**Association of Marijuana Smoking with Squamous Cell Carcinoma:**

**A Literature Review**

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**Abstract**

**Purpose:**

Marijuana is growing in popularity as both a medicinal and recreational drug. The debate of whether legalization is appropriate has been a controversial topic among communities and political agencies. Currently, the scientific literature is conflicting on the association between marijuana smoking and oral cancer. Squamous cell carcinoma accounts for 3% of cancers in men and 3% in women, and is the most common form of oral cancer.1 Therefore, the goal of the present literature review is to investigate the association of marijuana smoking with the development of oral squamous cell carcinoma (OSCC) and head and neck squamous cell carcinoma (HNSCC) using updated research articles.

**Methodology:**

A search in PubMed using relevant keywords from the Medical Subjects Headings (MeSH) database rendered 29 results. Inclusion criteria comprised of articles published in the last 10 years, articles using humans as subjects, articles published in English, and articles assessing marijuana smoking as a risk factor to OSCC development, as opposed to use as an analgesic. A total of six articles were ultimately selected.

**Results:**

Five of six studies suggested no correlation between marijuana smoking and OSCC or HNSCC development, while one suggested a positive correlation.

**Discussion:**

Further and more updated research needs to be conducted to confirm any association. The studies built on previous researched work but had confounding factors of their own.

**Conclusion:**

No association between marijuana smoking and the development of OSCC was found, as current research is equivocal. More powerful future studies are necessary to assess long-term effects.

**Keywords:** Marijuana, cannabis, cannabinoids, head and neck squamous cell carcinoma, oral squamous cell carcinoma, case-control, meta-analyses, systematic review.

**Introduction**

Marijuana is growing in popularity as both a medicinal and recreational drug. The debate of whether legalization is appropriate has been a controversial topic among communities and political agencies across the globe. The term Marijuana refers to the dried leaves, flowers, stems and seeds of either the *Cannabis sativa* or *Cannabis indica* plant.2 The active chemicals in Marijuana are referred to as cannabinoids and over 100 have been identified. Among these, delta-9-tetrahydrocannabinol (THC) has been the most widely researched and prevalent in use.3 THC can be an effective medicine for Post-Traumatic Stress Disorder, insomnia, inflammation, pain, appetite stimulation in HIV/AIDS patients, and symptom reduction in cancer treatment. On the other hand, the substance can be highly psychoactive and cause altered senses and moods, impaired physical movements, impaired cognition and memory, hallucinations, delusions and even psychosis.2 Long-term effects concern altered brain development, as cognitive abilities change especially in teenage users. Breathing problems, increased heart rate, pregnancy issues, and intense nausea and vomiting are also common health considerations. However, many governments are now promoting the legalization of the drug. Former United States of America President Barack Obama has stated his belief that the substance should be treated like other similar substances, such as tobacco or alcohol.4 Furthermore, Canadian Prime Minister Justin Trudeau and his cabinet are in the process of changing the law on the substance, hoping to legalize, regulate and restrict access.5 With the substance’s impending widespread legalization, dental agencies and practitioners should also assess the potential oral health implications. Oral cancer is one of high priority; in 2008, 1008 people died of oral cancer.6 Oral cancer is defined as the uncontrollable growth of abnormal cells in the oral cavity, leading to tumor formation. Currently, the negative oral health effects of tobacco smoke are known, as the risk of oral cancer development is five to ten times greater in smokers. Moreover, smokers are at an increased risk of dying from oral cancer than those who have never smoked. In 2002, research found half of deaths from oral cancer were due to smoking. Although no deaths have been reported in relation to marijuana use, the side effects can become severe. In addition, like tobacco smoke, dependency can ensue while addiction may be inevitable in frequent users. The popularity of marijuana as a recreational drug is increasing among young people. In a National Survey conducted in 2016, 44% of people ages 12 and older had used marijuana or its equivalent in their lifetime, with the highest usage in those aged 18 to 25 (51.8% over their lifetime, and 33% in the year).7,8 However, it is popular and prevalent across all age groups. As marijuana is often interpreted similar to tobacco, it is important to compile research on its effects on oral health. Currently, the scientific literature is conflicting on the association between marijuana smoking and oral cancer. Squamous cell carcinoma accounts for 3% of cancers in men and 3% in women, and is the most common form of oral cancer.1 Therefore, the goal of the present literature review is to investigate the association of marijuana smoking with the development of oral squamous cell carcinoma (OSCC) and head and neck squamous cell carcinoma (HNSCC) using updated research articles. For adults above the age of 18, is marijuana use a risk factor in the development of oral squamous cell carcinoma, compared to those who do not use any substances?

**Methodology:**

An advanced search in PubMed using the keywords “marijuana OR cannabis” AND “oral squamous cell carcinoma OR head and neck squamous cell carcinoma” from the Medical Subjects Headings (MeSH) database rendered 29 results. Inclusion criteria comprised articles published in the last 10 years, articles using humans as subjects and articles published in English. Articles were also required to assess marijuana smoking as a risk factor to the development of OSCC, as opposed its use as an analgesic. 19 articles were excluded; 17 articles were published more than ten years ago and two articles were published in French. There was no restriction on geographic location, age or gender. A total of six articles were ultimately selected, in which two are case-control studies, two are systematic reviews, two are meta-analyses of case-control studies.9-15 Data was analyzed and common themes were evaluated.

**Results:**

Five of six studies suggested no correlation between marijuana smoking and OSCC or HNSCC development and even suggested a negative association.10-13,15 Only one article suggested a positive correlation.14 All studies agreed that tobacco and alcohol usage were strong risk factors and frequently used in conjunction with marijuana. All studies also agreed that age was a risk factor but did not agree on which age group benefitted most from marijuana’s potential anti-carcinogenic properties. Nonetheless, all cases were age and sex matched.

**Discussion:**

A search was conducted to assess the association between marijuana use and the development of OSCC or HNSCC. Although the studies’ purpose seeks to investigate specifically the effects of marijuana smoke, data on the method of intake do not seem to be widely available.16-18 Nevertheless, smoking remains the most prevalent form of consuming cannabis. Five of six discussed articles suggested either no relationship or an inverse relationship between marijuana use and the development of OSCC or HNSCC. However, when conducting a comprehensive search with no publication date restriction, there were articles that suggested both the antitumor and tumorigenic properties.10,11,15,19,20 Most available raw data was drawn from case-control studies, although systematic reviews and meta-analyses were conducted as well. Case-control studies are classified Grade B when assessed according to the Oxford Centre for Evidence-based Medicine – Levels of Evidence document.21 However, the meta-analyses and systematic reviews must have sufficient homogeneity which is questionable in the studies used. Ethically, the exposure to disease cannot be induced solely for experimental reasons; therefore it is difficult to perform studies at a higher level of evidence. Individually, the studies seemed to conclude with robust results, suggesting a statistically significant positive or negative correlation between marijuana smoking and risk of OSCC or HNSCC. However, when pooled in either meta-analyses or systematic review, conflicting data led to inconclusive results. Further research with more power needs to be conducted in animal models or humans.

There were various strengths of the studies that were analyzed, including control for confounders, consistency of data obtained, and comprehensive review of past literature. All of the studies included marijuana usage in conjunction with another known risk factor, such as tobacco smoking or alcohol consumption. The inclusion of a known high-risk factor also acted as a control to assess the reliability of the study’s results. Additionally, confounders were controlled and accounted for. One study blinded the participants to the study’s hypothesis to control for the Hawthorne effect.15 Another study included sensitivity analyses to account for the misclassification of association of each outcome.11 All studies clearly defined inclusion data, and categorization methodology based on duration, frequency and amount of marijuana use. Demographic information was included and analyzed also to make general statements regarding the study population and easily distinguish potential biases. For the case-control studies, the data that was obtained in each study was consistent (within itself) and generally, all measures of marijuana use rendered similar results.14,15 Odds ratios (ORs) were conducted in with 95% confidence interval to account for biases in four of the studies.10,12,15 The review was limited to articles published in the last 10 years, which ensures an up-to-date, high-quality and comprehensive document. However, all studies discussed the power of the research results and suggest more research needs to be conducted and a definitive statement cannot be made due to equivocality.10-15

Limitations of the studies include the illegal status of the marijuana drug, misclassification of usage measures, disproportionate recruitment of cases, purity of the marijuana substance and the link to human papillomavirus (HPV). In many of the study locations, marijuana is an illegal substance; therefore, participants may be hesitant to report frequent or chronic usage.15,19 In all of the studies, data was drawn from research conducted in the United States of America, where use of marijuana is still prohibited by law.10-15 This may cause an under-reporting of exposure cases, or an over-reporting of control cases, leading to biases in the studies. This problem would apply in situations where questionnaires were distributed to participants, which is characteristic of case-control studies. In addition, there was misclassification of marijuana usage measures as different studies categorized frequency, duration, and amount differently. In one study, light smokers and drinkers were classified as never-users because of the lack of study participation.11 Another study did not convey the distribution of marijuana usage, only noting the dose-response relationship.14 This inaccuracy can skew results quite dramatically as those categorized as controls were actually exposed to the risk factor. Consequently, reliability is also compromised, as one cannot know whether the controls are truly control cases. It is difficult to draw conclusions from categories that do not align, as detailed in several studies.10,11,15,17 Unsurprisingly, all cases in the present studies reported a higher proportion (almost double) of those identifying as controls instead of exposure cases. The reason may arise from the legality issues discussed previously, but this difference in groups could also lower the expected reliability of the results. Since the exposure cases contain the dependent variable to be tested, it may be difficult to make valid conclusions based on a small number. Furthermore, all studies agreed that marijuana users are more likely to use tobacco and alcohol, which are known to be strong risk factors for the development of OSCC and HNSCC.10-15,22 The studies did not control for the use of these additional substances, and participants could have underreported or not been asked about the use of these substances in combination with marijuana. For example, in North Africa, it is common for tobacco to be mixed in with marijuana products.12,23 Thus, participants may not know the exact ingredients in the substance they are using. Due to the illicit nature of the drug, it is widely purchased from underground drug dealers whose product composition is questionable. Finally, the link to HPV-16 exposure (which is increased by sexual activity) could prove to have a synergistic effect on marijuana smoking and OSCC or HNSCC development.11,12,14,15,24 Although it is not currently considered an etiological factor for oral tongue cancers, it is still considered a confounding factor.25 Subsequently, more data that is specific, reliable and powerful must be collected to solidify the results of the previous studies.

The results of the present study align with past studies, as there is much conflicting research regarding the topic, and a consensus cannot be reached. An early study conducted by Zhang et al. found a strong positive correlation (two to three fold) between HNSCC and marijuana use, which was opposed by several other studies.15,19,26-31 However, these studies contained flaws. For example, Zhang et al. conducted a study in the hospital setting, including blood donors as participants.26 Inclusion may have skewed results as blood donors tend to be self-selected and lack high-risk behaviours. Moreover, the study excluded ever-users after 20 years of age, while the controls were included for all ages. More than half of the cases (23) were excluded leaving only 17 cases to analyze. Other issues with past studies include inadequate sample sizes/low participation and missing data. Consequently, the present review has summarized the most updated and accurate data but more research needs to be conducted to secure a definitive result.

**Conclusion:**

To conclude, the studies addressed the needs of the population and fulfilled its purpose. A comprehensive search was performed to investigate the relationship between marijuana (or cannabis smoking) and the development of OSCC or HNSCC. HPV-16-positive HNSCC is deemed a strong risk factor for HNSCC, but not as much for conditions inside the oral cavity. As a result, this was not further explored in the present review.11,25 Six studies were included in the present review after adjusting for exclusion data. Of the studies, five studies agreed that it is doubtful that there is any correlation, and even suggest that the drug has a protective effect.10-13,15 One study, found that marijuana use did have a significant effect on HPV-linked HNSCC.14 However the study did not divulge in detail the methodology and design of the study, simply stating the results. Therefore, its reliability may be questionable. Other issues arose within the studies, such as misclassification of data when conducting group analyses.10-13 Also, the studies were all conducted (or partly conducted in) the United States of America, where the status of marijuana is illegal. This could contribute to more conservative responses and skewed results. Past studies conducted although not included in this review due to the date restriction also rendered equivocal conclusions. More research needs to be conducted, as a definitive statement on the effects of marijuana use on the risk of developing OSCC still cannot be made. Nevertheless, meta-analyses and systematic reviews are higher levels of evidence and can provide the reader, clinician or client, with the most updated information regarding the topic. Although this information cannot be a conclusive guide for the future of dental hygiene education, its contribution into the direction of future research is recognized. Researchers are encouraged to conduct more studies at level 1 or 2 (Grade A) in the future, although this will be near impossible due to the sensitive nature of drug exposure.21 Tentatively, marijuana smoking cannot be confirmed and thus is not a risk factor in the development of OSCC or HNSCC. Further studies with more power need to be conducted to assess long-term effects.

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