Marijuana Smoking and Head and Neck Cancer

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A recent epidemiological study showed that marijuana smoking was associated with an increased risk of head and neck cancer. Among high school students and young adults, the prevalence of marijuana use was on the rise in the 1990s, with a simultaneous decline in the perception that marijuana use is harmful. It will be a major public health challenge to make people aware of the harmful effects of marijuana smoking, when some people view it as the illicit drug with the least risk. The carcinogenicity of Δ9-tetrahydrocannabinol (THC) is not clear, but according to laboratory studies, it appears to have antitumor properties such as apoptosis as well as tumor-promoting properties such as limiting immune function and increasing reactive oxygen species. Marijuana tar contains similar carcinogens to tar from tobacco cigarettes, but each marijuana cigarette may be more harmful than a tobacco cigarette since more tar is inhaled and retained when smoking marijuana. More molecular alterations have been observed in bronchial mucosa specimens of marijuana smokers compared to nonsmokers. Field cancerization may be occurring on the bronchial epithelium due to marijuana smoking exposure. Several case studies were suggestive of an association of marijuana smoking with head and neck cancers and oral lesions. However, in a cohort study with 8 years of follow-up, marijuana use was not associated with increased risks of all cancers or smoking-related cancers. Further epidemiological studies are necessary to confirm the association of marijuana smoking with head and neck cancers and to examine marijuana smoking as a risk factor for lung cancer. It will also be of interest to examine potential field cancerization of the upper aerodigestive tract by marijuana and to explore marijuana as a risk factor for oral premalignant lesions.

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78.6% of high school seniors considered regular use of marijuana to be a great risk, but in 1998, this percentage dropped to 58.5%. Perceived risk appears to be correlated directly with the level of marijuana use. It may be confusing for the public that marijuana is used for medicinal purposes and being investigated for potential beneficial uses yet may also have harmful effects on physical health. It is a public health challenge to make people aware of the harmful effects of marijuana smoking. More epidemiological studies are necessary to confirm the association of marijuana smoking with head and neck cancers and to examine the association with lung cancer. It seems biologically plausible that marijuana smoking may cause cancer. In this paper, we will review the potential carcinogens in marijuana, molecular alterations associated with marijuana, and case reports of oral lesions and marijuana. Inferring any causal role for marijuana and cancer will require an evaluation of observational data. There can be no randomized clinical trials assessing exposure. Therefore, it is important to consider potential confounders. The most important confounder to consider is exposure to tobacco. Marijuana smokers are also more likely to use tobacco. In addition, tobacco smokers who also currently smoke marijuana are less likely to be able to quit using tobacco. We will review a cohort study on marijuana use and all cancers, as well as the first case-control study on marijuana use and head and neck cancers.

LAB AND CARCINOGENICITY DATA

Potential Carcinogens in Marijuana

Δ⁹-tetrahydrocannabinol (THC) is the major psychoactive ingredient in marijuana. The amount of THC varies by how the marijuana is taken: marijuana or the flower tops of the plant is smoked (1%-5% THC), hashish or dried resin of the plant is smoked in a pipe (6%-10% THC), or hash oil is taken (30%-60% THC). It has been reported that there is little evidence that THC is mutagenic or carcinogenic. One study in which rats and mice received THC in corn oil reported that there was no evidence for the carcinogenicity of THC. In fact, some research groups examined THC and other marijuana constituents as antitumor agents. THC was shown to cause apoptosis in human prostate cancer cells PC-3 and in C6.9 glioma cells, as well as the regression of malignant gliomas in Wistar rats. Cannabigerol, a nonpsychoactive cannabinoid, was shown to inhibit growth of human oral epithelial carcinoma cell lines. In a review of the antitumor activity of the endocannabinoids (psychoactive cannabinoids), endocannabinoids such as anandamide and 2-arachidonoyl-glycerol were suggested as templates for therapeutic agents. The authors discuss that the endocannabinoids themselves may not be useful as therapeutic agents since they are degraded by cells. In another study, marijuana smoke suppressed the growth of primary and secondary tumors in Fisher rats implanted with murine sarcoma tumor cells, but administration of THC did not suppress tumors.

Although some studies report antitumor effects of THC, other characteristics of THC are suggestive of marijuana constituents playing a role in the biological mechanism for the association between marijuana and cancer. THC impaired the immune response and increased the growth of tumors in weakly immunogenic murine lung cancer models. Application of THC to human cell lines also showed a disadvantageous effect on the immune system. Exposing a human endothelial cell line to marijuana smoke containing 4% THC led to 80% higher reactive oxygen species formation than the controls and decreased glutathione levels (19% of control values). Though the reactive oxygen species formation was about the same for the cells exposed to marijuana smoke without THC. THC also activates the transcription of P4501A1 (CYP1A1), an enzyme that converts polycyclic aromatic hydrocarbons into carcinogens. According to laboratory studies, it seems that THC may have a dual effect, with characteristics that promote tumorigenesis such as limiting immune function and increasing reactive oxygen species, in addition to a protective effect against tumors with its antiproliferative properties. Examining the effects of THC in humans will be crucial, possibly with epidemiological studies that examine different modes of marijuana use.

Marijuana smoke contains similar carcinogens to tobacco, including phenols and polycyclic aromatic hydrocarbons such as benzo[a]pyrene. Benzo[a]pyrene is present at a higher concentration in marijuana tar than in tar from tobacco. Other substances, such as carbon monoxide, hydrogen cyanide, and nitrosamines, are present in marijuana smoke at similar levels to tobacco smoke. Marijuana smoking involves the inhalation of approximately three times the amount of tar and retention of one-third more the amount of tar in the respiratory tract relative to tobacco smoking. Subjects inhale marijuana with one-third greater volume and hold their breath with marijuana four times longer than for tobacco. These patterns of smoking a marijuana cigarette may expose the head and neck area, especially the oral cavity, to more smoke particulates than a to-
bacco cigarette. It seems that regardless of the THC content, marijuana smoking involves greater deposition of tar compared to tobacco smoking. This may explain the observation that smoking a few marijuana cigarettes and smoking more than 20 tobacco cigarettes had similar effects on the histopathology of the tracheobronchial epithelium. It is of interest to examine whether the effect of one marijuana cigarette is also more harmful to the head and neck region than smoking one tobacco cigarette.

Molecular Alterations

Bronchial mucosa biopsy specimens of marijuana smokers without any disease showed more molecular abnormalities than nonsmokers. This study included 28 nonsmokers and 76 subjects who smoked tobacco, marijuana, and/or cocaine. Among the smokers, 12 subjects smoked marijuana only. The molecular markers examined included Ki-67 (a proliferation marker), EGFR (epidermal growth factor receptor), p53 (tumor suppressor), and DNA ploidy (marker of genetic instability). Abnormalities in Ki-67, EGFR, and p53 were more common in subjects who smoked any of these three substances compared to nonsmokers. Subjects who only smoked marijuana had a higher percentage of abnormalities in Ki-67 (92%) than nonsmokers (29%) (p < 0.001). A higher percentage of abnormalities in EGFR was also shown for marijuana-only smokers (58%) than nonsmokers (7%) (p < 0.001). The prevalence of abnormal DNA ploidy was higher among marijuana smokers (13%) compared to nonsmokers (5%), though the difference was not statistically significant. The observation of multiple molecular alterations supports an association between marijuana and cancer through the mechanism of field cancerization effects on the bronchial epithelium. The field cancerization theory proposes that carcinogenic exposures can cause simultaneous genetic defects on the epithelium of the upper aerodigestive tract, putting the epithelium at high risk for the development of multiple lesions. Since marijuana smoking may cause field cancerization of the bronchial epithelium, studies need to be conducted to examine whether it can cause field cancerization of the upper aerodigestive tract.

CASE STUDIES

The available evidence on the possible carcinogenicity of marijuana and the similarities between marijuana and tobacco makes it plausible to determine if marijuana use is a risk factor for the development of head and neck cancer in humans. Several case studies from multiple countries indicate that marijuana use is more common than expected in young adults with head and neck cancer. One case series scanned surgical pathology records in one hospital for all cases of upper and lower respiratory tract squamous cell cancers in patients younger than 40 years of age. Taylor found that 7 of the 10 cases had regular or heavy marijuana use documented in their hospital records.

In addition to case studies for head and neck cancers and respiratory tract cancers, there have been a few case studies on oral lesions and marijuana use. Several case studies from various countries indicate that marijuana use is more common than expected in young adults with head and neck cancer. The field cancerization theory proposes that carcinogenic exposures can cause simultaneous genetic defects on the epithelium of the upper aerodigestive tract, putting the epithelium at high risk for the development of multiple lesions. Since marijuana smoking may cause field cancerization of the bronchial epithelium, studies need to be conducted to examine whether it can cause field cancerization of the upper aerodigestive tract.

Cohort Study

One prospective cohort study from Kaiser Permanente in California found that marijuana use, measured from a voluntary self-administered research questionnaire as part of a multiphasic health checkup, was not associated with increased risk of all cancers or smoking-related cancers after 8 years of follow-up. Nontobacco smokers who used marijuana did not smoke tobacco and 4 marijuana smokers did not drink alcohol. This case report suggests an association of marijuana with oral premalignant lesions, but epidemiological studies using well-conceived control groups are necessary to infer any association with confidence.

Case Control Study

A hospital-based case control study was conducted at Memorial Sloan-Kettering Cancer Center between 1992
The relationship between marijuana use and head and neck cancer was investigated using a case control study of 173 previously untreated cases with pathologically confirmed diagnoses of squamous cell carcinoma of the head and neck and 176 cancer-free controls. Exposure data were collected using a structured questionnaire, which included history of tobacco smoking, alcohol use, and marijuana use. The associations between marijuana use and head and neck cancer were analyzed by Mantel-Haenszel methods and logistic regression models. Controlling for age, sex, race, education, alcohol consumption, pack-years of cigarette smoking, and passive smoking, the risk of squamous cell carcinoma of the head and neck was increased with marijuana use (odds ratio [OR] comparing ever with never users = 2.6, 95% confidence interval [CI] = 1.1, 6.6). Dose-response relationships were observed for frequency of marijuana use per day (p for trend < 0.05) and years of marijuana use (p for trend < 0.05). These associations were stronger for subjects who were 55 years of age and younger (OR = 3.1, 95% CI = 1.0, 9.7). Possible interaction effects of marijuana use were observed with cigarette smoking, mutagen sensitivity, and, to a lesser extent, alcohol use. The results suggest that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern. The analysis indicated that marijuana use might interact with mutagen sensitivity and other risk factors to increase the risk of head and neck cancer. The results need to be interpreted with some caution in drawing causal inferences because of certain methodological limitations, especially with regard to interactions.

Two case control studies are currently under way to replicate these findings. As is true of most case control studies, a major issue is the selection of controls. The ongoing studies will be using community-based controls and identifying cases from more than one hospital.

**CONCLUSION**

The carcinogenicity of THC is not yet clear, but laboratory studies have found that THC exhibits antitumor properties such as apoptosis as well as tumor-promoting properties such as limiting immune function and increasing reactive oxygen species. It will be of interest to examine the association of THC levels and cancer in epidemiological studies, perhaps by examining different modes of marijuana use. The tar component of marijuana contains similar carcinogens to tobacco, but each marijuana cigarette may be more harmful than a tobacco cigarette due to the characteristics of marijuana smoking such as greater inhalation of tar, longer retention of marijuana smoke, and greater volume of marijuana smoke inhaled. Furthermore, marijuana smokers appear to have more molecular alterations on the bronchial mucosa than nonsmokers. Field cancerization may be occurring due to marijuana exposure on the bronchial epithelium. Case studies suggested an association of marijuana smoking with head and neck cancers, respiratory cancer, and oral premalignant lesions. A case control study reported an association between head and neck cancers and marijuana use, but a cohort study did not show an increased risk of cancers with respect to marijuana use. Further epidemiological studies are necessary to determine whether marijuana smoking can cause oral premalignant lesions and cancer, possibly due to field cancerization of the upper aerodigestive tract.

**REFERENCES**


