

ABSTRACT

Background: The relationship between marijuana smoking and lung cancer has become increasingly relevant, as cannabis is the most commonly used illegal drug worldwide¹. In addition, of all cancer related deaths, 27% will be specifically related to lung cancer; accounting for approximately 159,260 deaths per year². Through extensive research on cannabis, several pathways have been identified in relation to oncogenesis, in addition to the factors correlated with carcinogen content and smoking technique⁷. **Objective:** This study will focus on the association between smoking cannabis and the development of lung cancer. A literature review will be performed to assess this relationship and attempt to provide a logical conclusion to the phenomenon. **Methods:** This evaluation was conducted based on 11 peer reviewed articles retrieved from PubMed and The University of Ottawa Library Database by searching key words such as: cannabis, lung cancer and marijuana. **Results:** Although the relationship between marijuana smoking and lung cancer is unclear, the majority of the articles indicated a positive correlation between inhalation of cannabis and oncogenesis of the lungs. **Conclusion:** Based on the molecular, cellular and histopathologic findings, further mechanistic studies are required for definitive conclusions; however, physicians should make the potential of adverse health outcomes clear to their patients.

INTRODUCTION

Marijuana is the most commonly used illegal drug worldwide and its abuse has increased significantly in the past decade. In 2011, the global prevalence of marijuana use was estimated to be 3.9% of the adult population aged 15-64¹. Given the widespread use and increasing dependence on cannabinoids, it is of pivotal importance to explore the clinical consequences of this substance³. Contrary to popular belief, cannabis smoking may have a greater potential to cause lung cancer than tobacco smoking⁴. Benzopyrene, a carcinogenic polycyclic aromatic hydrocarbon, is found in both tobacco and marijuana smoke and has been implicated in mutations related to lung cancer³. The main psychoactive ingredient in marijuana is delta-9-tetrahydrocannabinol (THC); however, more than 60 compounds (cannabinoids) have been identified within the cannabis plant¹ and it contains twice the concentration of carcinogenic polyaromatic hydrocarbons⁴. Generally speaking, marijuana is smoked less frequently on a daily basis (compared to tobacco cigarettes)⁵; however, the pulmonary consequences of marijuana smoking may be amplified by the higher concentration of smoke, deeper inhalation⁴, the use of unfiltered marijuana cigarettes ("joints") and a relatively larger tar (a carcinogenic particulate matter) deposit on the lungs⁶. These factors result in a five-fold greater absorption of carbon monoxide from a cannabis joint compared to a tobacco cigarette⁴. In addition, experimental studies utilizing bronchial biopsies have demonstrated that marijuana users show airway inflammation as well as histopathological and/or molecular changes which indicate precancerous activity⁶.

Biological Pathways

Cancer is defined as a mutation in the body which results in uncontrolled and unspecialized cellular replication, typically leading to the development of a tumor⁷. Based on a vast amount of cannabis research, several main biological pathways have been indicated in oncogenesis. Cannabis is generally known to stimulate the mitogen activated protein kinase (MAPK) pathway, a major stimulant of uncontrolled cellular replication. In addition, chronic marijuana use is implicated with telomeric (end-chromosomal) damage in the male germ cells, which is associated with tumorigenesis. Together, "germ line chromosomal abnormalities... [and] MAPK stimulation constitute putative pathways of inheritable oncogenesis"⁷. Lastly, cannabis use has been linked to immunosuppressive properties involving the tumour surveillance process. This inhibition of the immune system has been implicated in cancer growth in both pre-clinical and metastatic stages of the disease⁷.

Conclusion

Epidemiologic evidence linking marijuana smoking and lung cancer is currently sparse. Considering the explicit causal relationship between tobacco smoking and lung cancer, there is a valid concern that smoking marijuana may be a risk for the development of lung and other cancers as well¹.

RESEARCH QUESTION

Does smoking marijuana increase the risk of developing lung cancer in individuals aged 15 years and older?

Figure 1. Age-standardized mortality rates for selected cancers, males, Canada, 1985-2014²

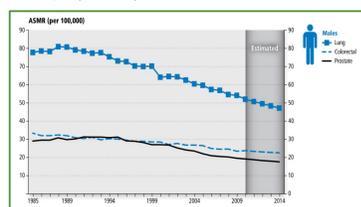
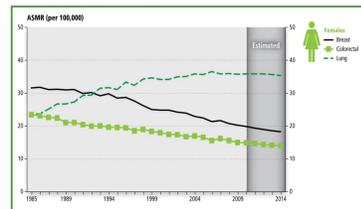


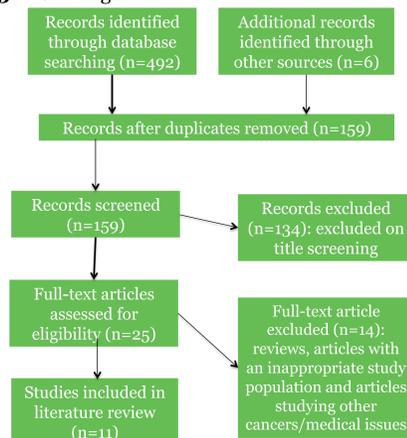
Figure 2. Age-standardized mortality rates for selected cancers, females, Canada, 1985-2014²



METHODS

- Data for this study was collected through a structured literature review.
- Peer reviewed articles were collected from research databases including PubMed and The University of Ottawa Library by searching key words such as 'marijuana smoking', 'cannabis' and 'lung cancer'.
- The database search resulted in 492 studies in which 11 peer reviewed articles were selected. These papers included case-control studies, cohort studies, systematic reviews and meta-analyses.
- Inclusion criteria consisted of studies that were published within the last 30 years, involved participants over the age of 15 and discussed the association between smoking marijuana and developing lung cancer.

Figure 3. Flow Diagram



RESULTS

Findings

Of the 11 studies analyzed in this literature review, 9 articles concluded that there was an association between marijuana smoking and the development of lung cancer (one of these studies only concluded this in men).

Table 1. Results

| Source & Population | Study Design | Results | Conclusion |
|--|--|--|---|
| Sridhar et al (10)- 110 lung cancer patients; ages 27-87 (mean=60.5 years) | Retrospective cohort; self-report questionnaire completed to confirm/deny the use of tobacco or marijuana | 13 (100%) of 13 patients < 45y/o reported ever smoking marijuana (p=0.000); 6 (6%) of 97 patients > 45y/o reported ever smoking marijuana (p=0.001) | Smoking marijuana exclusively may lead to aero-digestive cancers |
| Hashibe et al (11)-1212 cancer cases and 1040 controls; ages 18-65 | Case-control; interview with standardized questionnaire to determine the use of marijuana | Adjusted Odds Ratio (OR) for ≥ 60 joint years versus 0 joint years= 0.62, 95% Confidence Interval (CI)= 0.32- 1.2 | Long term or heavy use of marijuana is not strongly associated with lung cancer |
| Taylor, MD (12)- 10 patients w/ respiratory tract carcinoma; under 40 y/o | Retrospective cohort; Clinicians asked about their patient's smoking habits and ranked them: heavy, regular, possible and unlikely | 2 cases presented w/ lung cancer, 4 w/ larynx cancer and 4 w/ oropharynx cancer | Regular use of marijuana is a strong etiologic factor in the progression of respiratory tract carcinomas |
| Sidney et al (13)- 64855 participants; ages15-49 | Retrospective cohort; participants completed self-administered questionnaires to determine marijuana use | In those who smoked tobacco and marijuana the Relative Risk (RR)= 9.2, 95% CI= 2.0-42.0. In those who only smoked tobacco the RR= 10.3, 95% CI= 2.4-43.7 | Marijuana smoking and lung cancer were not associated and its combined use with cigarettes demonstrated a lower RR compared to only tobacco smokers |
| Berthiller et al (14)- 430 cases and 778 controls; mean age= 60 | Three hospital based case-control studies; questionnaires were administered to obtain information about smoking behaviours | After adjustments for 'lifetime tobacco pack-years' OR for 'ever' cannabis smokers = 2.3, 95% CI= 1.5-3.6. OR among current tobacco users and 'ever' cannabis smokers=18.2, 95% CI= 8.0- 41.0 | Cannabis smoking may be a risk factor for lung cancer development |
| Sasco et al (15)- 118 lung cancer cases and 235 controls; mean age=59 | Case- control; interviews and standardized questionnaires determine smoking behaviour | The OR for hashish/kiff (marijuana) smokers =4.84, 95% CI= 1.82-12.90; adjusted for tobacco smoking the OR for hashish/kiff smokers= 1.99, 95%CI= 0.63-6.30 | Hashish/kiff are etiologic factors in the development of lung cancer |
| Callaghan et al (6)- 49321 men; ages 18-20 | Cohort; participants completed self-report questionnaires to determine cannabis use and frequency | Heavy cannabis smoking was associated with a two-fold increased risk of developing lung cancer (hazard ratio=2.12, 95% CI=1.08-54.14) | Cannabis use may increase the risk of lung cancer |
| Voirin et al (8)- 149 lung cancer cases and 188 controls; mean age =57 | Case - control; hospital based questionnaire was used to determine cannabis smoking habits | Age-adjusted OR= 3.7, 95% CI= 1.8-7.5; OR for participants who smoked marijuana <5 years= 4.7, 95% CI= 1.7-13.2. OR for participants who smoked marijuana ≥ 5 years =3.4, 95% CI= 1.1-10.1 when compared to never cannabis smokers | No clear dose-response relationship was observed; however, it is likely that marijuana smoking is a risk factor for lung cancer |
| Aldington et al (4)- 79 cases of lung cancer and 324 controls; ages ≤ 55 | Case- control; questionnaires given to participants to determine smoking history | >10.5 'joint-years' RR= 5.7, 95% CI=1.5-21.6 ; 5% of lung cancer may be attributable to cannabis smoking. | Long term cannabis smoking increases the risk of lung cancer in young adults. |
| Khalid et al (16)- 13 studies | Systematic Review and Meta Analysis | Cumulative analysis indicated a RR=1.22, 95% CI= 0.999- 1.5, p=0.05 | Cannabis use is linked to an increased risk of developing lung cancer |
| Mehra et al (3)- 219 studies | Systematic Review | --- | It is likely that an association exists |

(#)- number that the article appears in the reference list

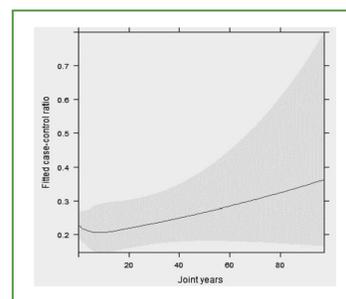


Figure 4. Non-linear association between cannabis smoking and the risk of lung cancer in all subjects showing the fitted odds of being a case versus being a control. Grey area= 95% confidence interval. Model was adjusted for age, sex, race, highest education, tobacco smoking status & pack-years, and study¹⁷.

DISCUSSION

This literature review ascertains a positive association between lung cancer and cannabis smoking; however, the current epidemiologic evidence still remains sparse and relatively inconclusive. These discrepancies are likely due to methodological concerns in this area of research including selection bias, response bias, recall bias and confounding factors⁶. Prospective cohort studies need to be conducted with larger sample sizes of cannabis smokers in their late adolescence or early adulthood. The participants should include a full range of users from light-to-heavy marijuana use and the study should extend their follow-up period into late-adulthood when lung cancer typically manifests⁶. This would provide more conclusive evidence in terms of the causal pathway between marijuana smoking and lung cancer; as opposed to case-control studies which have yet to show a definitive conclusion for this phenomenon. In addition, many studies utilized a hospital based environment for the selection of cases and controls, which could restrict the external validity of the findings. By recruiting participants from the general population, the issue of selection bias can be avoided in future studies.

Since marijuana is an illegal substance, its use is surrounded by a social stigma encompassing laziness, stupidity and immaturity. Due to this belief, many participants could be reluctant to accurately admit their use of marijuana and will likely underestimate the amount consumed in their lifetime⁸. This response and recall bias can be avoided with the use of anonymous questionnaires or trained interviewers who identify as past cannabis users. Lastly, the most significant issue in concluding the relationship between lung cancer and marijuana smoking is the confounding factor of tobacco use. Since the majority of people who smoke marijuana are also tobacco users⁹, it is difficult to link the cause of lung cancer directly to marijuana. Future studies should develop a rigorous inclusion criterion to exclude any individual who smokes tobacco (within certain limits).

Limitations

- Two French articles were excluded due to a language barrier.
- Two articles were excluded due to monetary fees
- The majority of the studies were observational, which is a lower form of evidence. Randomized control trials would be difficult to conduct on this topic because it is unethical to experiment with or administer an illegal drug.
- The external validity of this review is weak because the majority of the studies took place in a (controlled) hospital based setting with participants who were already diagnosed with lung cancer.

Future Implications

Large prospective cohort studies need to be conducted with a detailed assessment of marijuana exposure, control for tobacco use, and definitive diagnosis of lung cancer³. If deemed ethical, this type of study can be conducted in a region where marijuana is already legal; eliminating a portion of the response bias, recall bias and stigma that penetrates marijuana research. Public health initiatives should also be taken through social media campaigns to ensure the dissemination of this information to members of society. Lastly, in terms of clinical practice, health care professionals should educate their patients of the risk associated with smoking marijuana and developing lung cancer to ensure that people are thoroughly aware of this plausible link.

CONCLUSIONS

- This literature review indicates that smoking marijuana is a possible risk factor in the development of lung cancer in individuals aged 15 years and older.
- Health care professionals should educate their patients of this plausible link and public health initiatives should be developed to raise awareness in the general public.
- Future research should be conducted in the form of prospective cohort studies to determine definitive causality.

*References are provided on a separate hand-out