}85}\) These data were expressed in the original articles in a number of distinct units (joint-years, times/week, ounces/week \(\times\) years, times, quartiles). To analyze exposure dependence, these units were assigned to low, intermediate, intermediate plus, and high-exposure categories, as shown in Table 4. The mean and 95% CIs of log(RR) were determined for each exposure category, then the data were converted back to RR.

Results
The results of the PubMed, MEDLINE, Web of Science, and Google Scholar searches are presented in Figure 1. The search yielded a total of 34 studies reporting risk ratios,\(^{57\text{-}90}\) and these studies provided 55 risk ratio data points from a variety of cancer sites (Table 1). Five data points did not provide numbers of user and nonuser cancer-positive and cancer-negative patients and could not be used in the JASP meta-analysis.

The remaining 50 data points could be analyzed in the meta-analysis (Fig. 2A). These included data from the head and neck (\(N = 18\)), esophageal cancer (\(N = 1\)), lung (\(N = 7\)), melanoma (a single study reported risk separately for men and women; these were treated as independent data points; \(N = 2\)), prostate (\(N = 1\)), colorectal cancer (\(N = 2\)), testicular cancer (\(N = 8\)), anal cancer (a single study reported risk separately for men and women; these were treated as independent data points, \(N = 2\)), penis (\(N = 1\)), bladder cancer (\(N = 2\)), glioma (\(N = 1\)), breast cancer (\(N = 1\)), non-Hodgkin’s lymphoma (\(N = 3\)), and cervical cancer (\(N = 1\)).

Relative risk
Analysis of the entire data set indicated a trend toward an association with reduced cancer risk in Cannabis users, but this trend was not significant (meta-analytic RR = 0.90, 95% CI = 0.81–1.01, \(p = 0.065\), \(df = 49\); Table 2). No significant evidence of publication bias was apparent (funnel plot asymmetry \(p = 0.725\)). Following removal of data for high risk of selection and performance bias (as defined), the remaining data support an association with reduced risk of cancer in Cannabis users (meta-analytic RR = 0.86, 95% CI = 0.76–0.97, \(p = 0.017\), \(df = 23\); Table 2), with no significant evidence of publication bias (Funnel plot asymmetry \(p = 0.66\); Fig. 2B). Heterogeneity remained high, however (\(I^2 = 74.9\)) after removing these data (Table 2).
The entire data set was divided into the following categories of cancer types: (1) head and neck cancers (airways of the head and neck), (2) lung, (3) testes, (4) obesity-related, and (5) other types; these categories were analyzed separately.

Head and neck cancers showed a significant negative association between Cannabis use and cancer risk (meta-analytic RR = 0.83, 95% CI = 0.72–0.97, N = 18, p < 0.05; Table 2; Fig. 3). Analyses of lung cancer data are shown in Figure 4, testicular cancer data in Figure 5, cancer types associated with obesity in Figure 6, and cancer types other than head and neck, lung, testicular, and obesity-related in Figure 7. The remaining categories showed RR values that were not statistically different from 1. Of the categories, only testicular cancer showed RR > 1.0, although this was not significant (meta-analytic RR = 1.12, 95% CI = 0.9–1.4, N = 9, p = 0.3; Table 3). Elimination of testicular cancers from the data set resulted in a significant decrease in RR in the remaining data (meta-analytic RR = 0.87, 95% CI = 0.78–0.98, N = 41, p < 0.025; Table 4). None of the other cancer site categories resulted in RR statistically different from one when removed (Table 4).

Analysis of heterogeneity
There was high heterogeneity among the data. The initial data set (including all data) yielded a residual heterogeneity of $Q = 177.3$ ($p < 0.001$), $I^2 = 72.4\%$, $df = 49$ (Table 2; Fig. 2). Heterogeneity remained high after removal of studies with high risk of selection and performance bias: $Q = 91.8$ ($p < 0.001$), $I^2 = 74.9\%$, $df = 23$ (Table 2). Heterogeneity was explored further.
by analyzing each category of cancer types separately, and by determining the impact of removing each category of cancer types on measures of heterogeneity. Among the five categories of cancer types, heterogeneity was high in head and neck cancers and “other” cancer types, and much lower within lung, testicular, and obesity-related cancers (Table 3). Removal of any one category of cancer types failed to substantially reduce heterogeneity (Table 4).

Effect size
Effect size for the entire data set was determined to be small (Hedges g corrected for bias = 0.23 (Ref. 95).

by analyzing each category of cancer types separately, and by determining the impact of removing each category of cancer types on measures of heterogeneity. Among the five categories of cancer types, heterogeneity was high in head and neck cancers and “other” cancer types, and much lower within lung, testicular, and obesity-related cancers (Table 3). Removal of any one category of cancer types failed to substantially reduce heterogeneity (Table 4).

Effect size
Effect size for the entire data set was determined to be small (Hedges g corrected for bias = 0.23 (Ref. 95).
Removal of data with high risk of selection and performance bias resulted in an increase in Hedges $g$ to 0.66, an effect size between medium and large. Following separation of the data into categories, effect size of cancers of the head and neck was moderate (head and neck: Hedges $g$ corrected for bias = 0.55) and of obesity-related cancers was between medium and large (Hedges $g$ = 0.69). In contrast, effect size was small or negligible for lung, testicular, and other cancer types (0.23, 0.02, and 0.1, respectively; Table 3).

Exposure level dependence
Preliminary analysis of exposure-dependent data suggests that all exposure categories are associated with reduced cancer risk (Fig. 8). Column effects (exposure) and row effects (study) were both statistically significant (2—way analysis of variance, column effects: $F$-value = 3.19, $p < 0.025$; row effects: $F$-value = 3.096, $p < 0.006$) suggesting differences in response to exposure as well as to study/cancer type. All exposure categories show significantly reduced risk relative to the no-use category (95% CIs exclude 1.0; Fig. 8). There are no significant differences among exposure levels.

### Table 2. Meta-analysis of the Entire Data Set, and Effects of Removing Data with High Risk of Selection and/or Performance Bias

| Data set                        | RR  | 95% CI   | $p$     | $Q$ (p)   | $I^2$ | $t^2$ | df | $p$ Funnel plot asym | Hedges g |
|--------------------------------|-----|---------|---------|-----------|-------|-------|----|-----------------------|----------|
| All data                       | 0.90| 0.81–1.01| 0.065   | 177.3 (<0.001) | 72.4  | 0.084 | 49 | =0.725                | 0.23     |
| Removed selection              | 0.97| 0.71–1.31| 0.82    | 32.77 (<0.001) | 75.6  | 0.141 | 8  | =0.61                 |          |
| Remaining selection            | 0.90| 0.81–1.01| 0.066   | 135.4 (<0.001) | 69.7  | 0.073 | 41 | =0.88                 |          |
| Removed Performance            | 1.0 | 0.76–1.34| 0.99    | 41.72 (<0.001) | 61.65 | 0.210 | 16 | >0.48                 |          |
| Remaining performance          | 0.91| 0.81–1.01| 0.067   | 142.4 (<0.001) | 77.5  | 0.079 | 32 | >0.28                 |          |
| Elim. selection, performance   | 0.86| 0.76–0.97| 0.017   | 91.8 (<0.001)  | 74.9  | 0.060 | 23 | >0.60                 | 0.66     |

Data are analyzed with a Dersimonian–Laird model in the statistical software program JASP. Data in italics show RR significantly different from 1.0. CI, confidence interval; JASP; RR, relative risk.
categories once the no-use category was removed \((p > 0.9)\) suggesting that low and high exposures have similar impact on cancer risk. Most of these data are from cancers of the head and neck, and the risk of selection bias in these data is therefore very high.

**Conclusions**

The hypothesis that *Cannabis* use increases cancer risk is not supported by the available data. The data instead show a trend toward a negative association between *Cannabis* use and cancer risk (all data:

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**FIG. 3.** Analysis of head and neck cancer data. (A) Forest plot. (B) Funnel plot. Data are plotted and analyzed as logRR. Corresponding meta-analytic summary RR value = 0.83 (95% CI = 0.72–0.99; Table 4). Analyzed with Dersimonian–Laird model.
meta-analytic RR = 0.90, \( p = 0.065 \), \( N = 50 \)). This trend reaches statistical significance upon removal of data determined to be at high risk of selection and performance bias (meta-analytic RR of remaining data = 0.86, \( p < 0.02 \)), or removal of data from testicular cancers (meta-analytic RR of remaining data = 0.87, \( p < 0.025 \)).

Of the five categories of cancer sites, only one, testicular cancer, showed an RR value > 1, (meta-analytic RR = 1.12), although the data did not reach statistical
FIG. 5. Analysis of testicular cancer data. (A) Forest plot. (B) Funnel plot. Data are plotted and analyzed as logRR. Corresponding meta-analytic summary RR value = 1.12 (95% CI = 0.9–1.40; Table 4). Analyzed with Dersimonian–Laird model.
FIG. 6. Analysis of cancer types associated with obesity. (A) Forest plot. (B) Funnel plot. Data are plotted and analyzed as logRR. Corresponding meta-analytic summary RR value $= 0.89$ (95% CI $= 0.73–1.09$; Table 4). Analyzed with Dersimonian–Laird model.
FIG. 7. Analysis of cancer types other than head and neck, lung, testicular, and obesity-associated cancers. (A) Forest plot. (B) Funnel plot. Data are plotted and analyzed as logRR. Corresponding meta-analytic summary RR value = 0.91 (95% CI = 0.69–1.20; Table 4). Analyzed with Dersimonian–Laird model.
The current analysis suggests an association of *Cannabis* use with a substantial decrease in risk of nontesticular cancers, with moderate effect size, and a nonsignificant increase in risk of testicular cancer, with negligible effect size. This suggests that *Cannabis* use may substantially decrease the death rate from cancer in the United States. However, the available data provide little confidence in this conclusion. There appear to be different responses among cancer types, and there are no data, or few/poor data, available for many cancer types.

There is high heterogeneity among studies that is not explained by chance, and no studies estimate the RR of all cancer types in *Cannabis* users relative to nonusers. Cancers of the head and neck, with the lowest metaanalytic RR of any cancer type, are over-represented in the data, and cancers associated with obesity are under-represented. Furthermore, the data used are epidemiological, rather than experimental, and thus can show association but not causation. It is therefore necessary to exercise caution in interpreting these data. Nevertheless, data suggest that *Cannabis* use may decrease the risk of cancer in the United States.

Decreased cancer risk in *Cannabis* users should not be surprising, as *Cannabis* and cannabinoids decrease obesity, inhibit chronic inflammation, reduce fasting insulin levels and insulin sensitivity, and have direct antitumor actions. Furthermore, the airways and bladder would be exposed to the highest levels of carcinogens from *Cannabis* smoke, yet risk of cancers of the oral, pharyngeal and laryngeal regions, and the bladder are significantly decreased in *Cannabis* users (current

### Table 3. Examination of Individual Categories of Cancer Types

| Cancer type category | RR    | 95% CI       | p       | Q (p)  | I²     | r²     | df | p Funnel plot asym | Hedges g |
|----------------------|-------|--------------|---------|--------|--------|--------|----|--------------------|----------|
| Head and neck        | 0.83  | 0.72–0.99    | 0.044   | 81.8 (<0.001) | 79.2   | 0.10   | 17 | 0.60               | 0.55     |
| Lung cancer          | 0.93  | 0.76–1.14    | 0.47    | 10.17 (>0.11) | 41.0   | 0.026  | 6  | 1.0                | 0.23     |
| Testicular           | 1.12  | 0.90–1.40    | 0.30    | 10.9 (>0.13)  | 26.7   | 0.03   | 8  | 0.26               | 0.02     |
| Obesity              | 0.89  | 0.73–1.09    | 0.26    | 7.6 (>0.17)   | 34.6   | 0.021  | 5  | >0.72              | 0.69     |
| Other                | 0.91  | 0.69–1.20    | 0.49    | 38.3 (<0.001) | 76.5   | 0.124  | 9  | <0.02              | 0.10     |

Data are analyzed with a Dersimonian–Laird model in JASP. Data in italics show RR significantly different from 1.0.

significance (*p* > 0.3) and the effect size was negligible (Hedges *g* = 0.02). The remaining cancer sites showed nominal RR values < 1, but only cancers of the head and neck showed a statistically significant decrease in risk (meta-analytic RR = 0.83, *p* < 0.05, *N* = 18) with medium effect size (Hedges *g* = 0.55). This was also the cancer site with the greatest amount of data.

Heterogeneity was high in the data set. Exploration of this heterogeneity suggests that it arises at least in part from differences among cancer sites rather than from selection or performance bias. When the data were separated into sites, heterogeneity remained high in cancers of the head and neck, and “other” sites, but was substantially reduced in cancers of the lungs, testes, and obesity-related cancers.

The current analysis suggests that *Cannabis* use in the United States may decrease risk of cancer by 10% (meta-analytic RR = 0.90). Only testicular cancers show an RR > 1.0, although this was not statistically significant. Upon removal of testicular cancers from the data, the remaining data show an RR significantly below 1.0 (*p* < 0.05; Table 3).

If cancer types do respond differently to *Cannabis* use, the overall impact of *Cannabis* use on cancer will depend on the impact of *Cannabis* use on each cancer type, and the number of cases of and deaths from each cancer type in the population. For example, there are ~1.7 million cancer cases, and 600,000 deaths, in the United States in 2019 (Ref.1). Of these, ~7900 cases and 370 deaths are from testicular cancer (2013 data from Centers for Disease Control and Prevention [CDC]: https://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm).

### Table 4. Effects of Removing Data from Individual Cancer Categories on Results of Meta-analysis

| Data set removed               | RR    | 95% CI       | p       | Q (p)  | I²     | r²     | df | p Funnel plot asym | Hedges g |
|--------------------------------|-------|--------------|---------|--------|--------|--------|----|--------------------|----------|
| Head and neck removed          | 0.95  | 0.835–1.08   | 0.44    | 89.6 (<0.001) | 65.4   | 0.075  | 31 | 0.615              |          |
| Lung cancer removed            | 0.90  | 0.79–1.01    | 0.075   | 167.0 (<0.001) | 76.6   | 0.099  | 42 | 0.77               |          |
| Testicular cancer removed      | 0.87  | 0.78–0.98    | 0.021   | 165.2 (<0.001) | 74.9   | 0.092  | 41 | 0.56               |          |
| Obesity-associated cancer removed | 0.91  | 0.80–1.03   | 0.129   | 168.3 (<0.001) | 77.4   | 0.109  | 42 | 0.66               |          |
| Other cancer types removed     | 0.91  | 0.81–1.02    | 0.115   | 116.4 (<0.001) | 71.5   | 0.081  | 39 | 0.825              |          |

Data are analyzed with a Dersimonian–Laird model in JASP. Data in italics show RR significantly different from 1.0.
analysis and Ref.85). This demonstrates that the anti-
cancer effects of Cannabis outweigh the carcinogenic
effects even in the airways and bladder, where carcino-
gen exposure is high.

It is possible that the actual decrease in cancer risk due
to Cannabis use is even greater than the estimated 10%
decrease in risk emerging from the current analysis, as
few data are available for the impact of Cannabis use
on the RR of cancers that are not exposed to the carcino-
gens of smoke, for example, those associated with obe-
sity. Cannabis users show decreased BMI and obesity
rates.4,97 This decrease is known to be associated with de-
creased risk of obesity-related diseases, including DM
and nonalcoholic fatty liver disease.34–38,104

Many cancer types are positively associated with
obesity, including cancers of the liver, breast, colon
and rectum, prostate, stomach (cardia), pancreas, uter-
ine corpus, gallbladder, esophagus, kidney, ovary, and
thyroid, as well as multiple myeloma.20–26 Cannabis
use4,97 may decrease the risk of these obesity-related
cancer types simply due to the reduction in BMI asso-
ciated with Cannabis use. In addition, however, most of
these cancer types are known to be inhibited or
destroyed by cannabinoids in laboratory studies.47–56
Cannabis use is therefore very likely to be associated
with a substantial reduction in the risk of, and mortal-
ity from, obesity-related cancers.

Unfortunately, no recent data, and few data over-
all, are available for the RR of obesity-related cancers
in Cannabis users. Data providing risk ratios for
obesity-related cancers are limited to six data points
from two studies. The first study, using data from the
early 1990s in California, provided data for esophageal
(RR=0.67), colorectal (RR men=0.9, RR wom-
en=0.6), prostate (RR=1.3), and breast (RR=1.0) can-
cers.84 Another study, from 2006, also included data on
esophageal cancer (AOR=0.67, RRconv=0.69).57
These data provide a mean meta-analytic RR of 0.89,
95% CI=0.72–1.09. While not statistically significant,
this is consistent with decreased risk. Note that these
are likely to underestimate the impact today, as the obe-
sity rate in the United States was about 25% lower at the
time these data were collected than it is today (data
from CDC).

Data can be used to provide a rough, preliminary es-
timate of the potential magnitude of the impact of Can-
nabis use on cancer diagnoses and deaths. This can be
obtained as the product of the annual number of cancer
deaths or diagnoses, the fraction of the population
using Cannabis, and the decrease in risk of cancer in
Cannabis users (1 minus the RR). There are projected
to be 1.7 million diagnoses and 607,000 deaths from
cancer in the United States in 2019 (Ref.1). According
to current census data, the U.S. population age 18 years
and above is ~255 million. A recent poll suggests that
55 million, or about 21%, of these people use Cannabis,
and 35 million, or ~14%, are regular users.96 If the 10%
decrease in cancer risk indicated by the current analysis is
accurate, and applies across all cancer types, then Can-
nabis use would prevent as many as 23,800 to 35,700 cancer
diagnoses (1,700,000×0.14 or 0.21×0.10), and 8498 to
12,747 cancer deaths (607,000×0.14 or 0.21×0.10)
each year.

Some cancer types are relatively common while others
are rare, and some types have much greater mortality
rates than others. In the current data set, only testicular
cancers show a trend to increasing risk in Cannabis
users, and testicular cancer is a relatively uncommon
cancer with a high survival rate. Furthermore, there is
high heterogeneity in the data and no data are available
for many cancers. The actual impact of Cannabis use on
on cancer cases and deaths therefore cannot be estimated
with any degree of confidence with the data available
at this time. However, given the large number of cancer
diagnoses, and the large numbers of people using Can-
nabis, even a moderate impact on cancer risk will have
significant public health implications.

There is increasing awareness that Cannabis provi-
des therapeutic medical benefits. By decreasing risk of
cancer, obesity, and DM,4,34–38,97 leading causes of pre-
mature death and disability, it is becoming clear that
Cannabis use may also meet the definition of preven-
tive medicine. Like all medicines, Cannabis has harm-
ful effects, especially if misused. However, Cannabis
use rarely results in fatalities, and is thus safer than
many pharmaceuticals.98–103 Therefore, moderate,
adult Cannabis use may be associated with a net im-
provement in public health.

Exposure level dependence
Even the lowest category of use appears to be associated
with a significant decrease in cancer risk (Fig. 4). This re-
sembles data in which individuals using Cannabis only
one to four times per month show decreased BMI and obesity risk relative to nonusers,34 due at least in part
by long-lasting downregulation of CB1 in response to
Cannabis use.4 Thus, use of Cannabis only one to four
times per month may be sufficient to significantly reduce
risk of cancer, DM, and fatty liver disease while avoiding
the harmful effects of heavy or frequent use.
How does the current analysis compare with previous studies?

Several prior reviews and meta-analyses have addressed the relationship between Cannabis use and cancer risk.\textsuperscript{105–110} Three of these reviews detected no association between Cannabis use and cancer risk,\textsuperscript{105,108,109} one hypothesized a decrease in risk\textsuperscript{106} and two concluded that Cannabis use is associated with an increased risk of cancer,\textsuperscript{107,110} of the testes and lungs, respectively.

The current review differed by being the only study to convert AOR data to RR before analysis, then use log RR data in a meta-analyses. The current review also differs from those studies by including all available cancer data, rather than focusing on a specific cancer type.

Table 5. Cancer Types and Exposure Units used to Evaluate Potential Exposure Dependence of the Association between Cannabis Use and Cancer Risk

| Cancer type       | Exposure units       | Lowest | Intermed | Intermed + | Highest | Ref. |
|-------------------|----------------------|--------|----------|------------|---------|------|
| Oral              | Joint-years          | >0 to <1 | 1–10     | >10        | >30     | 57   |
| Pharyngeal        | Joint-years          | >0 to <1 | 1–10     | >10        | >30     | 57   |
| Laryngeal         | Joint-years          | >0 to <1 | 1–10     | >10        | >30     | 57   |
| Lung              | Joint-years          | >0 to <1 | 1–10     | >10        | >30     | 57   |
| Esophageal        | Joint-years          | >0 to <1 | 1–10     | >10        | >30     | 57   |
| HNSCC             | Tertile              | 1      | 2        | 3          |         | 59   |
| Oral              | Joint-years          | >0–2    | >2–5     | >5         |         | 61   |
| Pharyngeal        | Joint-years          | >0–2    | >2–5     | >5         |         | 61   |
| Laryngeal         | Joint-years          | >0–2    | >2–5     | >5         |         | 61   |
| HNSCC             | Ounces/week·years    | 0–1/16  | 1/16 to <3 | 3 to <7.5 | 7.5+    | 75   |
| Oral              | Joint-years          | 0–2    | 2–10     | >10        |         | 80   |
| Oropharyngeal     | Joint-years          | 0–2    | 2–10     | >10        |         | 80   |
| Oral              | Times/week           | 1      | 1–7      | 7+         |         | 82   |
| Bladder           | Times                | 11–99  | 100–499  | >500       |         | 85   |
| \(N\)             |                      | 14     | 14       | 14         | 6       |      |

N-values for each exposure group are shown in bold.  
Relative risk data associated with these exposure units are presented in Figure 8.  
HNSCC, head and neck squamous cell carcinoma.
current study is also the only one to determine the impact of removing studies with high risk of selection bias or those with low sample sizes among Cannabis users or controls. The differences in data selection criteria and treatment of the data resulted in differences in summary measures of risk among these studies.

Implications for use of Cannabis as a cancer cure or treatment

There is an emerging trend in which patients turn away from more mainstream chemotherapy methods and instead attempt to use Cannabis as a stand-alone cancer cure.\textsuperscript{111} The current analysis does not support average recreational levels of Cannabis use as an effective stand-alone cure for cancer. However, the results do suggest that, in addition to providing significant improvements in the quality of life of cancer patients, adding Cannabis therapy to established cancer treatment regimens may well improve treatment efficacy without stimulating tumor growth.

Limitations

At present, reliable estimates of RR are not available for most cancer types, and no risk data at all are available for many cancer types while certain cancer types (head and neck, lung, testicular) are over-represented in the data. Few data are available for cancer types correlated with obesity, and Cannabis use is associated with reduced risk of obesity.\textsuperscript{4} No single study addresses the relationship between Cannabis use and the overall risk of cancer. Instead, available studies focus on one or several specific cancer types. Furthermore, the data are associative, rather than a result of controlled clinical trials or interventions. Therefore, the overall impact of Cannabis use on cancer risk cannot be determined with confidence using the available data.

A statistically significant decrease in risk (at $p < 0.05$) was not apparent in the original data set, but emerges after elimination of data with high risk of selection and performance bias, as defined. The elimination of these data was to accomplish two explicit goals. The first goal is to specifically determine the likely impact of Cannabis use on cancer risk in the United States. This was accomplished by rejecting data from North Africa, where Cannabis is consumed with tobacco,\textsuperscript{57} and data that failed to adjust for tobacco use, as these data conflate the effects of tobacco use with the impact of Cannabis itself. The second goal was to increase the accuracy and reduce the variance of the results by reducing the risk of performance bias introduced by small sample sizes. This may have eliminated data from rare cancers. Elimination of data for testicular cancers in the examination of heterogeneity also resulted in a significant decrease in risk in the remaining data.

A limitation to using the results to estimate the overall impact on cancer rates and deaths arises because the overall impact of Cannabis use on risk of cancer depends on its impact on risk of each individual cancer type, and the frequency of that cancer type in the population. For example, if Cannabis increases risk of a rare cancer, but decreases the risk of a common cancer by an equal amount, the overall effect would be an overall decrease in cancer diagnoses in the population, and vice versa. Similarly, effects of Cannabis use on risk of cancer types with high mortality rates are more significant than effects on risk of less-aggressive cancers or cancers for which established treatment methods are more successful.

The risk ratios used in the analysis arise from self-report data. These are not optimal as patients may be reluctant to divulge Cannabis use. Furthermore, much of the data used in the analysis are from comparisons of ever users versus never users, and so by implication includes people with little or no recent exposure to Cannabis. However, Ngueta and Ndjaboue\textsuperscript{38} observed lingering impacts of Cannabis use on obesity rates that remained after long-term abstinence, and it is possible that the same is true of cancer, especially considering the strong links between obesity and cancer.\textsuperscript{20–27} Furthermore, a subset of the data was amenable to exposure dependence analysis, and includes respondents who used Cannabis at high levels, or for long periods of time (30 years or more). These data did not show appreciably different risk in low and high exposure categories of users (Fig. 8).

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