Cannabis Smoke and Cancer: Assessing the Risk

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Presumptions regarding cannabis use as a risk factor for the development of certain types of cancer, particularly lung cancer, warrant critical examination. Epidemiologic studies over the past several decades have established causation between alcohol consumption and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon and rectum, among others.[1] Tobacco use, particularly cigarette smoking, has also been determined to cause various similar aerodigestive tract (ADT) cancers, as well as cancers of the pancreas, kidneys and bladder, and is implicated with cancers of the stomach and liver, among others.[2]

To date, similar epidemiologic and/or clinical studies on the use of cannabis and cancer are few and not definitive. However, the public and policy-makers should interpret the ambiguity of these results with caution – neither construing them at this time as an endorsement of cannabis' safety nor as an indictment of its potential health hazards.

Cannabis Smoke Versus Tobacco Smoke

Cannabis smoke contains many of the same carcinogens as tobacco smoke, including greater concentrations of certain aromatic hydrocarbons such as benzopyrene,[3] prompting fears that chronic marijuana inhalation may be a risk factor for tobacco-use related cancers. However, marijuana smoke also contains cannabinoids such as THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol), which are non-carcinogenic[4] and demonstrate anti-cancer properties *in vivo* and *in vitro*.[5] By contrast, nicotine promotes the development of cancer cells and their blood supply.[6] In addition, cannabinoids stimulate other biological activities and responses that may mitigate the carcinogenic effects of smoke, such as down-regulating the inflammatory arm of the immune system that is responsible for producing carcinogenic free radicals (unstable atoms that are believed to accelerate the progression of cancer.)[7]

Cannabis smoke – unlike tobacco smoke – has not been definitively linked to cancer in humans, including those cancers associated with tobacco use.[8] However, certain cellular abnormalities in the lungs have been identified more frequently in long-term smokers of cannabis compared to non-smokers.[9] Chronic exposure to cannabis smoke has also been associated with the development of pre-cancerous changes in bronchial and epithelium cells in similar rates to tobacco smokers.[10] Cellular abnormalities were most present in individuals who smoked both tobacco and marijuana, implying that cannabis and tobacco smoke may have an additive adverse effect on airway tissue.[11] The results suggest that long-term exposure to cannabis smoke, particularly when combined with tobacco smoking, is capable of damaging the bronchial system in ways that could one day lead to respiratory cancers. However, to date, no epidemiologic studies of cannabis-only smokers have yet to reveal such a finding. Larger, better-controlled studies are warranted.

Cannabis consumers who desire the rapid onset of action associated with inhalation but who are concerned about the potential harms of noxious smoke can dramatically cut down on their intake of carcinogenic compounds by engaging in vaporization rather than smoking. Cannabis vaporization

limits respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190 degrees Celsius), but below the point of combustion where noxious smoke and associated toxins (i.e., carcinogenic hydrocarbons) are produced (near 230 degrees Celsius).[12] Because vaporization can deliver doses of cannabinoids while reducing the users intake of carcinogenic smoke, it is considered to be a preferred and likely safer method of cannabis administration than smoking marijuana cigarettes or inhaling from a water pipe. According to the findings of a recent clinical trial, use of the Volcano vaporizing device delivered set doses of THC to subjects in a reproducible manner while suppressing the intake of respiratory toxins. "Our results show that with the Volcano, a safe and effective cannabinoid delivery system seems to be available to patients," investigators at Leiden University's Institute of Biology (the Netherlands) concluded. "The final pulmonal uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking."[13]

Head, Neck and Lung Cancers

While a handful of anecdotal reports and one small case-control study[14] associate heavy marijuana use among younger adults with increased incidents of head, neck and lung cancers, no large scale population studies have replicated these results. Investigators at John Hopkins University in Baltimore reported that neither "lifetime use" nor "ever use" of cannabis were associated with head, neck or lung cancer in younger adults in a large, hospital-based case-control study of 164 oral cancer patients and 526 controls. Researchers concluded, "The balance of evidence from this, the largest case-control study addressing marijuana use and cancer to date, does not favor the idea that marijuana as commonly used in the community is a major causal factor for head, neck or lung cancer in young adults."[15]

More recently, the results of a 2004 population-based case-control study of 407 individuals diagnosed with oral squamous cell carcinoma and 615 healthy controls found "no association" between cannabis use and incidents of oral cancer, regardless of how long, how much or how often individuals had used it.[16] A second 2004 case-control study of 116 oral cancer patients and 207 matched controls also failed to identify any association between self-reported cannabis use and oral cancers in adults age 45 years old or younger, although only 10 percent of patients in the study identified themselves as heavy users of cannabis.[17]

A 1997 retrospective cohort study examining the relationship of marijuana use to cancer incidence in 65,171 men and women 15 to 49 years of age in California found that cannabis use was not associated with increased risks of developing tobacco-use related cancers of the lung and upper aerodigestive tract, and in fact, no cases of lung cancer were identified among men and women who used marijuana but did not smoke tobacco.[18] Critics charge that volunteers in the study were relatively young and that the follow up period was fairly short,[19] arguing that "such a study could not have been expected to detect any relationship between marijuana and lung cancer if the lag period were comparable to that seen with tobacco," which typically occurs after at least 20 years of smoking cigarettes and/or among adults over age 60. The study's author responds: "[I]n contrast to users of

tobacco and alcohol, most cannabis users generally quit using cannabis relatively early in their adult lives. … Therefore, even diseases that might be related to long-term use of cannabis (e.g. lung cancer) are unlikely to have a sizeable public health impact because most people who try cannabis do not become long-term users."[20]

Government reviews investigating a possible link between cannabis use and lung cancer have also failed to find a definitive causal connection between the two. A 1998 report by the British House of Lords Science and Technology Committee concluded, "There is as yet no epidemiological evidence for an increase risk of lung cancer" in cannabis smokers, though authors did concede that studies have revealed cellular changes in the airways of cannabis smokers that could potentially be pre-cancerous.[21] An 18-month study by the US National Academy of Science Institute of Medicine also concluded, "There is no conclusive evidence that marijuana causes cancer in humans, including cancers generally related to tobacco use," but added that cellular studies and a handful of poorly controlled case studies suggest that cannabis smoke may be "an important risk factor" for the development of upper aerodigestive or lung cancers.[22] A 2002 Canadian Senate review further commented that among the small number of case studies present in the literature: "[N]one compare the prevalence of cancer with a control group or evaluates the use of cannabis in a standardized way. Interpretation is also limited by the fact the patients smoked tobacco and drank alcohol."[23]

More recent reviews of the subject published in the journals *Alcohol* and *Lancet Oncology* reach similar conclusions. A review of two cohort studies and 14 case-control studies assessing the association of marijuana and cancer risk by Hashibe and colleagues concluded, "[R]esults of cohort studies have not revealed an increased risk of tobacco related cancers among marijuana smokers."[24] Authors did highlight a pair of African case control studies citing marijuana use as a possible elevated risk factor for lung cancer, though they added that investigators failed to assess either the durations of cannabis use or quantify the amount of tobacco used by subjects in conjunction with marijuana. A second 2005 review by Hall and colleagues conclude, "There is a conspicuous lack of evidence on the association between cannabis smoking and lung cancers," and recommends the subject receive additional study.[25]

A large US case-control study funded by the US National Institutes of Health assessing the effects of marijuana smoking on the risks of lung cancer and upper aerodigestive tract cancers among 2,400 Los Angeles County residents less than 60 years of age is ongoing.[26] Preliminary data from the study, presented by investigators at the 2005 annual conference of the International Cannabinoid Research Society (ICRS), report that those who self-reported using moderate levels of cannabis had no greater odds of suffering from lung or UAT cancers than controls.[27]

Childhood Cancers

Acute myeloid leukemia (AML) comprises approximately 16 percent of leukemias diagnosed in individuals younger than 15 years of age. A 1989 study suggested that prenatal exposure to marijuana increased the risk of childhood leukemia.[28] However, a more recent 2006 study – the largest epidemiological study of childhood AML to date in the US – rebuts this premise.

"Overall, no positive associations between parental marijuana use and childhood AML were observed," investigators at the University of North Carolina at Chapel Hill found. They concluded: "The previously reported positive association between maternal marijuana use before or during pregnancy and childhood AML was not confirmed in this study. Parental marijuana use is unlikely as a strong risk factor for childhood AML."[29]

Investigators also noted evidence of an "inverse association" between cannabis use and a decreased risk of childhood AML, though they suggested that this result was likely due to "recall bias" (e.g., case mothers may have been less likely than control mothers to report having used marijuana before or during pregnancy) rather than any potential protective effects of cannabis. At least one prior large, population-based case-control study also reports an inverse association between marijuana use and a reduced risk of cancer. That study, published in the *American Journal of Epidemiology* in 1999, reported that lifetime use of cannabis was associated with a reduced risk of adult, non-Hodgkin's lymphoma. "Marijuana was the only recreational drug that remained associated with a reduced risk for non-Hodgkin's lymphoma after adjusting for potential cofounding factors, investigators determined.[30] (A second study on marijuana use and non-Hodgkin's lymphoma found no association between cannabis use and onset of the disease.)[31]

A review of the literature reveals two additional case-control studies suggesting an increased risk of certain childhood cancers in offspring of mothers who reported using cannabis.[32,33] However, neither study was a planned investigation of the potential association between maternal cannabis use and childhood cancers; rather, marijuana use was one of several possible confounding variables measured, making it impossible for investigators to ascribe causation. To date, neither of these findings has been replicated.

Other Cancers

Sidney and colleagues, in their 1997 retrospective cohort study of 65,171 men and women, determined that "ever" and "current use" of cannabis was not associated with an increased risk of tobacco-use related cancers or cancers of the colon, lung, skin, prostate, breast and cervix. "Compared with nonusers/experimenters (lifetime use of less than seven times), … marijuana use [was] not associated with increased risk of cancer … in analyses adjusted for sociodemographic factors, cigarette smoking, and alcohol use," investigators determined.[34] A 2005 review of case studies by Hashibe and colleagues also failed to note evidence of a strong association between cannabis use and either anal or penile cancer.[35]

A second cohort study by University of Hawaii researchers investigating the risk for malignant primary onset glioma (brain cancer) associated with cigarette smoking and other lifestyle behaviors did report an increased incidence risk for individuals who smoked cannabis at least once per month, after adjustment for sex, race, education, smoking status, alcohol consumption, and coffee intake.[36] However, no dose-response relation was observed -- by contrast, drinkers of >7 cups of coffee per

day had a 70 percent increased risk for glioma – and cannabis was only incidentally assessed as a potential confounding factor

The above finding is curious in light of several recent preclinical studies demonstrating that the administration of cannabinoids selectively inhibit the growth of glioma cells in a dose dependent manner. Among these, an Italian research team, writing in the 2004 issue of the *Journal of Pharmacology and Experimental Therapeutics* demonstrated that the administration of the non-psychoactive cannabinoid cannabidiol (CBD) to nude mice significantly inhibited the growth of subcutaneously implanted U87 human glioma cells. Authors wrote, "In conclusion, … CBD was able to produce a significant antitumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent (an agent that inhibits the growth of malignant cells.)"[37] More recently, investigators at the California Pacific Medical Center Research Institute reported that the administration of THC on human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced apoptosis (programmed cell death) more rapidly than did the administration of an alternative synthetic cannabis receptor agonist.[38]

Finally, a team of investigators from Stanford University and the Medical College of Georgia recently reported an association between marijuana exposure and bladder cancer in a pilot study of Vietnam-era veterans aged less than 60 years old.[39] However, 77 percent pf the cancer patients in the study reported smoking both tobacco and marijuana, and only six subjects (11 percent) admitted to having used marijuana and not tobacco. A 2006 case report published in the journal *Urology* also suggests heavy cannabis use (up to five cigarettes daily for more than 30 years) as a potential risk factor in a 45-year-old man with transitional cell carcinoma.[40] Follow-up, large-scale epidemiological studies may be warranted in this area.

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