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REVIEW

The association of bladder cancer and *Cannabis*: A systematic review

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Summary

Objective: To assess the association between Cannabis use and bladder cancer.

Methods: A systematic literature review was performed using studies published in electronic databases including PubMed, MEDLINE, and Google Scholar. Due to the scarcity of literature on this topic, the search was not limited to a specific design, year of publication, or human studies. The studies were screened by two reviewers in the following steps; first, the studies were discovered according to the predetermined search strategy; second, the unrelated studies and duplicates were eliminated by screening the abstracts, titles, and keywords; third, the full text of relevant and eligible papers were critically appraised and assessed for the risk of bias using the respective tool.
The two review authors independently assessed the risk of bias and outcome levels using the Newcastle-Ottawa Scale for the outcomes in observational studies. Any disagreements were settled by a third party.
Results: The search strategy yielded 39 research articles. After removing 21 duplicates, 18 publications were eligible for title and abstract review. Thirteen studies were found to be irrelevant and subsequently excluded. Only three full-text articles were evaluated and included in the qualitative synthesis.
Conclusions: The role of Cannabis in bladder cancer has been seldom studied. The small number of studies show contradictory findings; potential carcinogenic versus protective effect.
The growing interest in Cannabis use after legalization necessitates further investigations with a robust design to assess the long-term effect of Cannabis on bladder cancer.

KEY WORDS: *Bladder cancer; Cannabis; Cannabinoids; Marijuana; Legalization.*

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INTRODUCTION

Cannabis (also known as *marijuana*) is a term used to describe a vast array of products that can be produced from any part of the *Cannabis sativa*, *Cannabis indica*, or *Cannabis ruderalis* plants individually, or in combination. The three most common administration routes for *Cannabis* are smoking, vaporizing, and eating (1). When it comes to elimination, *Cannabis* and its byproducts pass through both the gastrointestinal and urinary tracts that can lead to a direct contact and respective responses in the corresponding organs (2). Accordingly, many studies on the role of *Cannabis* in different types of cancer have mainly focused on the oral cavity, the lungs, the gastrointestinal tract, and genitourinary system. Upon legalization of *Cannabis* in Canada in October 2018, social acceptance and prevalence of *Cannabis* use have been rising dramatically in parallel with the concern about the disadvantageous and long-term consequences. Considering the direct exposure, bladder can be potentially impacted by *Cannabis* use to a considerable extent, i.e. general bladder health, and bladder cancer occurrence and prognosis (3). However, there is a scarcity of data on the link between *Cannabis* use and bladder cancer. To investigate the link between *Cannabis* use and bladder cancer, we conducted a systematic review.

MATERIALS AND METHODS

Study objective

Study objective was to assess the association between *Cannabis* use and bladder cancer. It is noteworthy that the review method was established prior to the conduct of the review, from which there was no significant deviation.

Search strategy

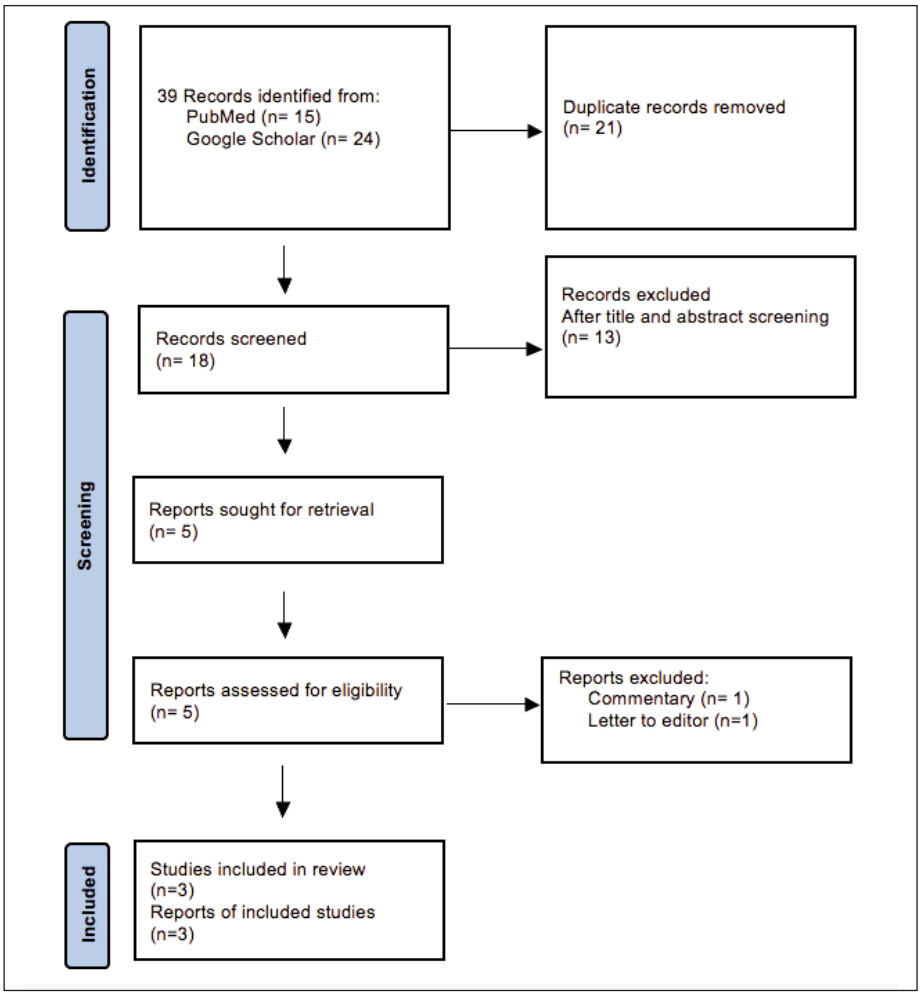
A systematic literature review was performed using studies published in electronic databases including *PubMed*, *MEDLINE*, and *Google Scholar*.
Based on the Boolean search strategy, a variety of combinations contained the following search terms were applied in different search engines to ensure the comprehensiveness of the result. In addition, the reference lists of the retrieved studies were manually screened. The search terms included "*marijuana* OR *marihuana* OR tetrahydrocannabinol OR dronabinol OR cannabinoid OR *Cannabis*, AND bladder cancer OR bladder carcinoma OR bladder tumor OR bladder neoplasm OR urothelial carcinoma OR transitional cell carcinoma.

Selection criteria

We did not restrict the search with specific design, year of publication or human studies due to existing scarcity of literature on this topic. We just excluded the commentary and letter to editor. We enquired two experts in the fields to avoid missing any published or unpublished papers.

No conflict of interest declared.

Figure 1.
PRISMA flowchart of the results of the literature search.



Screening data

The studies were screened by two reviewers in the following steps; first, the studies were discovered according to the predetermined search strategy; second, the unrelated studies and duplicates were eliminated by screening the abstracts, titles, and keywords; third, the full text of relevant and eligible papers were critically appraised and assessed for the risk of bias using the respective tool.

Data extraction

The following information was extracted from each selected study:
Population characteristics, type of study, country, and key relevant findings. As noted, the data extraction was performed in duplicate by the two reviewers. The consensus on what information should be extracted and included was achieved.

Methodological quality (Risk of Bias)

The two review authors (VM and SDL) independently assessed the risk of bias and outcome levels using the Newcastle-Ottawa Scale for the outcomes in observational studies (6). Any disagreements were settled by a third party (AK and MEH).

Results

Study selection

Figure 1 depicts the PRISMA flowchart of the study selection process. The search strategy yielded 39 research articles. After removing 21 duplicates, 18 publications were eligible for title and abstract review. Thirteen studies were found to be irrelevant and subsequently excluded. Following full-text evaluation, two papers (one commentary and one letter to the editor) were excluded.
Only three full-text articles were evaluated and included in the qualitative synthesis.

Table 1.
Summary of clinical studies on Cannabis *and bladder cancer.*

Author	Study design	Country	Population	Intervention/Exposure	Comparator	Outcome	ROB
Chacko et al. 2006 (4)	Case control	USA	124 Patients with bladder cancer	Use of marijuana	Age-matched control	A history of habitual marijuana use in 88.5% and 69.2% of transitional cell carcinoma patients and age-matched controls, respectively (p = 0.008). The association between marijuana use and tumor stage, grade, and number of recurrences of transitional cell carcinoma.	Moderate
Thomas et al. 2015 (5)	Cohort	USA	84170 Participants in a multiethnic cohort of men aged 45-69 years	*Cannabis* users	Not reporting *Cannabis* use	Incident bladder cancer 0.3% among *Cannabis* users versus 0.4% among men not reporting *Cannabis* use (p < .001). *Cannabis* use associated with a 45% reduction in bladder cancer incidence (HR, 0.55; 95% CI, 0.31-1.00).	Moderate
Nieder et al. 2006 (11)	Case report	USA	1 Case with bladder cancer	Use of marijuana	NA	Inhaling up to five marijuana cigarettes per day for 30 days as the only risk factor for transitional cell carcinoma.	NA

ROB: Risk of bias. NA: Not applicable.

Included studies characteristics

Three studies with moderate risk of bias (mainly due to limited information regarding the average marijuana exposure and inadequate adjustment for key confounders) were included for review.

Table 1 shows the specific details of each.

Discussion

Cannabinoids have been shown in studies to inhibit tumor cell growth and induce apoptosis in a variety of cancer cells (5-7). Despite widespread *Cannabis* use and evidence of cannabinoids' antitumor activity, little is known about the carcinogenic effects of *Cannabis*, which has been highlighted after *Cannabis* legalization. The findings on the effect of *Cannabis* on other urinary malignancies vary. The only clinical study on penile cancer and *Cannabis* found no link (7). *Cannabis* use appears to be an independent risk factor for the development of testicular germ cell tumors (9-11).

The result of a study on the effect of *Cannabis* on prostate cancer did not find a link between *Cannabis* and prostate cancer risk (8); however, *in vitro* and animal studies strongly suggest that cannabinoids protect against prostate cancer development (9). The clinical studies on renal cancer merely characterized cannabinoid receptor expression in renal neoplasms (10). Two studies yielded contradictory results on *Cannabis* and bladder cancer according to our review. *Chacko et al*. compared 52 men under the age of 60 with transitional cell urothelial carcinoma to 104 age-matched controls.

Their findings revealed that habitual marijuana use was present in 88.5% of patients with bladder cancer while 69.2% of the control group (p = 0.008), implying that marijuana use is associated with an increased risk of bladder cancer (4). This is consistent with the findings of a case report of 45-year-old man in whom excessive marijuana smoking (up to five marijuana cigarette daily more than 30 years was found to be the only risk factor for developing bladder cancer (11).

A recent study by *Thomas et al.*, which examined the records of 84170 men aged 45-69 years from the *California Men's Health Study* and followed them for 11 years, discovered that bladder cancer developed in 0.3% of men who used *Cannabis* and 0.4% of men who did not use *Cannabis* (p = 0.001), leading the authors to conclude that *Cannabis* use was associated with a 45% risk reduction in the bladder cancer incidence (5). However, the studies were limited by insufficient adjustment for confounders.

Knowing the physiology of the tissue expression of cannabinoid receptors can shed more light on the potential role of *Cannabis* in bladder cancer. *Tyagi et al*. found CB1 and CB2 receptors in the urothelium of human bladder (12). Both receptors were present in the bladder urothelium and detrusor muscles, but CB1 expression was found to be significantly higher than CB2. CB1 and CB2 receptor expression was twice as high in urothelium as it was in detrusor muscles (12). *Cannabis* has primarily been studied in terms of regulating inflammation and urgency in the treatment of bladder conditions. CB2 agonists have been shown to reduce the severity of murine bladder inflammation when locally administered after acrolin, an inflammatory agent (13). As part of the *Cannabinoids in Multiple Sclerosis* (CAMS) study, *Freeman et al*. investigated the effect of cannabinoids on urge incontinence.

They assigned 630 patients with multiple sclerosis to receive either *Cannabis* extract, THC, or a matched placebo via oral administration. Urge incontinence was significantly reduced with *Cannabis* (38%), and THC (33%), versus placebo (18%) (14). *Kavia et al.* also found that Sativex (THC + cannabidiol) can also a positive impact on overactive bladder symptoms in patients with multiple sclerosis (15).

The existing small body of evidence indicates that *Cannabis* has a direct effect on the bladder during elimination where the resulting direct contact with the bladder urothelium can cause change in urine peptides and urothelial expression of CB1 and CB2 receptors.

Although it is currently difficult to study *Cannabis*'s effects on the bladder, legalization may increase this possibility due to the increased openness of the population regarding their use of *Cannabis*. Because of the long latency nature of bladder cancer development, more robustly designed studies with long-term follow-up are warranted.

Given the gaps in current knowledge, the authors pose the following dire questions for future observation and study: Will *Cannabis* reduce or increase the incidence of BC? Will *Cannabis* influence BC aggression in a positive or negative way? Will new pathological types of BC emerge? Many questions may arise, but only observation and ongoing research will allow us to begin finding true, conclusive evidence.

Conclusions

The role of *Cannabis* in bladder cancer has been seldom studied. The small number of studies show contradictory findings; potential carcinogenic vs protective effect.

The growing interest in *Cannabis* use after legalization necessitates further investigations with a robust design to assess the long-term effect of *Cannabis* on bladder cancer.

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