RISK SCIENCES INTERNATIONAL

# FINAL REPORT

# Rapid Review of Evidence on Cannabis Use and Cancer Risk

**Prepared for:**
Canadian Partnership Against Cancer

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## Executive Summary

**OBJECTIVE**: The objective of this rapid review is to assess the current evidence base on cannabis use and cancer risk for the Canadian Partnership Against Cancer. This report addresses the following research question:

- Is there a link between cannabis use and increased risk of cancer?

**METHODS**: A comprehensive search of literature from 2013 to the present was developed and conducted using five bibliographic databases, Medline, Embase, CINAHL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. References captured by the search and identified through supplementary sources underwent two levels of screening for eligibility: stage 1 title and abstract screening, and stage 2 full-text evaluation. The selection of studies for inclusion was performed independently by two reviewers using the eligibility criteria developed prior to the conduct of this review. Any discrepancies were resolved by consensus.

**RESULTS**: A total of nine review articles and eight original studies are included in this report. RSI's observations based on a review of the articles identified as eligible are summarized in the table below.

| Cancer type | Review Article Findings | Original Study Findings |
|---|---|---|
| Head & neck cancers | • Reviews either find no association with cannabis use, or characterize existing evidence as inconsistent or insufficient to support either a negative or positive association (decreased or increased risk of cancer)<br>• The strength of evidence for no association is characterized as low to moderate. | • No relevant original studies were identified that were not covered by the reviews included in this synthesis. |
| Lung cancer | • Reviews either find no association with cannabis use, or characterize existing evidence as inconsistent or insufficient to support either negative or positive association (decreased or increased risk of cancer)<br>• The strength of evidence for no association is characterized as low to moderate. | • No relevant original studies were identified that were not covered by the reviews included in this synthesis. |
| Testicular cancer | • Reviews find evidence for an association between current, frequent, or chronic cannabis smoking and increased risk of testicular cancer, specifically non-seminoma tumors.<br>• The strength of evidence for positive association (increased risk) is characterized as limited or insufficient. | • One recent original study provides additional evidence for a positive association between heavy cannabis use and increased risk of testicular cancer. This study is the first cohort study examining the association between cannabis use and testicular cancer; previous studies used a case-control design. The study has no information on the histology of the testicular cancers. |

| Cancer type | Review Article Findings | Original Study Findings |
|---|---|---|
| Other cancers | • Reviews characterize the evidence for other cancers as insufficient or inconclusive. | • Two recent studies of liver cancer in populations with pre-existing liver diseases associated with HCV infection or alcohol abuse show either no effect or a protective effect of cannabis.<br>• One study not covered by the reviews shows an increased risk of cervical intraepithelial neoplasia in cannabinoid users; however, the authors believe the observed association is a result of confounding. |

All studies point to methodological limitations, including limitations related to difficulties in assessment of exposure to cannabis, and the potential for confounding.

## Background

The federal government in Canada has approved the use of medical cannabis when prescribed by a physician since 2013, initially under the *Marihuana for Medical Purposes Regulations*, and since 2016 under the new *Access to Cannabis for Medical Purposes Regulations.* These Regulations allow Canadians who have been prescribed cannabis for medical purposes to access legal sources of medical cannabis (in fresh, dried or oil form) via licensed producers; alternatively, they may produce, or designate someone to produce, a limited amount of cannabis for their own medical purposes. In October 2018, cannabis was legalized for recreational (non-medical) use in Canada under the *Cannabis Act*.

The Canadian Partnership Against Cancer (the Partnership) is assessing the current evidence base on cannabis use and cancer risk and benefits during cancer treatment. Risk Sciences International (RSI) was contracted to provide support to the Partnership through conducting a rapid review of evidence on cannabis use and cancer risk.

## Objectives

The research question of interest to the Partnership for the current rapid review is the following:

- Is there a link between cannabis use and increased risk of cancer?

## Approach

### *Literature search*

The search strategy was established prior to the conduct of this review and was based on two concepts, cannabis and cancer, as outlined in Figure 1. Five electronic literature databases were consulted during the conduct of this work: Medline, Embase, CINAHL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. Since there is a significant (98%)[1] overlap between PubMed and Medline, and PubMed allows only limited control over search terms, a literature search in PubMed was not performed.

All searches were conducted on January 15, 2019 and restricted to references published from 2013 through to that date. References captured by the search were imported into an EndNote database, and duplicates removed. Additionally, the reference lists of review articles were scanned to supplement the primary search.

The search consisting of keywords and MeSH terms developed for the use in Medline is presented in Figure 1. These search terms were then adapted for the use in other electronic databases and have been provided in Appendix 1.

[1] See, for example: https://kemh.libguides.com/library/search_tips/faqs/difference_between_pubmed_medline_embase

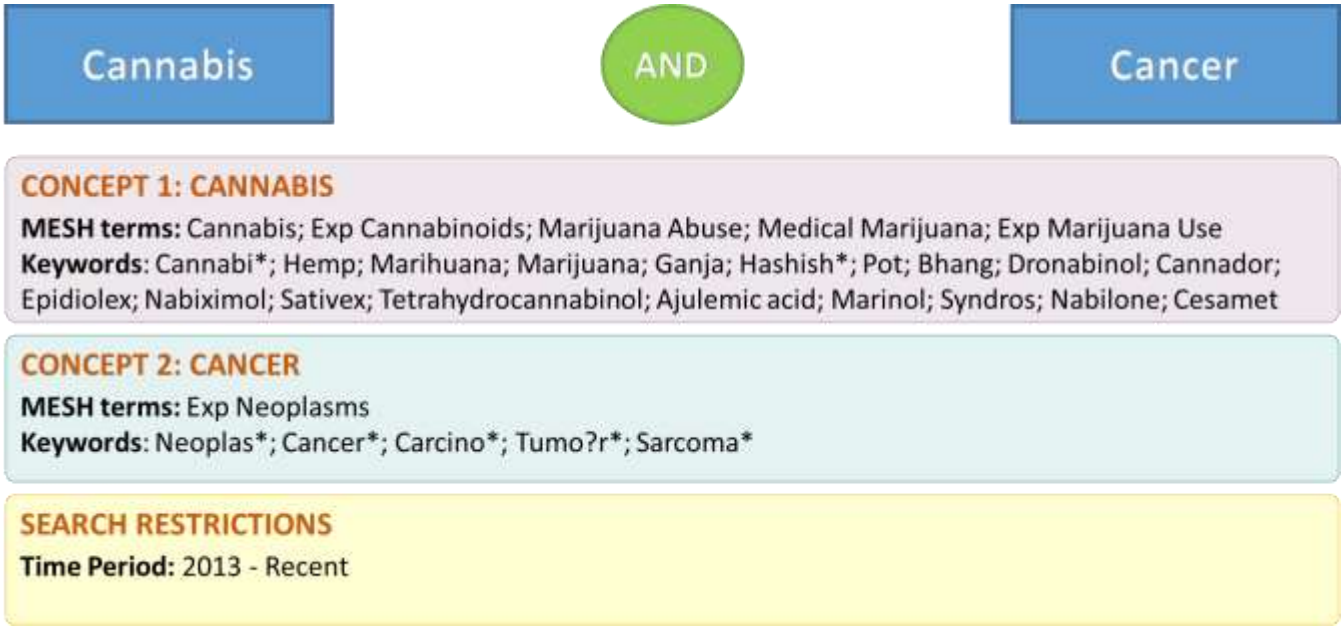


**Figure 1. Concepts and search terms used in developing the literature search strategy.**

### *Eligibility criteria and study selection*

Articles captured by the current search strategy and identified through other sources were subject to Level 1 (title and abstract) and Level 2 (full text) screening using eligibility criteria (Table 1) that were developed in collaboration with the Partnership prior to the conduct of this review. The restriction by study location (region/country) was not applied when screening for reviews, as they may consist of studies conducted across several countries, some of which may be listed as part of the current inclusion criteria. The selection of studies was independently performed by two reviewers; any discrepancies were resolved by consensus.

**Table 1. Eligibility criteria for studies on cannabis use and cancer risk.**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| **Study/Document Type** | |
| • Peer-reviewed literature<br>• Primary human studies (observational studies)<br>• Systematic reviews and meta-analyses<br>• Overviews of systematic reviews<br>• Quasi-systematic reviews | • Grey literature<br>• Animal or cell studies<br>• News articles, narrative reviews, editorials, conference abstracts, case reports, risk projections, research protocols |
| **Publication Date** | |
| • 2013 - Current | • Prior to 2013 |
| **Publication Language** | |
| • English | • All other languages |
| **Region/Country** | |
| • Canada<br>• Australia | • All other countries |

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • New Zealand<br>• Northwest Europe:<br>• Other G7 countries: USA, France, Germany, Italy, Japan, United Kingdom | |
| **Exposure** | |
| • All forms and routes of cannabis use | • None |
| **Outcomes** | |
| • All cancer sites | • Non-cancer outcomes |

### *Data abstraction*

In preparation for populating tabular summaries of key findings, data abstraction forms were developed for both review and original research articles.

Information abstracted from review articles included research objectives and health endpoints, comprehensiveness, whether meta-analysis was performed, main results and authors' conclusions, limitations reported by study authors, and any RSI comments.

Information abstracted from original research articles included study and participant characteristics, data on exposure (form, route, intensity); study outcome and method of its ascertainment; main quantitative results and adjustment covariates, authors' conclusion and author's reported limitations, and any RSI comments.

## Results

As described in Figure 2, the search of five electronic databases retrieved a total of 2,174 references. Following the removal of duplicates and supplementation with articles identified from reference lists of review articles, 1,841 references were retained and screened by title and abstract (level 1) for relevance.

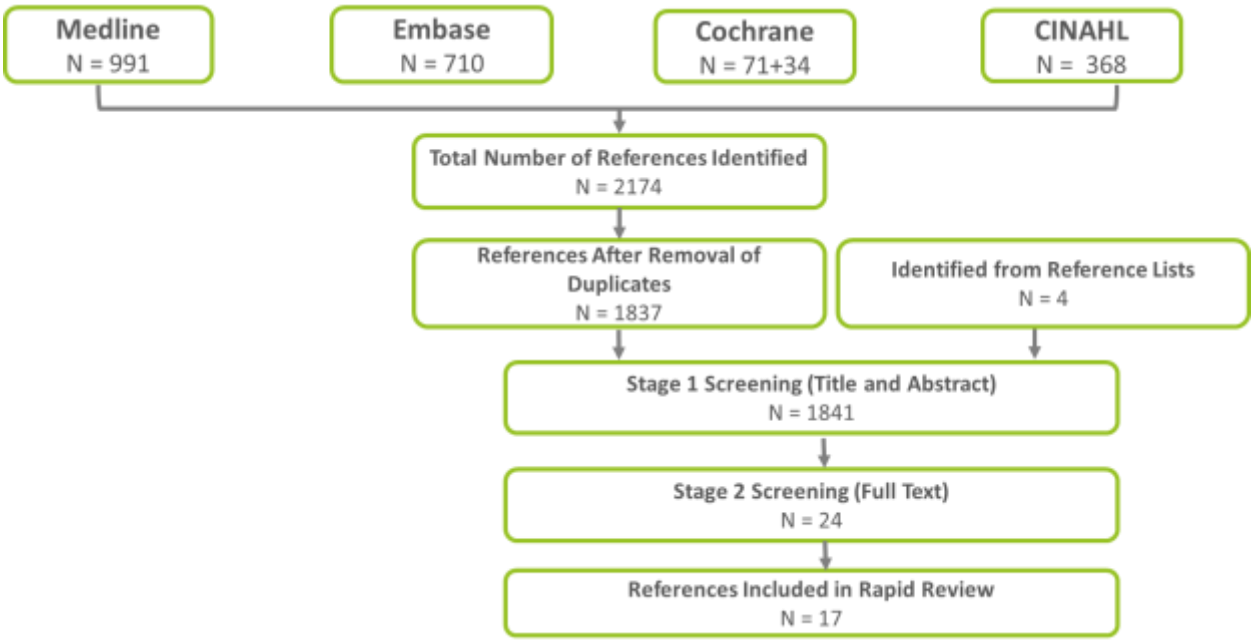


**Figure 2. Flow diagram illustrating the search results from the applied search strategy.**

Seven articles listed in Appendix 2 were eliminated at level 2 (full text) evaluation for eligibility. Seventeen studies investigating the association between cannabis use and cancer risk were selected for data abstraction: this included nine reviews, and eight original research articles (Appendix 3). Tabular summaries of eligible studies can be found in Appendix 4.

### *Characteristics of eligible studies*

Although several reviews are not described by their authors as systematic, they have key features of a systematic review and were used for data abstraction. As indicated in Table 2, the reviews partially overlap.

Original studies are summarized in Table 3. Four of the eight original studies are not covered by the reviews and thus provide additional information on possible association between cannabis use and the risk of cancer.

**Table 2. Characteristics of reviews**

| First author, year | Cancer studied | Meta-analysis | Conclusions | Comment |
|---|---|---|---|---|
| de Carvalho, 2015 | Head and neck | Yes | • "No association" with cannabis use<br>• "insufficient epidemiological evidence to support a positive or negative association" | • Included in the weight of evidence evaluation by NASEM 2017 (see below) |
| Radoi and Luce 2013 | Oral cavity | No | • Only one study of oral cavity cancers is reviewed (pooled-analysis of five case–control studies); the study shows no association with cannabis use | • This is a review of risk factors for oral cavity cancer; marijuana smoking was only one of the factors considered. |
| Martinasek, 2016 | Lung | No | • No conclusion on the risk of lung cancer associated with cannabis use; only a summary of included studies which provide inconsistent results. | • Lung cancer was one of several respiratory effects considered in this review.<br>• This review includes epidemiological studies, case reports and experimental studies. |
| Gandhi, 2017 | Testicular | No | • Overview of studies with no conclusion | • Includes the systematic review by Gurney et al. 2015 (see below)<br>• Testicular cancer was not the focus of this review. The aim was to investigate "the antiproliferative effects of cannabinoids in urological malignancies", and the focus was on potential mechanisms of antiproliferative effects. |
| Gurney, 2015 | Testicular | Yes | • Positive association between current, chronic and frequent cannabis use and increased risk of non-seminoma testicular tumors<br>• Inconclusive evidence for association between ever- and former use and testicular tumors<br>• Insufficient evidence for association between cannabis use and seminoma tumours | • Included in the weight of evidence evaluation by NASEM 2017 (see below)<br>• Meta-analyzed studies are the same as those analyzed by Huang et al. 2015 (see below) |

| First author, year | Cancer studied | Meta-analysis | Conclusions | Comment |
|---|---|---|---|---|
| Huang, 2015 | Multiple sites | • Yes (testicular cancer)<br>• No (all other cancers) | • Inconsistent evidence for association of head and neck cancer with cannabis use<br>• "The lung cancer studies appear to be consistent with no association"<br>• "The three testicular cancer case–control studies were fairly consistent with one another in terms of an increased risk…"<br>• Other cancers: "insufficient data to make any conclusions" | • Included in NASEM 2017 weight of evidence evaluation (see below)<br>• The authors do not describe their review as systematic; however, they performed meta-analysis of studies on testicular cancer.<br>• Meta-analyzed studies are the same as those analyzed by Gurney et al. 2015 (see above) |
| Memedovich, 2018 | Multiple sites | No | • Head and neck cancers: no association with cannabis use<br>• Lung cancer: no association<br>• Testicular cancer: positive association, increased risk<br>• Other cancers: insufficient/inconclusive evidence | • Overview of systematic reviews<br>• Although the overall conclusion regarding lung cancer is that there is no association with cannabis use, on page E344 the evidence is characterized as "mixed". |
| NASEM[2], 2017 | Multiple sites | No | • Head and neck cancers: "moderate evidence of no statistical association"<br>• Lung cancer: "moderate evidence of no statistical association"<br>• Testicular cancer: limited evidence of a positive association between current, frequent, or chronic cannabis smoking and increased risk of non-seminoma testicular tumors<br>• Other cancers: "No or insufficient evidence to support or refute a statistical association" | • Includes the reviews by de Carvalho et al. 2015, Gurney et al. 2015, Huang et al. 2015 (see above)<br>• Weight-of-Evidence evaluation that has several features of the systematic review process |
| Nugent, 2017 | Multiple sites | No | • Head and neck cancers: no association with cannabis use; | |

[2] The National Academies of Sciences, Engineering and Medicine

| First author, year | Cancer studied | Meta-analysis | Conclusions | Comment |
|---|---|---|---|---|
| | | | strength of evidence for no association is low<br>• Lung cancer: no association; strength of evidence for no association is low<br>• Testicular cancer: "Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer…"; strength of evidence for the association: insufficient<br>• Transitional cell carcinoma: "1 very small case-control study with several methodological flaws" demonstrates increased risk associated with heavy use"; strength of evidence for the association: insufficient. | |

**Table 3. Characteristics of original studies**

| First author, year | Study design, Country | Cancer studied | Exposure assessment | Association | Included in reviews | Comment |
|---|---|---|---|---|---|---|
| Adejumo, 2018a | Cross-sectional, USA | Liver | Based on ICD codes in medical records | • No | No | Population: HCV-positive adults |
| Adejumo, 2018b | Cross-sectional, USA | Liver (hepatocellular carcinoma) | Based on ICD codes in medical records | • Negative (decreased risk) | No | Population: adults with past or current history of alcohol abuse |
| Callaghan, 2017 | Cohort, Sweden | Testicular | Self-reported | • Positive ("heavy" use, increased risk)<br>• No (ever use) | No | The first cohort study of cannabis and testicular cancer<br>No information on histology |
| Callaghan, 2013 | Cohort, Sweden | Lung | Self-reported | • Positive ("heavy" use, increased risk)<br>• No (ever use) | Yes | "…our results… did not show evidence of a clear dose–response…" |
| Zhang, 2015 | Case-control, Pooled analysis of data from 6 studies conducted in USA, Canada, UK and New Zealand | Lung | Self-reported | • No | Yes | |
| Kricker, 2013 | Nested case-control, Australia | Cervical intraepithelial neoplasia; Cervical cancer | Based on ICD codes in medical records | • Positive (increased risk of cervical intraepithelial neoplasia)<br>• No (cervical cancer) | No | The authors believe the observed association is the result of confounding. |
| Marks, 2014 | Case-control, Pooled analysis of data from 9 studies conducted in USA and Latin America | Oropharyngeal; Oral tongue | Self-reported | • "Possible positive" (increased risk of oropharyngeal cancer)<br>• Negative (decreased risk of oral tongue cancer) | Yes | |
| Thomas, 2015 | Cohort, USA | Bladder | Self-reported | • Negative (decreased risk) | Yes | |

### *Study Limitations*

All studies point to potential methodological limitations, particularly those related to assessment of exposure to cannabis, such as lack of information on the type or strain of cannabis (Adejumo, 2018b); mode of use, such as oral versus inhalation (Adejumo, 2018b); intensity and duration of use (Kricker, 2013; Adejumo, 2018b); and sensitivity and specificity of ICD coding for cannabis use (Adejumo, 2018a). In cohort studies (Callaghan, 2013, 2017; Thomas 2015), exposure to cannabis was assessed only at baseline, so that changes in cannabis use over the follow-up period was not accounted for.

The researchers also acknowledge the potential for residual confounding, particularly from commercial tobacco smoking (Callaghan, 2013) and/or from unmeasured confounders (Marks, 2014), such as occupational or environmental exposures (Thomas, 2015).

Limitations of studies on potential adverse health effects of cannabis are summarized by NASEM (2017):

> *Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific type of cannabis product used, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. Additionally, observational studies often have to contend with confounders related to polysubstance use, which obscures the ability to answer questions about the effects of "cannabis only" on the health effects. Moreover, in some cases, samples included different populations (i.e., adolescents versus adults), cannabis-use history (i.e., chronic versus acute), and patterns of use (i.e., frequency, dose, quantity)—all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. Additional limitations include a lack of longitudinal assessments and small study cohorts.*

## Summary and Conclusions

A summary of evidence from the present review can be found in Table 4.

Review articles included in the present synthesis suggest a positive association between current, frequent or chronic cannabis smoking and an increased risk of testicular cancer, specifically the risk of non-seminoma tumors. Although the strength of evidence for the association is characterized as limited or insufficient, one recent original study (Callaghan et al. 2017) not covered by the reviews supports an association between heavy cannabis use and increased risk of testicular cancer. This study has no information on histology of testicular tumors. Callaghan et al. (2017) is the first cohort study assessing the potential link between cannabis use and testicular cancer; previous studies were of the case-control design.

Regarding other cancers, there is either evidence for no association with cannabis use (strength of evidence for no association is characterized in the eligible reviews as low or moderate), or evidence is characterized as insufficient, inconsistent or inconclusive.

**Table 4. Summary of evidence from identified studies**

| Reviews | | Original studies | | | Overall Summary |
|---|---|---|---|---|---|
| **Reference (first author, year)** | **Conclusions** | **Reference (first author, year)** | **Conclusions** | **Comments** | |
| **Head and neck cancers (HNC)** | | | | | |
| **de Carvalho, 2015** | • "No association between lifetime marijuana use and the development of head and neck cancer was found."<br>• "insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of HNC" | **Marks, 2014** | • "evidence of a possible positive association of marijuana use with oropharyngeal cancer and a negative association with oral tongue cancer" | • Study included in reviews by De Carvalho et al. 2015 and Huang et al. 2015<br>• The authors acknowledge that the observed associations may be explained by residual or unmeasured confounding | • Review articles either conclude that there is evidence for no association or characterize existing evidence as insufficient/inconsistent to support negative or positive association.<br>• In the reviews, strength of evidence for no association is characterized as low (Nugent 2017) or moderate (NASEM 2017)<br>• No original studies published after search dates of the reviews have been identified. |
| **Huang, 2015** | • "The evidence is inconsistent" | | | | |
| **Memedovich, 2018** | • "No evidence of harm"/" No association" | | | | |
| **NASEM** [The National Academies of Sciences, Engineering and Medicine], **2017** | • "moderate evidence of no statistical association" | | | | |
| **Nugent, 2017** | • No association<br>Strength of evidence: low | | | | |
| **Radoi and Luce, 2013** | • This is a review of risk factors for oral cavity cancer; marijuana smoking was one of many factors considered.<br>• Only one study of oral cavity cancers is reviewed (pooled-analysis of five case– | | | | |

| Reviews | | Original studies | | | Overall Summary |
|---|---|---|---|---|---|
| **Reference (first author, year)** | **Conclusions** | **Reference (first author, year)** | **Conclusions** | **Comments** | |
| | control studies); the study shows no association | | | | |
| **Lung cancer** | | | | | |
| **Huang, 2015** | • "The lung cancer studies appear to be consistent with no association with marijuana, although affirming no association is inherently difficult." | **Callaghan, 2013** | • Heavy cannabis smoking, defined at baseline (age 18-20 years) as self-reported lifetime use of at least 50 times, was associated with a significant more than twofold increase in risk of lung cancer over 40-years of follow-up.<br>• No clear exposure-response | •Study included in reviews by NASEM 2017 and Nugent et al. 2017 | • Review articles either conclude that there is evidence for no association or characterize existing evidence as insufficient/inconsistent to support negative or positive association.<br>• In the reviews, strength of evidence for no association is characterized as low (Nugent 2017) or moderate (NASEM 2017).<br>• No new studies published after search dates of the reviews have been identified. |
| **Martinasek, 2016** | • No conclusion on the risk of lung cancer; only a summary of included studies which show inconsistent fiindings: "Eight of the studies indicated an increased risk of lung cancer from cannabis use or cases indicating lung cancer occurrence… and 4 studies found either no significant association or a lower risk for lung cancer." | **Zhang, 2015** | • "…little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effect for heavy consumption cannot be excluded."<br>• "suggestive association for adenocarcinoma" | Study included in reviews by Huang et al. 2015, Martinasek et al. 2016, NASEM et al. 2017, Nugent et al. 2017 | |
| **Memedovich, 2018** | • "No evidence of harm"/" No association"<br>Note: although the overall conclusion is that there is no association/harm, on page E344 the evidence is characterized as "mixed" | | | | |
| **NASEM** [The National Academies of Sciences, | • "moderate evidence of no statistical association" | | | | |

| Reviews | | Original studies | | | Overall Summary |
|---|---|---|---|---|---|
| **Reference (first author, year)** | **Conclusions** | **Reference (first author, year)** | **Conclusions** | **Comments** | |
| Engineering and Medicine], **2017** | | | | | |
| **Nugent, 2017** | • No association<br>Strength of evidence: low | | | | |
| **Testicular cancer** | | | | | |
| **Gandhi, 2017** | • Overview of 4 epidemiologic studies; no conclusion regarding possible association between cannabis use and testicular cancer; the aim was to investigate "the biological mechanism of action of the activity of endocannabinoids in testicular cancer." | **Callaghan, 2017** | • Heavy cannabis use defined as self-reported use of > 50 times in lifetime (at age 18-21 years) was associated with a significant 2.5-fold increase in the risk of testicular cancer. | • Study not included in any of the identified reviews.<br>• This is the first cohort study of testicular cancer. | • Review articles find evidence for positive association between current, frequent, or chronic cannabis smoking and increased risk of testicular cancer, specifically non-seminoma tumors.<br>• In the reviews, strength of evidence for positive association (increased risk) is characterized as limited (NASEM 2017) or insufficient (Nugent 2017).<br>• One recent study not covered by the reviews provides additional evidence for the association between heavy cannabis use and the risk of testicular cancer. The study had no information on the histology of the testicular cancers. |
| **Gurney, 2015** | • Current, chronic and frequent cannabis use is associated with non-seminoma testicular germ cell tumors (TGCT)<br>• "inconclusive evidence regarding the relationship between ever- and former-use of cannabis and TGCT development."<br>• "insufficient evidence to conclude that there is a relationship between seminoma tumours and cannabis use. | | | | |
| **Huang, 2015** | • "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." | | | | |
| **Memedovich, 2018** | "Evidence of harm"/"Association" | | | | |
| **NASEM** [The National | • "limited evidence of a statistical association" between current, frequent, or chronic cannabis smoking | | | | |

| Reviews | | Original studies | | | Overall Summary |
|---|---|---|---|---|---|
| **Reference (first author, year)** | **Conclusions** | **Reference (first author, year)** | **Conclusions** | **Comments** | |
| Academies of Sciences, Engineering and Medicine], **2017** | and non-seminoma-type testicular germ cell tumors | | | | |
| **Nugent, 2017** | • "Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer…"<br>• Strength of evidence: insufficient | | | | |
| **Other cancers** | | | | | |
| **Huang, 2015** | • "insufficient data to make any conclusions" regarding all cancers, childhood cancers, bladder, anal, penile cancers, non-Hodgkin lymphoma, malignant primary gliomas, Kaposi sarcoma | **Kricker, 2013** | • Statistically significant increase in the risk of cervical intraepithelial neoplasia (CIN) 2/3 and a non-significant increase in the risk of cervical cancer in cannabinoid users | • Study not included in identified reviews<br>• No adjustment for HPV infection due to lack of data; the authors explain the increase by risky sex behaviours and associated HPV infection in drug users rather than the effect of the drug itself. | • In review articles, evidence is characterized as insufficient or inconclusive.<br>• One study not included in the reviews shows an increase in the risk of cervical intraepithelial neoplasia in cannabinoid users; however, the authors believe the observed association is the result of confounding.<br>• Two studies (not included in identified reviews) show either no effect or a protective effect of cannabis on the development of liver cancer in populations with pre-existing liver diseases associated with HCV infection or alcohol abuse |
| **Memedovich, 2018** | • Insufficient/inconclusive evidence regarding bladder, prostate, penile, cervical and childhood cancers | **Thomas, 2015** | • "an inverse association between cannabis use and the development of bladder cancer." | • Study included in review by NASEM 2017 | |
| **NASEM** [The National Academies of Sciences, Engineering and Medicine], **2017** | • "No or insufficient evidence to support or refute a statistical association" between cannabis use and esophageal cancer (cannabis smoking), bladder, prostate, penile, cervical, anal cancers, malignant gliomas, non-Hodgkin lymphoma, Kaposi's sarcoma; subsequent risk of developing acute myeloid leukemia/acute non- | **Adejumo, 2018a** | • Conclusion: prevalence of liver cancer was not significantly different between cannabis users and non-users | • Population: HCV-positive adults<br>• Study not included in identified reviews | |

| Reviews | | Original studies | | | Overall Summary |
|---|---|---|---|---|---|
| **Reference (first author, year)** | **Conclusions** | **Reference (first author, year)** | **Conclusions** | **Comments** | |
| | lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) | | | | |
| **Nugent, 2017** | • Transitional cell carcinoma<br>• Findings: Risk of cancer with >40 joint-years cannabis use vs. none (OR, 3.4; unadjusted P = 0.012)."<br>• Strength of evidence: insufficient<br>Comments: "1 very small case-control study with several methodological flaws" | **Adejumo, 2018b** | • Conclusion: "…among alcohol users, individuals who additionally use cannabis (dependent and non-dependent cannabis use) showed significantly lower odds of developing…HCC [hepatocellular carcinoma] …" | • Population: adults with the past or current history of alcohol abuse<br>• Study not included in identified reviews | |

## Appendix 1: Search Strategy

***Medline***

| # | Searches | Results |
|---|---|---|
| 1 | Marijuana Abuse/ or CANNABIS/ or Cannabi*.mp. or exp Cannabinoids/ | 40529 |
| 2 | exp "Marijuana Use"/ | 4531 |
| 3 | Medical Marijuana/ | 748 |
| 4 | Hemp.mp. | 813 |
| 5 | Marihuana.mp. | 1118 |
| 6 | Marijuana.mp. | 17850 |
| 7 | Ganja.mp. | 52 |
| 8 | Hashish*.mp. | 574 |
| 9 | Bhang.mp. | 30 |
| 10 | Dronabinol.mp. | 6717 |
| 11 | Cannador.mp. | 3 |
| 12 | Epidiolex.mp. | 19 |
| 13 | Nabiximol.mp. | 3 |
| 14 | Sativex.mp. | 173 |
| 15 | Tetrahydrocannabinol.mp. | 6411 |
| 16 | Ajulemic acid.mp. | 44 |
| 17 | Marinol.mp. | 85 |
| 18 | Syndros.mp. | 4 |
| 19 | Nabilone.mp. | 301 |
| 20 | Cesamet.mp. | 18 |
| 21 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 | 47680 |
| 22 | exp Neoplasms/ | 3121661 |
| 23 | neoplas*.mp. | 2715423 |
| 24 | cancer*.mp. | 1618688 |
| 25 | carcino*.mp. | 962773 |
| 26 | tumo?r*.mp. | 1948933 |
| 27 | sarcoma*.mp. | 117553 |
| 28 | 22 or 23 or 24 or 25 or 26 or 27 | 4138188 |
| 29 | 21 and 28 | 2634 |
| 30 | limit 29 to yr="2013 -Current" | **991** |

***Embase***

| # | Searches | Results |
|---|---|---|
| 1 | Cannabi*.mp. or cannabis addiction/ or exp "cannabis use"/ or cannabis/ | 70029 |
| 2 | exp cannabinoid/ | 61950 |
| 3 | exp "Cannabis (genus)"/ | 243 |
| 4 | Hemp.mp. | 1064 |
| 5 | Marihuana.mp. | 1705 |
| 6 | Marijuana.mp. | 16086 |
| 7 | Ganja.mp. | 79 |
| 8 | Hashish*.mp. | 890 |
| 9 | Pot.mp. | 32374 |
| 10 | Bhang.mp. | 54 |
| 11 | Dronabinol.mp. | 7359 |
| 12 | Cannador.mp. | 44 |
| 13 | Epidiolex.mp. | 82 |
| 14 | Nabiximol.mp. | 15 |
| 15 | Sativex.mp. | 642 |
| 16 | Tetrahydrocannabinol.mp. | 12062 |
| 17 | Ajulemic acid.mp. | 1013 |
| 18 | Marinol.mp. | 573 |
| 19 | Syndros.mp. | 11 |
| 20 | Nabilone.mp. | 1304 |
| 21 | Cesamet.mp. | 256 |
| 22 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or<br>19 or 20 or 21 | 114018 |
| 23 | exp neoplasm/ or Neoplas*.mp. | 4576824 |
| 24 | exp neoplasm/ or Neoplas*.mp. | 4576824 |
| 25 | Cancer*.mp. | 3313786 |
| 26 | Carcino*.mp. | 1508533 |
| 27 | Tumo?r*.mp. | 3092550 |
| 28 | Sarcoma*.mp. | 169162 |
| 29 | 23 or 24 or 25 or 26 or 27 or 28 | 5752577 |
| 30 | 22 and 29 | 9057 |
| 31 | limit 30 to yr="2013 -Current" | 4246 |
| 32 | limit 31 to exclude medline journals | **710** |

***Cochrane Database of Systematic Reviews***

| # | Searches | Results |
|---|---|---|
| 1 | Cannabi*.mp. | 121 |
| 2 | Hemp.mp. | 6 |
| 3 | Marihuana.mp. | 20 |
| 4 | Marijuana.mp. | 67 |
| 5 | Ganja.mp. | 3 |
| 6 | Hashish*.mp. | 17 |
| 7 | Pot.mp. | 17 |
| 8 | Bhang.mp. | 3 |
| 9 | Dronabinol.mp. | 17 |
| 10 | Cannador.mp. | 2 |
| 11 | Epidiolex.mp. | 1 |
| 12 | Nabiximol.mp. | 0 |
| 13 | Sativex.mp. | 9 |
| 14 | Tetrahydrocannabinol.mp. | 25 |
| 15 | Ajulemic acid.mp. | 0 |
| 16 | Marinol.mp. | 9 |
| 17 | Syndros.mp. | 1 |
| 18 | Nabilone.mp. | 15 |
| 19 | Cesamet.mp. | 5 |
| 20 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 173 |
| 21 | Neoplas*.mp. | 1152 |
| 22 | Cancer*.mp. | 2518 |
| 23 | Carcino*.mp. | 996 |
| 24 | Tumo?r*.mp. | 1496 |
| 25 | Sarcoma*.mp. | 155 |
| 26 | 21 or 22 or 23 or 24 or 25 | 3210 |
| 27 | 20 and 26 | 57 |
| 28 | limit 27 to last 7 years | 43 |
| 29 | limit 28 to protocols | 9 |
| 30 | 28 not 29 | **34** |

### *Cochrane Central Register of Controlled Trials*

| # | Searches | Results |
|---|---|---|
| 1 | cannabi*.mp. or cannabis/ or exp cannabinoids/ | 2588 |
| 2 | Hemp.mp. | 30 |
| 3 | Marihuana.mp. | 112 |
| 4 | Marijuana.mp. or marijuana smoking/ | 1510 |
| 5 | Ganja.mp. | 3 |
| 6 | Hashish*.mp. | 10 |
| 7 | Pot.mp. | 115 |
| 8 | Bhang.mp. | 1 |
| 9 | Dronabinol.mp. | 791 |
| 10 | Cannador.mp. | 1 |
| 11 | Epidiolex.mp. | 8 |
| 12 | Nabiximol.mp. | 0 |
| 13 | Sativex.mp. | 100 |
| 14 | Tetrahydrocannabinol.mp. | 725 |
| 15 | Ajulemic acid.mp. | 47 |
| 16 | Marinol.mp. | 24 |
| 17 | Syndros.mp. | 0 |
| 18 | Nabilone.mp. | 124 |
| 19 | Cesamet.mp. | 5 |
| 20 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 | 3509 |
| 21 | Neoplas*.mp. or exp Neoplasms/ | 77050 |
| 22 | Cancer*.mp. | 113419 |
| 23 | Carcino*.mp. | 33003 |
| 24 | Tumo?r*.mp. | 54022 |
| 25 | Sarcoma*.mp. | 1956 |
| 26 | 21 or 22 or 23 or 24 or 25 | 162544 |
| 27 | 20 and 26 | 214 |
| 28 | limit 27 to yr="2013 -Current" | 100 |
| 29 | limit 28 to medline records | 29 |
| 30 | 28 not 29 | **71** |

***CINAHL***

| # | Searches | Results |
|---|---|---|
| S1 | ( (MH "Medical Marijuana") OR (MH "Cannabis") OR "Cannabi*" ) OR Hemp OR Marihuana OR Marijuana OR Ganja OR Hashish* OR Pot OR Bhang OR Dronabinol OR Cannador OR Epidiolex OR Nabiximol | 15,950 |
| S2 | Sativex OR Tetrahydrocannabinol OR Ajulemic acid OR Marinol OR Syndros OR Nabilone OR Cesamet | 455 |
| S3 | S1 or S2 | 16,028 |
| S4 | (MH "Neoplasms+") OR Neoplas* OR Cancer* OR Carcino* OR Tumo#r* OR Sarcoma* | 601,776 |
| S5 | S3 and S4 | 689 |
| S6 | S3 and S4 Limiters - Published Date: 20130101-20191231 | **368** |

## Appendix 2: Reasons for exclusion at stage 2 full text screening.

| # | Reference | Reason for Exclusion |
|---|---|---|
| **1.** | Bhattacharyya, S., Mandal, S., Banerjee, S., Mandal, G. K., Bhowmick, A. K., & Murmu, N. (2015). Cannabis smoke can be a major risk factor for early-age laryngeal cancer--a molecular signaling-based approach. [Research Support, Non-U.S. Gov't]. Tumour Biology, 36(8), 6029-6036. | • Study in India<br>• Did not conduct quantitative analysis of cancer risk associated with cannabis use. The authors demonstrated higher expression of key proteins linked to the epidermal growth factor receptor (EGFR) in tumor tissues of patients with laryngeal cancer who were cannabis smokers compared to laryngeal cancer patients who were non-smokers or smokers of cigarettes. Previous research demonstrated that EGFR overexpression was associated with decreased patient survival rates and resistance to various therapeutic regimens. The authors concluded that increased expression of the EGFR cascade may cause early onset of aggressive laryngeal cancer in cannabis smokers. |
| **2.** | Fischer, B., Imtiaz, S., Rudzinski, K., & Rehm, J. (2016). Crude estimates of cannabis-attributable mortality and morbidity in Canada-implications for public health focused intervention priorities. [Research Support, Non-U.S. Gov't]. Journal of Public Health, 38(1), 183-188. | • Risk projection |
| **3.** | Frasch, K., Larsen, J. I., Cordes, J., Jacobsen, B., Wallenstein Jensen, S. O., Lauber, C., et al. (2013). Physical illness in psychiatric inpatients: comparison of patients with and without substance use disorders. [Research Support, Non-U.S. Gov't]. International Journal of Social Psychiatry, 59(8), 757-764. | • Cannabis is one of many substances studied<br>• Although cancer is one of the studied comorbidities, logistic regression analysis of association between cannabis and cancer was not performed due to lack of data ("empty cells" see table 3 of the publication) |
| **4.** | Ortiz, A. P., Gonzalez, D., Ramos, J., Munoz, C., Reyes, J. C., & Perez, C. M. (2018). Association of marijuana use with oral HPV infection and periodontitis among Hispanic adults: Implications for oral cancer prevention. Journal of Periodontology, 89(5), 540-548. | • Study in Puerto Rico<br>• Looked at marijuana use in association with risk factors of oral cancer, such as oral HPV infection, severe periodontitis |
| **5.** | Osazuwa-Peters, N., Adjei-Boakye, E., Loux, T. M., Varvares, M. A., & Schootman, M. (2016). Insufficient Evidence to Support or Refute the Association between Head and Neck Cancer and Marijuana Use. The Journal of Evidencebased Dental Practice, 16(2), 127-129. | • Overview of a systematic review which was already captured by the current search strategy |
| **6.** | Sordi, M. B., Massochin, R. C., Camargo, A. R., Lemos, T., & Munhoz, E. A. (2017). Oral health assessment for users of marijuana and cocaine/crack substances. Pesquisa Odontologica Brasileira = Brazilian Oral Research, 31, e102 | • Study in Brasil<br>• Does not specifically look at cannabis alone but in combination with other illicit drugs |
| **7.** | Xie, M., Gupta, M. K., Archibald, S. D., Stanley Jackson, B., Young, J. E. M., & Zhang, H. (2018). Marijuana and head and neck cancer: an epidemiological review. | • Enrolled consecutive patients with head and neck cancer and demonstrated that patients who were recreational marijuana users differed from non-users in terms of some |

| | | |
|---|---|---|
| | Journal of Otolaryngology: Head and Neck Surgery, 47(1), 73. | demographic, socioeconomic, lifestyle and tumor characteristics, and treatment modalities. Descriptive statistics were used to compare users and non-users. |

## Appendix 3: List of eligible studies

**Systematic reviews**


1. de Carvalho, M. F., Dourado, M. R., Fernandes, I. B., Araujo, C. T., Mesquita, A. T., & Ramos-Jorge, M. L. (2015). Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies. Archives of Oral Biology, 60(12), 1750-1755.
2. Gandhi, S., Vasisth, G., & Kapoor, A. (2017). Systematic review of the potential role of cannabinoids as antiproliferative agents for urological cancers. Canadian Urological Association Journal, 11(3-4), E138-E142.
3. Gurney, J., Shaw, C., Stanley, J., Signal, V., & Sarfati, D. (2015). Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer, 15, 897.
4. Huang, Y. H., Zhang, Z. F., Tashkin, D. P., Feng, B., Straif, K., & Hashibe, M. (2015). An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiology, Biomarkers & Prevention, 24(1), 15-31.
5. Martinasek, M. P., McGrogan, J. B., & Maysonet, A. (2016). A Systematic Review of the Respiratory Effects of Inhalational Marijuana. [Review]. Respiratory Care, 61(11), 1543-1551.
6. Memedovich, K. A., Dowsett, L. E., Spackman, E., Noseworthy, T., & Clement, F. (2018). The adverse health effects and harms related to marijuana use: an overview review. CMAJ open, 6(3), E339-E346.
7. NASEM. (2017). The National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.
8. Nugent, S. M., Morasco, B. J., O'Neil, M. E., Freeman, M., Low, A., Kondo, K., et al. (2017). The Effects of Cannabis Among Adults with Chronic Pain and an Overview of General Harms: A Systematic Review. [Review]. Annals of Internal Medicine, 167(5), 319-331.
9. Radoï, L., & Luce, D. (2013). A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community Dentistry & Oral Epidemiology, 41(2), 97-109.


**Original research articles**


1. Adejumo, A. C., Adegbala, O. M., Adejumo, K. L., & Bukong, T. N. (2018). Reduced Incidence and Better Liver Disease Outcomes among Chronic HCV Infected Patients Who Consume Cannabis. Canadian Journal of Gastroenterology & Hepatology, 2018, 9430953.
2. Adejumo, A. C., Ajayi, T. O., Adegbala, O. M., Adejumo, K. L., Alliu, S., Akinjero, A. M., et al. (2018). Cannabis use is associated with reduced prevalence of progressive stages of alcoholic liver disease. Liver International, 38(8), 1475-1486.
3. Callaghan, R. C., Allebeck, P., Akre, O., McGlynn, K. A., & Sidorchuk, A. (2017). Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011. Cancer Epidemiology, Biomarkers & Prevention, 26(11), 1644-1652.
4. Callaghan, R. C., Allebeck, P., & Sidorchuk, A. (2013). Marijuana use and risk of lung cancer: a 40-year cohort study. [Research Support, Non-U.S. Gov't]. Cancer Causes & Control, 24(10), 1811-1820.

5. Kricker, A., Burns, L., Goumas, C., & Armstrong, B. K. (2013). Cervical screening, high-grade squamous lesions, and cervical cancer in illicit drug users. [Research Support, Non-U.S. Gov't]. Cancer Causes & Control, 24(7), 1449-1457.
6. Marks, M. A., Chaturvedi, A. K., Kelsey, K., Straif, K., Berthiller, J., Schwartz, S. M., et al. (2014). Association of marijuana smoking with oropharyngeal and oral tongue cancers: pooled analysis from the INHANCE consortium. Cancer Epidemiology, Biomarkers & Prevention, 23(1), 160-171.
7. Thomas, A. A., Wallner, L. P., Quinn, V. P., Slezak, J., Van Den Eeden, S. K., Chien, G. W., et al. (2015). Association between cannabis use and the risk of bladder cancer: results from the California Men's Health Study. Urology, 85(2), 388-392.
8. Zhang, L. R., Morgenstern, H., Greenland, S., Chang, S. C., Lazarus, P., Teare, M. D., et al. (2015). Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. International Journal of Cancer, 136(4), 894-903.

## Appendix 4: Tabular summaries of eligible studies

### *Review articles*

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| de Carvalho, 2015 | **Objective**<br>• "This study aimed to update the subject and conduct a systematic literature review and meta-analysis among nine case–control studies to answer the following question: Does marijuana use favor the development of HNC [head and neck cancer]?"<br>**Cancers**<br>• Head and neck cancers | **Databases searched**<br>• The Cochrane Library<br>• Pubmed<br>• Lilacs<br>• Embase<br>• BBO<br>• Bireme SciELO<br>**Coverage**<br>• Period: before July 2015<br>• Language: English<br>• Articles of high or moderate methodological quality were used in statistical analyses.<br>**Studies Included**<br>• Systematic review (N=10)<br>• Meta-analysis: N=6 articles (describing 9 case-control studies) | • Yes | • OR=1.021, 95% CI: 0.912-1.143)<br>• No association between lifetime marijuana use and the development of head and neck cancer was found.<br>• Despite the lack of an overall association between the risk of head and neck cancer, an association may exist for specific histological types of head and neck tumors.<br>• "Despite several inferences that have been made to date, there is currently insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of HNC, which was underscored by the meta-analysis presented here." | • The meta-analysis included only "ever marijuana smoking" as an exposure variable.<br>• Due to methodological differences among included studies, characteristics of cannabis use (type, method of use, quantity, frequency, age at first use, duration of use, cumulative use) were not included in the meta-analysis.<br>• The response rate in the included studies ranged from 39% to 90%<br>• "Meta-analysis was performed with case–control studies and therefore a small or long-term effect cannot be excluded. It is essential to conduct longitudinal studies of representative samples in order to increase the power of inference results. | Included in NASEM 2017 review (see below) |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | | | | | In addition, further studies should be performed in places where marijuana is legalized, which could avoid underestimation of users or sub-reports." | |
| Gandhi, 2017 | **Objective**<br>• "The aim of this review is to look at the current evidence on the antiproliferative effects of cannabinoids in urological malignancies, including renal, prostate, bladder, and testicular cancers."<br>**Cancers**<br>• Testicular cancer | **Databases searched**<br>• Medline<br>• PubMed ("hand-search")<br>**Coverage**<br>• Period: 1946-September 30, 2016<br>• Language: English<br>**Studies Included**<br>• Total (N=23)<br>• Epi studies (N=4) | • No | • No conclusion regarding possible association between cannabis use and testicular cancer; the aim was to investigate potential biological mechanisms | • | • Includes the systematic review by Gurney et al. 2015 (see below)<br>• The authors describe their review as systematic; however, only PubMed and Medline, which is a subset (≈ 98%) of PubMed[3] were searched.<br>• Only 4 of the 23 included studies were epidemiological studies. Other articles describe mechanistic studies of cannabinoids as antiproliferative agents. |
| Gurney, 2015 | **Objective**<br>• "In this manuscript, we review the evidence regarding the association | **Databases searched**<br>• Cinahl<br>• Cochrane Library<br>• Embase<br>• Medline | Yes | **Ever-cannabis use vs. never-use**<br>• Testicular germ cell tumors (TGCT): OR=1.19 (95% CI: 0.72-1.95) | • "…it must be noted that these observations were derived from only three published | • Included in NASEM 2017 review (see below<br>• Meta-analyzed studies are the same |

[3] NLM NIH at: http://wayback.archive-it.org/org-350/20180312141605/https://www.nlm.nih.gov/pubs/factsheets/dif_med_pub.html
Government of Western Australis at: https://kemh.libguides.com/library/search_tips/faqs/difference_between_pubmed_medline_embase

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | between cannabis use and testicular cancer development."<br>**Cancers**<br>• Testicular cancer | • ProQuest Central<br>• ProQuest Dissertations and Theses<br>• Scopus<br>• Web of Science<br>Reference lists of eligible articles were searched for additional relevant studies. Two experts were asked to identify any missed studies.<br>**Coverage**<br>• Period: 1 Jan 1980 – 13 May 2015<br>• Language: no limit<br>**Studies Included**<br>•N=3 (all case-control studies) | | • Seminoma: OR=0.87 (95% CI: 0.48-1.61)<br>• Non-seminoma: OR=1.38 (95% CI: 0.78-2.43)<br>**Current cannabis use**<br>• TGCT: OR=1.62 (95% CI: 1.13-2.31)<br>• Seminoma: OR= 1.25 (95% CI: 0.80-1.96)<br>• Non-seminoma: OR=2.09 (95% CI: 1.29-3.37)<br>**Weekly or greater cannabis use**<br>• TGCT: OR=1.92 (95% CI: 1.35 -2.72)<br>• Seminoma: OR=1.27 (95% CI: 0.77-2.11)<br>• Non-seminoma: OR=2.59 (95% CI: 1.60-4.19)<br>**>=10 years of cannabis use**<br>• TGCT: OR=1.50 (95% CI: 1.08-2.09)<br>• Seminoma: OR=1.04 (95% CI: 0.66-1.66)<br>• Non-seminoma: OR=2.40 (95% CI: 1.52-3.80)<br>• "…we observed that a) current, b) chronic, and c) frequent cannabis use is associated with the development of TGCT – particularly non-seminoma TGCT – at least when compared to never-use of the drug. We found inconclusive evidence regarding the relationship between | studies; that these studies were all conducted in the United States; and the majority of data collection occurred during the 1990's."<br>• Exposure assessment in the three included studies was based on self-reports, either during a face-to-face interview (2 studies) or on a questionnaire 9one study). There is no indication that the interviewers were blinded to the case/control status of the participants.<br>• Low and differential response rates<br>• Due to the "pervasiveness" of cannabis use, it is likely that "ever-use" category includes individuals with very low exposure; therefore, ever-use may not be "a true measure of meaningful cannabis exposure" | as those meta-analyzed by Huang et al. 2015 (see below) |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | | | | ever- and former-use of cannabis and TGCT development."<br>• "There was insufficient evidence to conclude that there is a relationship between seminoma tumours and cannabis use. | | |
| Huang, 2015 | **Objective**<br>• "We will evaluate whether there is evidence to support an association between marijuana use and cancer risk, or support the lack of association."<br>**Cancers**<br>• Upper aerodigestive tract cancers [also referred to as head and neck cancers]<br>• Lung cancer<br>• Testicular cancer<br>• Childhood cancers<br>• All cancers<br>• Anal cancer<br>• Penile cancer<br>• Non-Hodgkin lymphoma<br>• Malignant primary gliomas<br>• Bladder cancer<br>• Kaposi sarcoma | **Databases searched**<br>• PubMed/Medline<br>Reference lists of eligible articles were searched for additional relevant studies.<br>**Coverage**<br>• Period: up to August 2014<br>• Language: no information<br>**Studies Included**<br>• •upper aerodigestive tract cancers (N=11)<br>• lung cancer (N=6)<br>• testicular cancer (N=3)<br>• childhood cancers (N=6)<br>• all cancers (N=1)<br>• anal cancer (N=1)<br>• penile cancer (N=1)<br>• non-Hodgkin lymphoma (N=2)<br>• malignant primary gliomas (N=1)<br>• bladder cancer (N=1)<br>• Kaposi sarcoma (N=1) | • Yes (testicular cancer)<br>• No (all other cancers) | **Head and neck cancers**<br>• **"**Studies on head and neck cancer reported increased and decreased risks, possibly because there is no association, or because risks differ by human papillomavirus status or geographic differences."<br>• "The evidence is inconsistent but may be consistent with no association or with opposite directions of association depending on subgroups of populations."<br>**Lung cancer**<br>• "The lung cancer studies appear to be consistent with no association with marijuana, although affirming no association is inherently difficult."<br>**Testicular cancer** | • Not reported | • The authors do not describe their review as systematic; two overlapping databases (PubMed and Medline) were searched. However, for testicular cancer a meta-analysis was conducted.<br>• This review is Included in NASEM 2017 (see below)<br>• Table 1 shows that "upper aerodigestive tract cancers" are head and neck cancers (see NCI, 2017)[4] with one possible exception (Zhang et al., ref. 12) that also included cancer of the esophagus<br>• Meta-analyzed studies on testicular |

[4] NCI [National Cancer Institute. Head and Neck Cancers. Reviewed: March 29, 2017. Accessed on February 4, 2019 at: https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | | | | • Ever use: OR=1.19 (95% CI: 0.72-1.95)<br>• Frequency of use <1 day or week: OR=1.28 (95% CI: 0.51-3.22)<br>• Frequency of use ≥day or week: OR=1.56 (95% CI: 1.09-2.23)<br>• Duration of use <10 years: OR=1.31 (95% CI: 0.60-2.84)<br>• Duration of use ≥10 years: OR=1.50 (95% CI: 1.08-2.09)<br>• "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."<br>**Other cancers**<br>• "insufficient data to make any conclusions" | | cancer are the same as those meta-analyzed by Gurney et al. 2015 (see above) |
| Martinasek, 2016 | **Objective**<br>• "This systematic review focuses on respiratory effects of inhalational marijuana."<br>**Cancers**<br>• Lung cancer | **Databases searched**<br>• PubMed<br>• OVID[5]<br>• Web of Science<br>**Coverage**<br>• Period: 1967-2015<br>• Language: English<br>• Inhalation marijuana only<br>**Studies Included** | • No | "Eight of the studies indicated an increased risk of lung cancer from cannabis use or cases indicating lung cancer occurrence… and 4 studies found either no significant association or a lower risk for lung cancer." | • Not reported | • This review includes epidemiological studies, case reports and experimental studies<br>• Lung cancer was one of several respiratory effects considered. |

[5] Unclear, which OVID database was searched

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | | • Lung cancer - total (N=12), including case-control (N=4); secondary data analyses of cohort studies (N=4); secondary analysis of pathology reports (N=1); case reports (N=2); experimental study (N=1) | | | | |
| Memedovich, 2018 | **Objective**<br>• "The objective of this work was to synthesize comprehensively the evidence of the health effects and harms (e.g., mortality, mental health outcomes, respiratory illnesses and cardiovascular diseases) of nonmedical marijuana use within a general population, providing clinicians with a broad and comprehensive overview of possible health impacts."<br>**Cancers**<br>• Testicular cancer<br>• Head and neck cancers<br>• Lung cancer<br>• Other cancers (bladder, prostate, | **Databases searched**<br>• Medline<br>• The Cochrane Database of Systematic Reviews<br>• Embase<br>• PsycINFO<br>• The Cumulative Index to Nursing and Allied Health Literature (CINAHL)<br>• The Health Technology Assessment Database<br>Reference lists of identified articles were searched for additional eligible articled<br>**Coverage**<br>• Period: until May 2018<br>• Language: English or French<br>**Studies included**<br>• Systematic reviews (N=4) | No | **Lung cancer**<br>• Mixed evidence (page E344)<br>• "No evidence of harm" (Box 1 on page E343)/"No association" (Table 1)<br>**Head and neck cancers**<br>• "No evidence of harm" (Box 1 on page E343)/"No association" (Table 1)<br>**Testicular cancer**<br>• "Evidence of harm" (Box 1 on page E343)/ "Association" (table 1)<br>**Other cancers**<br>• Inconclusive (Box 1 on page E343)/Insufficient evidence to draw conclusions (page E344) | • "This review is limited in the range of potential harms…"<br>• "This review was limited to English and French reviews, which may have excluded some important reviews."<br>• "Additionally, this review protocol was not registered in PROSPERO." | • Overview of systematic reviews.<br>• Several databases were searched; search strategy is described, full texts were reviewed by 2 independent reviewers, and numbers of studies identified, excluded (with reason) and included are reported.<br>• Although the overall conclusion regarding lung cancer is that there is no association/harm, on page E344 the evidence is characterized as "mixed" |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | penile, cervical, childhood cancers) | | | | | |
| NASEM [The National Academies of Sciences, Engineering and Medicine], 2017 | **Objective**<br>• "The committee was tasked with conducting a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products."<br>**Cancers**<br>• Lung cancer<br>• Head and neck cancers<br>• Testicular cancer<br>• Esophageal cancers<br>• Other cancers in adults (prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, bladder cancer)<br>• Parental cannabis use and cancer in offspring | **Databases searched**<br>• Medline<br>• Embase<br>• the Cochrane Database of Systematic Reviews<br>• PsycINFO<br>**Coverage**<br>• Period: January 1, 1999, through August 1, 2016<br>• Primacy was given to recent systematic reviews (published since 2011) and high-quality primary research that was published after the most recent systematic review.<br>• Only reviews of good or fair quality were considered.<br>• Where no systematic review existed, primary research for the entire period was reviewed<br>• Language: English<br>**Studies Included**<br>[see pp. 141-142]<br>• Systematic reviews (N=3)<br>• Primary literature articles (N=3)<br>[Note: Zhang et al. 2015 characterized by the | No [weight-of-evidence evaluation] | "**There is moderate evidence of *no* statistical association between cannabis use and:**<br>• Incidence of lung cancer (cannabis smoking) …<br>• Incidence of head and neck cancers…<br>**There is limited evidence of a statistical association between cannabis smoking and:**<br>• Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) …<br>**There is no or insufficient evidence to support or refute a statistical association between cannabis use and:**<br>• Incidence of esophageal cancer (cannabis smoking) …<br>• Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal | • Although this is not a systematic review, it has several key features of the systematic review process[6].<br>• "…there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee." | • Weight-of-Evidence evaluation<br>• This review includes systematic reviews by de Carvalho et al. 2015; Gurney et al. 2015; Huang et al. 2015 |

[6] "First, the committee was not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, prespecification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict of interest policies."

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
|---|---|---|---|---|---|---|
| | | Committee as systematic review is a pooled analysis of raw data from several studies.] | | cancer, Kaposi's sarcoma, or bladder cancer…<br>• Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) …" | | |
| Nugent, 2017 | **Objective**<br>• "To review the benefits of plant-based cannabis preparations for treating chronic pain in adults and the harms of cannabis use in chronic pain and general adult populations."<br>**Cancers**<br>• Head and neck cancers<br>• Lung cancer<br>• Testicular cancer<br>• Transitional cell carcinoma | **Databases searched**<br>• Medline<br>• Embase<br>• PubMed<br>• PsycINFO<br>• Evidence-Based Medicine Reviews (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, and Cochrane Central Register of Controlled Trials)<br>• Grey literature<br>• Additional articles were identified from reference lists and expert recommendations<br>**Coverage**<br>• Period: through February 2016; the search for new RCTs and systematic | • No | **Lung cancer**<br>• Studies: "1 patient- level meta-analysis (57) of 6 case-control studies; combined N=2150. 1 high-ROB cohort study (58); N=49231"<br>• Findings: Meta-analysis found no association between light cannabis use and lung cancer"<br>• Strength of evidence: low<br>• Comments: "Recall bias; mostly light users, few heavy users; large cohort study had no information about exposure over time"<br>**Head and neck cancers**<br>• Studies: "Meta-analysis (59) of 9 case-control studies; combined N=5732"<br>• Findings: "No association between cannabis use | • Limitations of the evidence base: "In observational studies, the exact dose of exposure to cannabis was rarely known because of recall bias, and the potency (that is, in estimates of cannabis cigarettes smoked per day) was impossible to assess."<br>• Limitations in the approach to synthesizing the literature: "Given the broad scope of our review, we relied on existing systematic reviews to identify the best available evidence. However, we also | • Ref. 57: Zhang et al. 2015 - pooled analysis of individual data; see table summarizing original research<br>• Ref. 58: Callaghan et al. 2015; see table summarizing original research<br>• Ref. 59: de Carvalho et al. 2015 – see above<br>• Ref 60: Gurney et al. 2015 – see above.<br>• Ref. 61: Chacko JA, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. Urology. 2006 Jan;67(1):100-4. |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
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| | | reviews was updated in March 2017<br>• Language: English<br>• Studies assessing the effects of cannabis on non-pregnant adults<br>**Studies included**<br>• Systematic reviews (N=2)<br>• Pooled analysis of individual data (N=1)<br>• Original research (N=2) | | and cancer (OR, 1.02 [95% CI, 0.91–1.14]); generally consistent across studies and no evidence of dose-response"<br>• Strength of evidence: low<br>• Comments: "Imprecise exposure measurement with potential recall bias; ever-use among studies ranged from 1%–83%"<br>**Testicular cancer**<br>• Studies: "Meta-analysis (60) of 3 high-ROB case-control studies; combined N=719"<br>• Findings: "Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer (OR, 1.92 [95% CI, 1.35–2.72])"<br>• Strength of evidence: insufficient<br>• Comments: "Potential confounding from recall bias and tobacco use"<br>**Transitional cell carcinoma**<br>• Studies: "1 high-ROB VA case-control study (61); N=52"<br>• Findings: Risk of cancer with >40 joint-years cannabis use vs. none | comprehensively searched for and included newer primary studies, included only good-quality systematic reviews…" | |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
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| | | | | (OR, 3.4; unadjusted P = 0.012)."<br>• Strength of evidence: insufficient<br>• Comments: "1 very small case-control study with several methodological flaws" | | |
| Radoi and Luce 2013 | **Objective**<br>• "The aim of this work is to review the literature on risk factors of oral cavity cancer with a special attention to the definition of the cases, in order to highlight special features of these cancers and if possible of their subsites."<br>**Cancers**<br>• Oral cavity cancer (ICD-9 codes 140, 141, 143–145; or ICD-10 codes C00–C06) | **Databases searched**<br>• PubMed<br>• Reference lists were searched for additional relevant articles<br>**Coverage**<br>• Period: January 1980-December 2010<br>• Language:<br>**Studies included**<br>• Studies on marijuana smoking (N=1) | • No | • "A pooled-analysis of five case–control studies in INHANCE did not find an increased risk of oral cavity cancer associated with marijuana smoking (OR = 0.7, 95% CI 0.6–1.0), and there was no association with frequency (OR = 0.6, 95% CI 0.3–1.5 for marijuana smoking >3 times/day), duration (OR = 0.7, 95% CI 0.4–1.4 for marijuana smoking >20 years) or cumulative consumption (OR = 0.7, 95% CI 0.5–1.2 for >5 joint-years). In addition, the analysis restricted to never tobacco and never alcohol users did not find an association between head and neck cancer risk and marijuana smoking (62)."<br>• No conclusion was made regarding marijuana smoking as a risk factor | • "There is no standard definition of oral cavity cancer in the literature, making demonstration of the particular characteristics of oral cavity cancer risk factors is difficult. Even in anatomy textbooks, the boundaries of oral cavity and oropharynx are not clearly defined and it is not clear if some anatomical sites such as base of the tongue and soft palate belong to the oral cavity or to the oropharynx."<br>• "This literature review shows that few studies have examined other risk factors than alcohol and tobacco specifically for oral | • Although this work is described as "unsolicited systematic review", only one database was searched<br>• Marijuana smoking was not the focus of this review.<br>• Only one study on marijuana smoking and oral cavity cancers was reviewed.<br>• Ref 62: Berthiller et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev. 2009 May;18(5):1544-51 |

| Reference | Objective and Health endpoint | Comprehensiveness | Meta-analysis | Results and Authors' conclusions | Author's reported limitations | Comments |
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| | | | | | cavity. In addition, studies differentiating between subsites are rare, and most results come from case-series. It was not possible to perform meta-analyses because of the heterogeneity of the definition of the oral cavity across the included studies and the variability in the risk factors examined." | |

### *Original studies*

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| Adejumo, 2018a<br>• Cross-sectional<br>• USA | • HCV-positive adults (age ≥18 years) identified from hospital records<br>• N=4,728 (cannabis users); N=4,728 (cannabis non-users matched using a propensity-based matching system[7])<br>• Cannabis users: mean age 40 (SD 13) years; 55% males<br>• Cannabis non-users: mean age 53 (SD 14) years; 54% males | • Cannabis users were identified using ICD-9-CM codes (not specified)<br>• The code selects patients using Indian hemp, marijuana and cannabinoid-containing substances<br>• To approximate the quantity and frequency of use, cannabis users were categorized into dependent and non-dependent users based on ICD-9-CM codes | • Liver cancer identified using ICD-9-CM codes | • Adjusted prevalence rate ratio (aPRR)=0.79 (95% CI: 0.55-1.13)<br>• "adjusted by matching"<br>• Additional adjustment for cirrhosis in analyses of liver cancer | **Conclusion**<br>• Prevalence of liver cancer was not significantly different between cannabis users and non-users<br>**Limitations**<br>• "The major weaknesses in our study are the cross-sectional design, recall biases, coding errors in the ICD-9-CM application, lack of information on medications such as antiviral therapies, type of cannabis ingested, mode of cannabis use (oral versus inhalation), and sensitivity and specificity of ICD-9-CM coding for cannabis use disorder."<br>• "Absence of data on which patients received the new direct-acting antiviral therapy is a significant limitation, given that these medications are extremely effective and significantly modulate the progress of HCV liver disease."<br>• "…it is possible that additional unmeasured confounding factors might still impact our observations." | • Study not included in identified reviews<br>• aPRR of liver cancer was not reported separately for dependent and non-dependent cannabis users |
| Adejumo, 2018b | • Adults (age ≥18 years) with the | • To approximate an increasing | • Hepatocellular carcinoma | **Adjusted odds ratios (ORs)** | **Conclusion** | • Study not included in |

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144483/

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| • Cross-sectional<br>• USA | past or current history of alcohol abuse identified from hospital records based on ICD-9-CM codes<br>• N=319,541 (total); N=288,795 (non-cannabis users); N=26,382 (non-dependent cannabis users); N=4,337 (dependent cannabis users)<br>• ≈73% males<br>• Mean age not reported; distribution by age reported in table 1 of the publication | dose effect, cannabis users were categorized into dependent and non-dependent users based on ICD-9-CM codes<br>• ICD-9 CM codes for dependent cannabis use: 304.3, 304.30, 304.31, 304.32, 304.33<br>• ICD-9 codes for non-dependent cannabis use: 305.2, 305.20, 305.21, 305.22, 305.23<br>• {See supporting Materials] | (HCC) identified using ICD-9-CM code 155 [see Supporting Materials] | • Cannabis use vs. non-use: OR=0.62 (95% CI: 0.51-0.76)<br>• Non-dependent cannabis use vs. non-use: OR=0.67 (95% CI: 0.55-0.82)<br>• Dependent use vs. non-dependent use: OR=0.37 (95% CI: 0.15-0.91)<br>• Cannabis use vs. non-use additionally adjusted for alcoholic cirrhosis (AC): OR=0.80 (95% CI: 0.65-0.97)<br>• "…about 88% of the effect of CU [cannabis use] in reducing the odds of HCC was mediated through the reduction in AC prevalence…"<br>• Adjustment for age, gender, household income, insurance type, race, MS, overweight/obesity, DM, protein-energy malnutrition (PEM), hemochromatosis, tobacco use, HIV, HBV, and hyperlipidemia [see Supporting Materials] | • "Our study revealed that among alcohol users, individuals who additionally use cannabis (dependent and non-dependent cannabis use) showed significantly lower odds of developing…HCC…"<br>**Limitations**<br>• "As a cross-sectional methodology, our study cannot establish direct cause and effects."<br>• "There are other potential residual confounders, such as the type, duration and route of cannabis usage. Different cannabis strains contain a different ratio of CBD [cannabidiol] and THC [tetrahydrocannabinol], exerting a different net effect…. As we do not have data on what strain or how much CBD/THC was being consumed by the subjects in our study, we are unable to estimate how it influences our findings…" | identified reviews<br>• Unclear, what MS stands for |
| Callaghan, 2017<br>• Cohort<br>• Sweden | • Young men who underwent medical and psychological assessment for conscription for compulsory military service in 1969-1970 | • Cannabis use assessed based on responses to questions in the self-reported, non-anonymous conscription-assessment questionnaire | • Incident cases of testicular cancer identified from the National Patient Register, the Cancer | **Fully adjusted hazard ratios (HRs)**<br>• Ever cannabis use vs. never use of any drug: HR=1.42 (95% CI: 0.83-2.45)<br>• Lifetime level of use vs. never use of any drug<br>1-4 times: HR=0.95 (95% CI: 0.41–2.19) | **Conclusion**<br>• "In this Swedish record-linkage study, we found that self-reported 'heavy' cannabis use—defined as self-reported use of more than 50 times in lifetime at the conscription assessment period—was significantly associated with a | • Study not included in the identified systematic reviews<br>• Previous studies were case-control. |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | • N=45,250<br>• Age 18-21 years<br>• 135 testicular cancer cases during the follow-up period (1970-2011) | • Lifetime ever use (yes/no)<br>• Lifetime level of use: 1-4, 5-10, 11-50, >50 times | Register, and the Cause of Death Register using unique personal numbers for linkage, and the Swedish version of ICD-7/8/9/10 codes | 5-10 times: HR=2.15 (95% CI: 0.77–5.95)<br>11-50 times: HR=1.17 (95% CI: 0.28–4.85)<br>>50 times: HR=**2.57 (95% CI: 1.02–6.50**)<br>• Adjustment for age, cryptorchidism, family history of testicular cancer, tobacco use, and alcohol use | 2.5-fold increased hazard of subsequent testicular cancer. The study found no evidence of a significant relation between "ever" cannabis use and the development of testicular cancer. This null finding may be due to heterogeneity of cannabis use in the "ever" group, as this category contained only a minority who reported 'heavy' cannabis use and a majority of individuals indicating minimal lifetime cannabis exposure (e.g., 1–4 times in lifetime)."<br>• "The current study provides additional evidence to the limited prior literature suggesting cannabis use may contribute to the development of testicular cancer."<br>**Limitations**<br>• "The key variable instantiating conscripts' lifetime level of cannabis use relied on an indirect assessment of cannabis use. It was assumed that for those conscripts indicating "ever" cannabis use, the conscription survey question eliciting information about lifetime level of drug use (i.e., "How many times have you used drugs?") | • Large cohort followed for ≈40 years |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | | applied to individuals' cannabis use."<br>• "…the current study did not have information about cannabis use after the conscription assessment period… Even though unmeasured postconscription changes in cannabis use may have affected our results, such misclassification biases would tend to attenuate our HR estimates and push our findings toward the null."<br>• "…the study had no information on the histology of the testicular cancers." | |
| Callaghan, 2013<br>• Cohort<br>• Sweden | • Young men (age 18-20 years) conscripted for compulsory military service in 1969-1970.<br>• N=44,257<br>• 179 lung cancer cases during the follow-up period (1970-2009) | • Cannabis use assessed based on non-anonymous self-reported information collected at conscription<br>• Lifetime ever use (yes/no)<br>• Lifetime level of use: once, 2-4, 5-10, 11-50, >50 times | • Lung cancer cases (ICD 8/9 codes 162.x; ICD-10 codes C33.x or C34.x) identified from the Swedish Patient Register and the Cause of Death Register | **Fully adjusted hazard ratios (HRs)**<br>• Ever cannabis use vs. never use of any drug: HR=1.25 (95% CI: 0.84-1.87)<br>• Lifetime level of use vs. never use of any drug<br>Once: HR=1.52 (95% CI: 0.77-3.01)<br>2-4 times: HR=0.66 (95% CI: 0.27–1.62)<br>5-10 times: HR=0.68 (95% CI: 0.21–2.16)<br>11-50 times: HR=1.68 (95% CI: 0.77–3.66)<br>>50 times: HR=**2.12 (95% CI: 1.08–4.14)**<br>• Adjustment for age, cryptorchidism, family history of | **Conclusion**<br>• "Our population-based cohort study of young Swedish males aged 18–20 years old at conscription (1969–1970) found that heavy cannabis smoking, defined at baseline as self-reported lifetime use of at least 50 times, was significantly associated with more than a twofold risk… of developing lung cancer over the 40-year follow-up period, even after statistical adjustment for baseline tobacco use and other potential confounders." | • Study included in reviews by NASEM 2017 and Nugent et al. 2017<br>• Study subjects were 60-year old at the end of follow-up. Lung cancer incidence peaks at older ages[8]. |

[8] See, for example UK statistics at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-One

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | testicular cancer, tobacco use, and alcohol use | • "It is important to note, however, that our results… did not show evidence of a clear dose–response relationship between frequency of marijuana use and lung cancer outcomes."<br>• "Our primary finding, requiring further replication, does provide initial longitudinal evidence that cannabis use might elevate the risk of lung cancer."<br>**Limitations**<br>• "Our project did not include detailed assessment information of use patterns of cannabis or tobacco preceding the baseline conscription process; it also did not have any information about tobacco or marijuana use after conscription. … It is important to note that even though unmeasured post-conscription changes in marijuana or tobacco use may have affected our results, misclassification biases would tend to attenuate our hazard ratio estimates and push our findings toward the null."<br>• "…our primary finding may have been influenced by residual confounding due to tobacco smoking, as more than 91 % of heavy cannabis | |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | | users also reported some tobacco smoking at conscription. It is also possible that cannabis smokers in our study may have mixed tobacco into their marijuana cigarettes, a process that would unduly inflate the marijuana-related risk of lung cancer outcomes."<br>• "…conscripts gave nonanonymous reports of marijuana use, and even though they were reassured that their responses would not affect military placement, it is possible that the nonanonymity may have led to underestimates of marijuana use. Biased self-reports would likely inflate the cancer risk in the nonmarijuana-using groups—our reference group in our modeling strategies. An inflated lung cancer risk in the reference group would produce a downward bias in the association between marijuana use and lung cancer."<br>• "…we acknowledge the possibility of misclassification bias. The extent and direction of this is difficult to assess, though. | |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| Kricker, 2013<br>• Nested case-control<br>• Australia | • Women aged 20-54 years identified from hospital admission records in the Admitted Patient Data Collection (APDC) between 1 July 2000 and 31 December 2006<br>• N=213,788 (total)<br>• N=19,699 with drug-related hospital admission<br>• N=6,523 women with CIN 2/3 diagnosis; N=65,230 aged-matched controls<br>• N=239 cervical cancer cases; N=2,390 age-matched controls | • Drug users (women who had a hospital admission related to use of illicit drugs) identified using ICD-10-AM codes F11.0-F12.9, F14.0-F15.9, T40.1-T40.9, T43.6<br>• Any use of cannabinoids identified using ICD-10-AM codes F12 or T40.7)<br>• No drug use (women who "had an admission in the same year as cases and were the same age but had no illicit drug-related admission") | • Cervical intraepithelial neoplasia (CIN) 2/3 and cervical cancer identified by probabilistic linkage to data from the New South Wales (NSW) Pap Test Register and the population-based NSW Central Cancer Registry | **Adjusted odds ratios (ORs)**<br>• Cervical intraepithelial neoplasia (CIN) 2/3<br>Any cannabinoid use: OR=1.18 (95% CI: 1.06-1.32)<br>Any cannabinoid use, never smokers: OR=1.45 (95% CI: 1.22-1.72)<br>• Cervical cancer<br>Any cannabinoid use: OR=1.42 (95% CI: 0.77-2.60)<br>Any cannabinoid use, never smokers: OR=0.76 (95% CI: 0.23-2.54)<br>• Adjustment for number of years of pup tests, smoking [Because inclusion of SES changed the OR by <2%, it was not included in the final model.] | **Conclusions**<br>• "Our results suggest that drug users have less cervical screening and greater risks of CIN 2/3 and cervical cancer than do non-drug-users. The greater risks we observed were independent of differences in cervical screening and probably also of tobacco smoking between drug users and non-users. Of other potentially important behaviors, sex risk behaviors and the associated high risk of HPV are the most likely explanations for the apparently increased risk of CIN 2/3 and cervical cancer in drug users."<br>• "There was no strong evidence that use of cannabinoids was more strongly associated with CIN 2/3 or cervical cancer than other drug types."<br>**Limitations**<br>• "lack of information on HPV or HIV status and on co-infection with other STDs"<br>• "…we are unable to estimate the degree to which the APDC provides a representative sample of NSW women though, as indicated, reasons for admissions in non-drug-users in our study were very | • Study not included in identified reviews<br>• Although the risk of CIN 2/3 is significantly increased in cannabinoid users, the authors explain the increase by risky sex behaviours and associated HPV infection in drug users rather than the effect of the drug itself. |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | | similar to all Australian women aged 20–54."<br>• "Our use of diagnosis codes in hospital admission records to identify drug users is likely to misclassify some users as non-users. Misclassification of users as non-users would tend to weaken associations of drug use with the outcomes we investigated rather than to create spurious associations."<br>• "Lack of information on the intensity and duration of smoking is a weakness, particularly because it would lead to incomplete control of confounding by smoking in the analysis."<br>• "…we were unable to exclude the estimated 6 % of women who have had a hysterectomy in NSW by 54 years of age" | |
| Marks, 2014<br>• Case-control<br>• Pooled analysis of data from 9 studies conducted in USA and Latin America | • Individual data from nine studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium<br>• N=2,325 cases (1,921 oropharyngeal | • 4 studies asked subjects to report the average frequency of marijuana use over their lifetime<br>• For 5 studies that obtained information about marijuana use during | • Oropharyngeal cancers: tumors of the oropharynx (ICD-02 codes C10.0–C10.9), base of tongue (ICD-02 code C0.19), tonsils (ICD-02 codes C09.0–C09.9, C02.4), soft palate (ICD-02 | **Oropharyngeal cancer; adjusted odds ratios (ORs)**<br>• Ever vs. never use: OR= 1.24 (95% CI: 1.06–1.47)<br>• Use per week vs. never use<br>≤3: OR=1.24 (95% CI: 1.02–1.52)<br>>3: OR=1.19 (95% CI: 0.94–1.52)<br>P trend= 0.046<br>• Duration of use vs. never use<br>≤10 years: OR=1.11 (95% CI: 0.91–1.36)<br>>10 years: OR=1.28 (95% CI: 1.02–1.61) | **Conclusions**<br>• "Using pooled data from 9 case–control studies that contributed to the INHANCE consortium, we found evidence of a possible positive association of marijuana use with oropharyngeal cancer and a negative association with oral tongue cancer."<br>• "…the inconsistent association across studies in | • Study included in reviews by De Carvalho et al. 2015 and Huang et al. 2015<br>• ICD-02 – International Classification of Diseases for Oncology second edition. |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | and 365 oral tongue)<br>• N=7,639 controls | different periods of the subject's lifetime, the lifetime average frequency of use was calculated.<br>• Categorization of use: ever/never; frequency per week (never, ≤3, >3), duration of use (never, ≤10, >10 years); cumulative use (never, >0-1, 2-10, >10 joint-years) | code C05.1), and uvula (ICD-02 code C05.2).<br>• Oral tongue cancers: tumors of the dorsal surface (ICD-02 code C02.0), border (ICD-02 code C02.1), and ventral surface (ICD-02 code C02.2) of the tongue.<br>• Analyses were restricted to squamous cell carcinomas (SCC) using histologic codes provided by the ICD-02 (8050–8084). | P trend = 0.031<br>• Cumulative exposure vs. never use<br>>0-1 joint-year: OR=1.12 (95% CI: 0.87–1.45)<br>2-10 joint-years: OR=1.34 (95% CI: 1.04–1.71)<br>>10 joint-years: OR=1.14 (95% CI: 0.85–1.52)<br>P trend=0.055<br>**Oropharyngeal cancer; adjusted odds ratios (ORs) in <u>never tobacco smokers/never drinkers</u>**<br>• Ever vs. never use: OR= 2.11 (95% CI: 0.97–4.62)<br>• Use per week vs. never use<br>≤3: OR=2.35 (95% CI: 0.92–5.99)<br>>3: OR=1.61 (95% CI: 0.31–8.50)<br>P trend= 0.117<br>• Duration of use vs. never use<br>≤10 years: OR=1.82 (95% CI: 0.72–4.62)<br>>10 years: OR=2.66 (95% CI: 0.63–11.24)<br>P trend = 0.08<br>• Cumulative exposure vs. never use<br>>0-1 joint-year: OR=1.57 (95% CI: 0.53–4.66)<br>2-10 joint-years: OR=2.83 (95% CI: 0.66–12.1)<br>>10 joint-years: OR=3.94 (95% CI: 0.59–26.3)<br>P trend=0.037<br>**Oropharyngeal cancer; adjusted odds ratios (ORs) from 4 studies** | this pooled analysis combined with an attenuation in the association after adjustment for smoking and drinking make the effect of residual and unmeasured confounding highly plausible."<br>• "…the positive association of marijuana use and oropharyngeal cancer may be dependent on exposure to HPV."<br>**Limitations**<br>• "We acknowledge the possibility that misclassification in the measurement of marijuana use between cases and controls may explain some of these findings. … it cannot be ruled out that either differential or nondifferential misreporting of marijuana exposure may explain the observed associations of marijuana use with oropharynx and oral tongue cancers." | |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | **with data on HPV 16 L1 antibody status**<br>• Ever vs, never use<br>No adjustment for HPV status: OR=0.89 (95% CI: 0.65-1.19)<br>Adjusted for HPV status: OR=0.87 (95% CI: 0.66-1.16)<br>Individuals seronegative for HPV: OR=0.54 (95% CI: 0.34-0.85)<br>Individuals seropositive for HPV: OR=1.19 (95% CI: 0.72-1.98)<br>**Oral tongue cancers; adjusted ORs**<br>• Ever vs. never use: OR= 0.47 (95% CI: 0.29–0.75)<br>• Use per week vs. never use<br>≤3: OR=0.47 (95% CI: 0.25–0.89)<br>>3: OR=0.47 (95% CI: 0.23–0.95)<br>P trend= 0.005<br>• Duration of use vs. never use<br>≤10 years: OR=0.43 (95% CI: 0.23–0.77)<br>>10 years: OR=0.44 (95% CI: 0.21-0.94)<br>P trend = 0.002<br>• Cumulative exposure vs. never use<br>>0-1 joint-year: OR=0.39 (95% CI: 0.18-0.88)<br>2-10 joint-years: OR=0.64 (95% CI: 0.31-1.29)<br>>10 joint-years: OR=0.31 (95% CI: 0.11–0.89)<br>P trend=0.004<br>• Adjustment for age, sex, education, race/ethnicity, pack-years of cigarette smoking, ever | | |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | pipe/cigar smoking, intensity of alcohol drinking | | |
| Thomas, 2015<br>• Cohort<br>• USA | • Men aged 45-69 years at enrollment (in January 2000) in the California Men's Health Study (CMHS) cohort<br>• N=82,050<br>• 279 bladder cancer cases during the follow-up (up to December 31, 2011) | • Data on cannabis use from mailed questionnaires completed between 2002 and 2003<br>• Questions included the number of times of cannabis use (none, 1-2, 3-10, 11-99, 100-499 or >500 times). | • Bladder cancer ascertained by linkage with cancer registries | **Adjusted hazard ratios (HRs)**<br>• Cannabis use only vs. neither cannabis nor tobacco: HR=0.55 (95% CI:0.31-1.00)<br>• Cannabis and tobacco use vs. neither cannabis nor tobacco: HR=1.28 (95% CI: 0.91-1.80)<br>• Adjustment for age, body mass index (BMI), race/ethnicity<br>• Cannabis use only vs. neither cannabis nor tobacco<br>Age 45-54 at baseline: HR=0.26 (95% CI: 0.07-0.92)<br>Age 55-69 at baseline: HR=0.67 (95% CI: 0.35-1.27)<br>•Cannabis and tobacco use vs. neither cannabis nor tobacco<br>Age 45-54 at baseline: HR=0.98 (95% CI: 0.45-2.12)<br>Age 55-69 at baseline: HR=1.28 (95% CI: 0.88-1.86)<br>Adjustment for race and BMI<br>• By number of times of cannabis use vs. non-use of cannabis<br>1-2: HR= 1.10 (95% CI: 0.71-1.70)<br>3-10: HR= 0.57 (95% CI: 0.34-0.96)<br>11-99: HR= 0.66 (95% CI: 0.41-1.07)<br>100-499: HR= 0.86 (95% CI: 0.49-1.52)<br>>500: HR= 0.69 (95% CI:0.38-1.27)<br>• Adjustment for age, body mass index (BMI), race/ethnicity, smoking | **Conclusion**<br>• "In this multiethnic cohort of 82,050 men, we found that cannabis use alone was associated with a decreased risk of bladder cancer."<br>• "In conclusion, we observed an inverse association between cannabis use and the development of bladder cancer."<br>**Limitations**<br>• "The CMHS is a prospective observational study, which may be affected by participation and response biases."<br>• "…we did not evaluate other risks factors for bladder cancer, which might also play a role in the development of bladder cancer such as environmental or occupation exposures."<br>• "The CMHS was limited to men, and therefore, we could not assess this relationship in women."<br>• "…we did not assess the time course between cannabis use and the association of bladder cancer incidence. It is plausible that there may be an additional difference in the association of bladder cancer | Study included in review by NASEM 2017 |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | | risk in current vs former cannabis users." | |
| Zhang, 2015<br>• Case-control<br>• Pooled analysis of data from 6 studies conducted in USA, Canada, UK and New Zealand | • Individual data from 6 case-control studies within the International Lung Cancer Consortium<br>• N=2,159 lung cancer cases<br>• N=2,985 controls | • "Data on individual-level cannabis smoking consumption were based on self-reported responses to questions on study-specific questionnaires."<br>• Lifetime habitual use of cannabis was defined as a cumulative consumption of at least 1 joint-year (i.e., smoking 1 joint/day for 1 year).<br>• "Joint-equivalent was defined as the average cannabis plant matter contained in a typical joint or 0.75 g/joint when the unit of reporting was weight or the mode of | • Lung cancer | **Odds ratios (ORs)**<br><u>All lung cancers</u><br>• Habitual vs. non-habitual smoker: OR=0.96 (95% CI: 0.66-1.38)<br>• Intensity (joints/day) vs. nonhabitual smoker<br><1: HR= 0.77 (95% CI: (0.51–1.16)<br>≥1: HR= 0.88 (95% CI: 0.63-1.24)<br>Continuous: HR= 1.02 (95% CI: 0.92-1.13)<br>• Duration (years) vs. non-habitual smoker<br>>0-<20: HR=0.94 (95% CI: 0.70–1.26)<br>≥20: HR=1.03 (95% CI: 0.54–1.98)<br>Continuous: HR=0.99 (95% CI: 0.97-1.02)<br>• Joint-years vs. Non-habitual smoker<br>1-<10: HR=0.69 (95% CI: 0.41-1.17)<br>≥10: HR=0.94 (95% CI: 0.67-1.32)<br>Continuous: HR=1.00 (95% CI: 0.99-1.00)<br>• Age of start, years vs. non-habitual smoker<br>>18: HR=0.75 (95% CI: 0.53-1.08)<br>≤18: HR=0.86 (95% CI: 0.62-1.19)<br>• "Use of restricted cubic splines to examine the dose-response associations between cannabis use and lung-cancer incidence did not exhibit monotonic associations for average joints per day or duration of use… There was, however, a positive | **Conclusions**<br>• "In our pooled results, we found little or no association between the intensity, duration, cumulative consumption or age of start of cannabis smoke and the risk of lung cancer in all subjects or never smokers, and suggestive association for adenocarcinoma. The evidence for the association with other histological subtypes is limited by the small sample size. In the spline analyses, there was a weak increasing trend over long-term and high levels of cumulative cannabis smoking exposure. The confidence intervals were wide due to the limited number of observations at the high exposure levels, but the results are more compatible with an association with lung cancer at high levels of cannabis exposure than with no association."<br>• "Results from our pooled analyses provide little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the | Study included in reviews by Huang et al. 2015, Martinasek et al. 2016, NASEM et al. 2017, Nugent et al. 2017 |

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| | | consumption was other than joint." | | monotonic association between joint-years of cannabis use and lung cancer… but the 95% confidence bands were wide, especially for higher exposure levels."<br><u>All lung cancers in never tobacco smokers</u><br>• Habitual vs. non-habitual smoker: OR=1.03 (95% CI: 0.51-2.08)<br>• Intensity (joints/day) vs. nonhabitual smoker<br><1: HR=1.33 (95% CI: 0.61-2.93)<br>≥1: HR=0.49 (95% CI:0.11-2.25)<br>Continuous: HR=1.08 (95% CI: 0.91-1.30)<br>• Duration (years) vs. non-habitual smoker<br>>0-<20: HR=0.89 (95% CI: 0.39-2.00)<br>≥20: HR=1.64 (95% CI: 0.45-6.00)<br>Continuous: HR=0.97 (95% CI: 0.93-1.01)<br>• Joint-years vs. non-habitual smoker<br>1-<10: HR=1.26 (95% CI: 0.57-2.75)<br>≥10: HR=0.54 (95% CI: 0.12-2.55)<br>Continuous: HR=1.00 (95% CI: 0.93-1.07)<br>• Age of start, years vs. non-habitual smoker<br>>18: HR=1.25 (95% CI: 0.47-3.29)<br>≤18: HR=0.85 (95% CI: 0.32-2.31)<br><u>Adenocarcinoma</u><br>• Habitual vs. non-habitual smoker: OR=0.99 (95% CI: 0.73-1.33)<br>• Intensity (joints/day vs. nonhabitual smoker | possibility of potential adverse effect for heavy consumption cannot be excluded."<br>**Limitations**<br>• "limited number of observations at the high exposure levels"<br>• "…misclassification of cannabis use no doubt occurred and may have flattened or distorted the dose-response relation." | |

| Study | Study participants | Exposure | Outcome | Main quantitative results [covariates adjusted for] | Authors' conclusion and Author's reported Limitations | Comments |
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| | | | | <1: HR=0.72 (95% CI: 0.48-1.10)<br>≥1: HR=1.73 (95% CI: 0.75-4.00)<br>Continuous: HR=1.04 (95% CI: 0.93-1.17)<br>• Duration (years) vs. non-habitual smoker<br>>0-<20: HR=0.98 (95% CI: 0.69-1.39)<br>≥20: HR=1.08 (95% CI: 0.60-1.96)<br>Continuous: HR=0.99 (95% CI: 0.97-1.02)<br>• Joint-years vs. Non-habitual smoker<br>1-<10: HR=0.67 (95% CI: 0.41-1.11)<br>≥10: HR=1.74 (95% CI: 0.85-3.56<br>Continuous: HR=1.00 (95% CI: 0.99-1.00)<br><u>Squamous cell carcinoma</u><br>• Habitual vs. non-habitual smoker: OR=1.55 (95% CI: 0.35-6.87)<br>• Smoking for >20 years vs. non-habitual smoker: OR=1.58 (95% CI: 0.48-5.20)<br>• Cumulative exposure of ≥10 joint-years vs. less than 1 joint-year: OR=2.35 (95% CI: 0.48-11.46)<br>• Adjustment for age, sex, race, education, tobacco smoking | | |