

Does Smoking Marijuana Contribute to the Risk of Developing Lung Cancer?

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Lung cancer has emerged as the most common cause of cancer-related death in men and women in the United States (Edmondson, 2008; Swaney, 2002). Marijuana, a product of the *Cannabis sativa* plant, is the most frequently used illegal substance in the United States (Mehra, Moore, Crothers, Tetrauld, & Fiellin, 2006). The question explored here is whether evidence links marijuana use to lung cancer development.

Tobacco use was known to Native Americans, but the first recorded harvest of a tobacco crop in North America was in 1611 in the Jamestown colony (Cruz et al., 1998). Marijuana has a world history that dates back to 4000 BC, when it was grown in China for the hemp fibers. Oral traditions from China list medical uses for marijuana as far back as 2700 BC (Zuardi, 2005). Marijuana use in the United States dates to the early 1900s, when it was used as a cure for morphine addiction (Cruz et al., 1998). Marijuana primarily is obtained from the leaves and flower heads of the female *Cannabis sativa* plant. The active ingredient is delta-9 tetrahydrocannabinol (THC), with the highest content found in the flower heads and decreasing in concentration from the stems down to the seeds (Campbell, 1999; Hall & Solowij, 1998).

Biologic Damage

Tashkin (2001) cited studies showing a relationship between smoking marijuana and potentially serious damage to the epithelium of the central airway, present in the absence of clinical or physiologic evidence of lung disease. Immunohistopathologic studies from the University of California, Los Angeles, showed

overexpression in marijuana users of Ki-67 (a cell proliferation marker), epidermal growth factor receptor, and *p53* (a suppressor gene that becomes altered in cancer states), suggesting a biologic basis for increased risk of lung cancer. Tashkin also reported that different concentrations of THC stimulate formation of reactive oxygen species in cells that are exposed to smoke from the distal end of the “joint,” indicating that cell damage is caused by toxic gas in the smoke. THC exposure also may cause changes in alveolar macrophages that are crucial to the lung’s immune defense system. The damage may be caused by impairment of pro-inflammatory cytokines, interferon- γ , and granulocyte macrophage-colony-stimulating factor production. Tashkin proposed that marijuana and tobacco together appear to produce an additive effect on bronchial epithelial histopathology and concluded that regular marijuana use could potentially predispose an individual to pulmonary infection and respiratory cancer.

Mehra et al. (2006) also discussed a THC-induced cellular proliferation in a murine-based (mouse) model, suggesting that tumor growth is caused by inhibition of antitumor immunity from a cannabinoid-2 receptor-mediated pathway. A literature review conducted by Mehra et

al. included two case control studies of marijuana users who did not smoke tobacco. The control studies demonstrated more metaplastic cells, macrophages, pigmented macrophages, and columnar cell presence in marijuana smokers who did not smoke tobacco. The two studies also demonstrated that alveolar macrophages from marijuana smokers alone, or in combination with tobacco use, were more

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likely to show DNA damage, although these alveolar changes were not statistically significant. Another study reviewed by Mehra et al. showed decreased levels of glutathione and a dose-dependent THC content and reactive oxygen species generation. Mehra et al. concluded that alveolar macrophages exposed to marijuana smoke were less tumoricidal and had an increased likelihood of damaging DNA; therefore, marijuana smokers are more likely to have basal, goblet, and squamous cell hyperplasia; stratification; cell disorganization; nuclear variation; increased nuclear cytoplasmic ratio; basement membrane thickening; squamous cell metaplasia; mitotic figures; abnormal expression of Ki-67; and increased epidermal growth factor receptor compared

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to nonsmokers. Polynuclear aromatic hydrocarbons have been linked to carcinogenesis and are 50%–70% higher in marijuana smoke than tobacco smoke (Cruz et al., 1998).

In a 2006 meeting of the American Thoracic Society, Tashkin stated that biochemical and preclinical studies suggest a biologic link between marijuana smoke and an increased risk for lung cancer, based on the accelerated and malignant changes in lung tissue (Fuerst, 2006). Tashkin hypothesized that molecular changes in bronchial biopsy tissues may partially be caused by more particles being delivered to the lungs from the lack of a filter and the loose packing of marijuana joints. However, the results of a large epidemiologic study with the group found no increased risk of lung cancer in marijuana smokers when compared to controls (Fuerst); however, the study did show a 20-fold increase in the risk of lung cancer for cigarette smokers.

Chemical Exposure

Both marijuana and cigarette smoke contains nitrosamines, phenols, aldehydes, polyvinyl chlorides, polyaromatic hydrocarbons, and tar. Cigarettes can be filtered to reduce the tar absorption; however, marijuana is not filtered and is packed more loosely than cigarettes, allowing for a higher thermal exposure (Mehra et al., 2006; Tashkin, 2001). In addition, marijuana smoke inhalation generally is deeper and the smoke is held in the lungs longer than cigarette smoke (see Table 1).

Risk Factors

Although studies related to marijuana use may show a biologic basis for cancer development (Mehra et al., 2006), studies do not show an association between a history of marijuana use and an increased risk of lung cancer (Fuerst, 2006). One explanation may be that most of the U.S. population who used marijuana did so as adolescents and young adults and stopped relatively early in the adult stage (Merline, O'Malley, Schulenberg, Bachman, & Johnston, 2004). The majority of marijuana users do not continue use into midlife and beyond, as cigarette smokers often do (Sidney, 2003). Illegal substance abuse generally peaks in adolescence

Table 1. Marijuana and Cigarette Comparisons

VARIABLE	MARIJUANA	CIGARETTES
Inhalation	Increased delivery to lungs caused by holding inhaled smoke for a longer period of time	Shorter breaths limit tar intake.
Filters	None; may lead to more tar intake	May be filtered
Packing	Burns at a higher temperature from less dense packing, leading to an increased risk of thermal injury to lungs	Burns at a lower temperature because of dense packing
Hydrocarbons	Polynuclear aromatic hydrocarbon concentrations are 50%–70% higher than in tobacco.	Has lower polynuclear aromatic hydrocarbon concentrations than marijuana
Use	Less common prolonged use and less frequent daily use	Prolonged use is more common with more frequent daily use.
Biologic effects	Biologic changes to tissue do occur but have not been linked to risk for lung cancer.	Biologic changes to tissue do occur and are proven risk factors for lung cancer.
Legality	Illegal in the United States	Legal in the United States

and young adulthood before decreasing based on various factors, such as age, educational level, marital status, and parenthood (Merline et al., 2004).

Sidney (2003) stated that after age 35, only 18% of previous marijuana users continued to report use. However, self-reporting of marijuana use frequently is retrospective and involves admitting use of an illegal substance, which may lead to a decrease in reporting or a desire not to report use. Cigarette smoking is legal and, therefore, more likely to be accurately reported (Sidney).

Cessation Benefits

Lung cancer typically occurs after about 20 years of smoking exposure (Swaney, 2002). The risk of lung cancer in cigarette smokers decreases to 50% after 10 years of cessation and as much as 80%–90% after 15 years of cessation (Swaney). Given the younger age when general marijuana cessation occurs, the lack of long-term exposure, and the amount of time after exposure, the effect of marijuana on lung cancer development may not be readily apparent. Sidney (2003) suggested, however, that continuing to follow older adults who continue to smoke marijuana regularly and over a long period of time may reveal an association with morbidity that has not yet been proven.

Conclusion

Biologic evidence shows changes to lung tissue that could theoretically progress to lung cancer; however, an evidence base does not exist that directly links marijuana inhalation to risk for lung cancer. The lack of evidence may be related to under-reporting or an inability to separate the risk factors of marijuana use from cigarette smoking. Evidence does exist regarding decreased cancer risk with smoking cessation. Although no proven link exists between marijuana smoke and lung cancer, cessation time may be a factor based on the average age of use and cessation. To answer the question of marijuana use and whether it causes lung cancer: Biologic evidence suggests an increased risk of lung changes that may contribute to cancer from marijuana use, but no definitive link has been proven at this time.

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