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Senate Committee on Business and General Government
Oregon State Legislature
Salem, Oregon

Via email only to: sbgg.exhibits@oregonlegislature.gov

TESTIMONY REGARDING SB639

Chair Riley and Committee Members:

I regret that I am unable to be in Salem for the hearing on this critically important legislation and respectfully request that you consider this letter as my testimony.

I am a lawyer and cannabis law reform activist who has attended each Legislative Session since 1999 as an unpaid citizen activist. I also helped write the Oregon Medical Marijuana Act and Ballot Measure 91. In 2018, I received lifetime achievement awards from the National Organization for the Reform of Marijuana Laws and the Oregon State Bar's Cannabis Law Section, a section I co-founded.

It is neither trite nor false to say that although we have legalized cannabis in Oregon, you can't consume it indoors or outdoors. The 'public view' exception to legalized use is workable, but the Indoor Clean Air Act's (ICAA) restriction is untenable. And, truth be told, it's not an issue for folks like me who are self-employed, or workers fortunate enough to be employed by employers like me. And, as my wife and I (and the bank) own our home, it's not the issue that it would be for renters in an age where standard residential rental agreements include prohibitions on cannabis cultivation or onsite consumption.

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Which is to say that the sick, disabled, and poor are the victims of the policy that excludes their being able to safely consume their medicine, or chosen means of relaxation.

Those who oppose this bill, and particularly the provision which would create a carve-out to the ICAA, due so on the guise of 'public health' and rely on an argument that cannabis smoke is no different than tobacco smoke. This is as fake science as the 'science' of the climate change deniers.

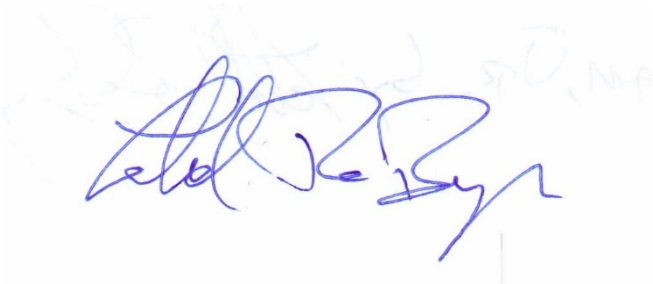
The definitive study on this issue was authored by Dr. Donald P. Tashkin, a Medical School Professor at UCLA. The study, *Effects of Marijuana Smoking on the Lung*, was published in Annals of the American Thoracic Society in 2013 and is both available online here: https://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201212-127FR and I've attached a copy to this testimony. The abstract to this study concludes:

In summary, the accumulated weight of evidence implies far lower risks for pulmonary complications of even regular heavy use of marijuana compared with the grave pulmonary consequences of tobacco.

I respectfully request that you pass this bill out of committee, as drafted and without amendment, with a DO PASS recommendation.

Thank you for the opportunity to comment on this important proposed legislation.

Respectfully submitted,



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Effects of Marijuana Smoking on the Lung

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Abstract

Regular smoking of marijuana by itself causes visible and microscopic injury to the large airways that is consistently associated with an increased likelihood of symptoms of chronic bronchitis that subside after cessation of use. On the other hand, habitual use of marijuana alone does not appear to lead to significant abnormalities in lung function when assessed either cross-sectionally or longitudinally, except for possible increases in lung volumes and modest increases in airway resistance of unclear clinical significance. Therefore, no clear link to chronic obstructive pulmonary disease has been established. Although marijuana smoke contains a number of carcinogens and cocarcinogens, findings from a limited number of well-designed epidemiological studies do not suggest an increased risk for the development of either lung or upper airway cancer from light or moderate use, although evidence is mixed concerning possible carcinogenic risks of heavy, long-term use. Although regular marijuana smoking leads to bronchial epithelial ciliary loss and impairs the microbicidal function of alveolar macrophages, evidence is inconclusive regarding possible associated risks for lower respiratory tract infection. Several case reports have implicated marijuana smoking as an etiologic factor in pneumothorax/pneumomediastinum and bullous lung disease, although evidence of a possible causal link from epidemiologic studies is lacking. In summary, the accumulated weight of evidence implies far lower risks for pulmonary complications of even regular heavy use of marijuana compared with the grave pulmonary consequences of tobacco.

Keywords: marijuana; chronic bronchitis; lung function; chronic obstructive lung disease; lung cancer

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Marijuana is the second most widely smoked substance in our society after tobacco. In 2011, 36.4% of high school seniors in the United States reported using marijuana within the past year, 22.6% within the past month, and 6.6% on a daily basis (1). By comparison, daily use of tobacco was reported by 10.3% of 12th graders. Because the principal route of marijuana use is by inhalation of the smoke from a cigarette ("joint") or a water pipe ("bong"), there is obvious concern over the potential harmful effects on the lung, by analogy with the well-known pulmonary consequences of tobacco smoking, including chronic obstructive pulmonary disease (COPD), lung cancer, and an increased risk of lower respiratory tract infections. This concern is heightened by the finding that the smoke contents of marijuana and a comparable quantity of tobacco (unfiltered Kentucky reference cigarette) include roughly similar amounts of volatile constituents (including ammonia, hydrocyanic acid, and nitrosamines) and qualitatively similar tar components (including phenols, naphthalene, and the procarcinogenic benzopyrene and benzanthracene) with the major exceptions of nicotine (found only in tobacco) and Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in marijuana, and a number of other THC-like (cannabinoid) compounds that are found only in marijuana (2, 3). Many of the components common to tobacco and marijuana smoke have toxic effects on respiratory tissue. Consequently, the similarity in these potentially injurious smoke contents raises the possibility that marijuana smoking might be a risk factor for the development of COPD and lung cancer. This review examines the evidence from largely human studies concerning potential associations between marijuana smoking and tobacco-related pulmonary consequences.

What Are the Acute Effects of Smoking Marijuana on Airway Physiology?

The acute effects of smoking marijuana on the lung have been assessed mainly by studying its effects on bronchial dynamics. Smoking a single tobacco cigarette causes a modest degree of acute bronchoconstriction, which has been attributed to an irritant effect of the smoke leading to cholinergically mediated reflex bronchospasm (4). In contrast,

smoking a single "joint" of marijuana (7 mg/kg) containing 2% THC by weight caused acute bronchodilation in healthy subjects, the degree of which exceeded that produced by nebulized isoproterenol (1.25 mg) (5). This effect, which persisted for at least 1 hour, was due to the THC content of the "joint" because the effect was not seen when the THC was extracted but was subsequently reproduced after the "joint" was spiked with synthetic THC. Similar results were reported by Vachon and colleagues (6). Smoking a single marijuana cigarette (2% THC) also produced bronchodilation in subjects with mild asthma with a rapid onset and duration of at least 2 hours (7) and acutely reversed methacholine- and exercise-induced bronchospasm (8). Rodent studies suggest that the mechanism of THC-induced bronchodilation may be mediated by binding to cannabinoid type 1 (CB1) receptors expressed on axon terminals of postganglionic vagal nerves in the airway, resulting in inhibition of acetylcholine release from the nerve endings with reduction in bronchomotor tone (9). Interestingly, the bronchodilator properties of marijuana were recognized in the nineteenth century when marijuana was used for the treatment of asthma (10).

What Are the Chronic Effects of Habitual Smoking of Marijuana on the Lung?

These have been examined in both experimental animal and human studies.

Animal Studies

Animal exposure studies have shown histopathologic alterations in the airways and lung parenchyma after chronic exposure to various amounts of marijuana smoke (11–14). On the other hand, exposure of rats to various amounts of marijuana smoke for up to 1 year did not reveal any morphologic or physiological evidence of emphysema, in contrast to emphysematous changes that developed in similar animals exposed to comparable amounts of tobacco smoke (15).

Human Studies

Most human studies have compared the effects of smoking marijuana with those of smoking tobacco. Because the quantity of tobacco smoked by most regular tobacco cigarette smokers (usually approximately 20 cigarettes per day or more) generally exceeds the quantity of marijuana smoked by most regular users of marijuana (usually less than a few joints per day), it is a plausible concept that differences in the effects of regular tobacco versus regular marijuana smoking on the lung could be attributable, at least in part, to differences in the quantity of the two substances smoked, rather than to qualitative or quantitative differences in the composition of the contents of the two plant substances. On the other hand, the amount of exposure of the lung to the smoke components from each type of plant substance is determined not only by the number of cigarettes (or joints) smoked but also by differences in smoking topography for the two substances. For example, it has been shown that regular marijuana smokers take larger puffs, inhale the smoke more deeply into their lungs, and hold their breath approximately four times longer compared with regular tobacco cigarette smokers (16). These differences in smoking technique are responsible for an approximately fourfold increase in the amount of tar deposited in the lower respiratory tract from the smoke of marijuana compared with the smoke generated from the same quantity of tobacco, thus potentially amplifying the impact of smoking a given amount of marijuana compared with the same quantity of tobacco (16).

Effects on chronic respiratory symptoms. Several studies (Table 1) have compared responses to respiratory symptom questionnaires in samples of regular marijuana smokers with responses in age-matched nonsmokers of marijuana, controlling for concomitant tobacco smoking. One study examined a convenience sample from Los Angeles County of 144 habitual (near-daily for ⩾5 yr) smokers of marijuana alone (MS), 135 habitual smokers of both marijuana and tobacco (MTS), 79 regular tobacco-only smokers (TS), and 97 nonsmokers of any substance (NS) (mean ages, 31.6–37.0 yr) (17). In the smokers of marijuana alone, tobacco alone, or marijuana plus tobacco, the prevalence of chronic cough (18–24%), sputum production (20–26%), wheeze for at least 3 weeks/year (25–37%), and at least two prolonged episodes of acute bronchitis during the previous 3 years (10–14%) were significantly higher than in the nonsmokers ($P < 0.05$), but no differences in the prevalence of cough, sputum, or wheeze were noted between smokers of marijuana only, tobacco only, and combined smokers of both marijuana and tobacco. Analogous findings were reported by Bloom and colleagues (18) in a stratified random sample of residents of Tucson, Arizona (mean age, 27–29 yr) comprising 38 marijuana-only smokers, 209 tobacco-only smokers, 56 smokers of both marijuana and tobacco, and 502 nonsmokers, with the exception that chronic cough and sputum were less frequent in the marijuana-only smokers (32 and 26%, respectively) than in the tobacco-only smokers (54 and 43%, respectively) and the effects of combined

Table 1. Effects of regular use of marijuana alone on chronic respiratory symptoms and lung function in comparison with nonsmoking control subjects

Symptoms
Increased prevalence of chronic cough or sputum (17, 18, 20–22), wheezing (17, 18, 20–22), and shortness of breath (20)
Increased incidence of acute bronchitic episodes (17) or clinic visits for acute respiratory illness (19)
Lung Function
No difference in FEV_1 or FVC (17, 20, 21)
Increase in FVC (23, 27, 29)
Increase in FEV_1 (23)
Decrease in FEV_1/FVC (18, 20)
No difference in single-breath nitrogen washout measures (17, 25)
No differences in FRC, TLC, or RV (17, 21)
Increases in FRC, TLC, and RV (27)
Increase in Raw and decrease in SGaw (17, 25, 27)
No difference in D_{LCO} (17, 21, 27)

Definition of abbreviations: D_{LCO} = single-breath diffusing capacity for carbon monoxide; FRC = functional residual capacity; Raw = airway resistance; RV = residual volume; SGaw = specific airway conductance; TLC = total lung capacity.

smoking of marijuana and tobacco on cough and sputum appeared to be additive (68 and 63%, respectively). These differences from the Los Angeles study results might be attributed to the fact that the marijuana-only smokers in the Tucson sample smoked marijuana less frequently than their Los Angeles counterparts. A 2-year follow-up study of 452 daily marijuana-only smokers and 450 nonsmokers among Kaiser Permanente Medical Care Program participants revealed a small but significant increase in outpatient visits for respiratory illnesses among the marijuana smokers (relative risk [RR], 1.19; 95% confidence interval [CI], 1.01–1.41) (19), consistent with the finding among the daily marijuana-only smokers in the Los Angeles study of a significant increase in acute bronchitic episodes.

Respiratory symptoms were also assessed in 943 adults, 21 years of age, from a birth cohort of subjects born in Dunedin, New Zealand, of whom 9.7% were cannabis-dependent (20). After controlling for tobacco use, early morning sputum production, wheezing apart from colds, nocturnal awakenings with chest tightness, and exercise-induced shortness of breath were increased among the cannabis-dependent subjects by 144% ($P < 0.01$), 61%, 65%, and 72% (all $P < 0.05$), respectively, compared with nonsmokers (20). In another New Zealand study that examined a random population-based sample (supplemented by a convenience sample) of adult residents of Wellington, New Zealand, comprising 75 marijuana-only smokers, 92 tobacco-only smokers, 91 smokers of both marijuana and tobacco, and 81 nonsmokers (mean ages, 41–46 yr) (21), odds ratios (95% CI) for the association of cough with marijuana smoking and tobacco smoking were 1.5 (1.1–1.7) and 1.9 (1.4–2.6), respectively, and of chronic sputum production were 2.0 (1.4–2.7) and 1.6 (1.2–2.2), respectively, without evidence of any additive effects of marijuana and tobacco, consistent with the findings in the Los Angeles study.

Respiratory effects of marijuana have also been reported for self-reported marijuana-smoking participants in the U.S. National Health and Nutrition Examination Survey (NHANES III) (22). Odds ratios (ORs) (95% CI) for respiratory symptoms in the 414 marijuana users versus 4,789 nonsmokers (controlling for sex, age, current asthma, and concomitant tobacco use) were 2.17 (1.1–4.26) for chronic cough, 1.89 (1.35–2.66) for chronic sputum, and 2.98 (2.05–4.34) for wheeze. By comparison, the ORs (95% CI) among tobacco-only smokers for chronic cough, sputum production, and wheeze versus nonsmokers were 5.02 (3.58–7.04), 3.71 (2.45–5.62), and 3.39 (2.54–4.53).

In a survey of a random sample of 878 older adults (≥40 yr) residing in Vancouver, Canada, as part of the Burden of Obstructive Lung Diseases (BOLD) study, the OR for chronic respiratory symptoms was not increased among the 49% of respondents who reported ever using marijuana alone (23). However, concurrent use of marijuana and tobacco was associated with a higher OR for respiratory symptoms (OR, 2.59; 95% CI, 1.58–3.62) than was smoking tobacco alone (OR, 1.50; 95% CI, 1.05–2.14), consistent with a possible synergistic interaction between marijuana and tobacco.

Taken together, the weight of evidence points to a significant association of marijuana use with symptoms of chronic bronchitis that may be comparable to or less than that of tobacco smoking alone, possibly dependent on the frequency and quantity of marijuana smoked. Evidence is mixed regarding the possibility of additive or synergistic effects of combined smoking of marijuana and tobacco on chronic respiratory symptoms. However, cessation of marijuana smoking by marijuana-only smokers has been associated with resolution of preexisting symptoms of chronic bronchitis (24).

Effects on lung function. Lung function has been assessed in several studies (Table 1) conducted in either convenience or population-based samples of smokers and nonsmokers of marijuana. In the Los Angeles cohort study (17), no differences were noted between the 135 marijuana-only smokers and 99 nonsmokers in spirometric measures, indices derived from single-breath nitrogen washout or the single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}); however, airway resistance (Raw) was slightly (26%) but significantly elevated in the marijuana-only smokers compared with both the nonsmokers and tobacco-only smokers ($P < 0.05$); similar findings had been noted in an earlier study of 50 habitual marijuana-only smokers compared with matched control subjects from a population-based cohort in the same geographic area (25). Longitudinal assessment of the age-related decline in FEV_1 over 8 years in 65% of the Los Angeles subjects who volunteered to undergo follow-up studies revealed no significant difference between the marijuana-only smokers (30.8 ml/yr) and the nonsmokers (25.3 ml/yr), whereas tobacco-only smokers showed a significantly higher rate of decline (56.5 ml/yr) (26). In the Tucson study, the ratio of FEV_1 to FVC was significantly lower in marijuana-only smokers (0.90) than in nonsmokers (0.98) ($P < 0.05$). Consistent findings were reported in the Dunedin, New Zealand, birth-cohort study in which a significantly higher proportion of cannabis-dependent subjects than nonsmokers at age 21 years had an FEV_1/FVC ratio less than 0.80 (20). On the other hand, in the Wellington, New Zealand, study, no significant differences were noted in spirometry, lung volumes or D_{LCO} in marijuana-only smokers compared with nonsmokers (20). Moreover, in an extended follow-up of the Dunedin birth cohort, at age 32 years (n = 841–919), no association was found between marijuana use (after adjustment for the concomitant use of tobacco) and lung function (spirometry, lung volumes, and D_{LCO}), except for increases in FVC, total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), and Raw and a decrease in specific airway conductance (SGaw) (27); longitudinal analysis of spirometry performed in this cohort since age 18 years revealed that marijuana smoking was associated with a significant increase in FVC without any significant change in FEV_1. The authors concluded that the isolated decrease in FEV_1/FVC ratio previously reported among marijuana-only smokers versus nonsmokers at age 21 years from the same birth cohort (20) may have been a spurious finding attributable to an increase in FVC. Significant increases in both FVC ($P < 0.001$) and FEV_1 ($P < 0.05$) have also been noted in marijuana smokers compared with those with no history of marijuana use in the Vancouver BOLD study (23). The mechanism of the observed increase in FVC is not clear but might be related to "stretching" the lung from the repeated deep inhalations characteristic of marijuana-smoking topography (16), analogous to the elevated vital capacity noted in elite athletes (28).

In an observational study of a cohort of 5,115 current and former smokers and nonsmokers of tobacco or marijuana in four U.S. cities monitored for more than 20 years with serial measurements of lung function,

no significant association was found between decrements in FEV_1 and intensity of current marijuana smoking or cumulative lifetime exposure to marijuana (joint-years), although a significant association was noted between joint-years and an increase in FVC (29). Using cubic spline analysis the authors found a nonlinear association between heavy lifetime exposures (>20 joint-years) and lower levels of FEV_1; however, the latter findings need to be interpreted cautiously because less than 1% of the observations were made in subjects with more than 20 joint-years of use.

In summary, most cross-sectional, as well as longitudinal, studies have failed to find a significant association between marijuana use (in the absence of, or controlling for, concomitant tobacco use) and measures of airflow obstruction. Moreover, no additive adverse effects of marijuana when smoked along with tobacco have been reported. These findings argue against the concept that smoking marijuana, by itself, is a risk factor for the development of COPD.

Effects on lung structure, including emphysema. Thoracic high-resolution computed tomography scans (slices of 1 mm in thickness at 1-cm intervals) were performed in 75 marijuana-only smokers, 91 smokers of both marijuana and tobacco, 92 tobacco-only smokers, and 81 nonsmokers participating in the Wellington, New Zealand, study (21). The proportion of marijuana-only smokers with a relative area of lung occupied by attenuation values lower than –950 Hounsfield units as a percentage of total lung area (RA950) in an apical slice was significantly higher in marijuana-only smokers (7.3%) than nonsmokers (6.1%). However, the proportion with low attenuation averaged over three apical slices in marijuana-only smokers (6.7%) was comparable to that in nonsmokers (6.3%). Moreover, no significant increase was observed in the proportion of marijuana-only smokers with macroscopic emphysema (1.3%) compared with that of nonsmokers (0%); in contrast, macroscopic emphysema was noted in 18.5% of tobacco-only smokers and 16.5% of smokers of both marijuana and tobacco. These findings provide further evidence against the notion that marijuana is a risk factor for the development of emphysema, although the low-attenuation findings at the apices could be clinically relevant regarding potential risks for barotrauma and bullous lung disease (*see below*).

Effects on bronchial pathology. Few investigational bronchoscopic studies have been conducted in otherwise healthy smokers of marijuana and control subjects. Videobronchoscopy was performed in 40 healthy young smokers of marijuana or tobacco (10 each for marijuana-only smokers, tobacco-only smokers, smokers of both marijuana and tobacco, and nonsmokers), 20–49 years of age, participating in the Los Angeles cohort study (30); the videotapes were scored by an independent observer for three components of the bronchitis index (erythema, edema, mucous secretions) (31) on a scale of 0 to 3, 3 representing the most abnormal finding. The bronchitis index score was significantly higher for the marijuana-only smokers (8.2 $\pm$ 5.4 SD) than for the nonsmokers (4.4 $\pm$ 1.6 SD) ($P < 0.05$) and comparable to the bronchitis index score for the tobacco-only smokers (8.0 $\pm$ 2.5 SD). Pronounced edema that narrowed lobar and segmental airways was often noted in the marijuana-only smokers (30), possibly accounting for the increase in airway resistance observed in physiological studies of marijuana-only smokers (16, 24, 26). Endobronchial biopsies at five different sites revealed vascular proliferation in 70% of marijuana-only smokers versus 0% of nonsmokers and 56% of tobacco-only smokers, submucosal edema in 75% of marijuana-only smokers versus 20% of nonsmokers and 88% of tobacco-only smokers, and goblet cell hyperplasia in 60% of marijuana-only smokers versus 20% of nonsmokers and 89% of tobacco-only smokers ($P < 0.05$ for all comparisons with nonsmokers). These findings indicate that regular smoking of marijuana by young adults is associated with significant airway inflammation/injury that is similar to that observed in tobacco smokers.

Endobronchial biopsies performed in 40 marijuana-only smokers, 44 smokers of both marijuana and tobacco, 31 tobacco-only smokers, and 53 nonsmokers participating in the University of California (Los Angeles, CA) cohort study revealed a significantly higher percentage of histopathologic alterations in marijuana-only smokers compared with nonsmokers ($P < 0.05$) and a similar percentage compared with tobacco-only smokers: reserve cell hyperplasia (73% marijuana-only smokers, 12% nonsmokers, 75% tobacco-only smokers); goblet cell hyperplasia (68% marijuana-only smokers, 29% nonsmokers and 77% tobacco-only smokers); squamous cell metaplasia (33% marijuana-only smokers, 6% nonsmokers, 31% tobacco-only smokers); cellular disorganization (58% marijuana-only smokers, 33% nonsmokers, 53% tobacco-only smokers); and increased nuclear-to-cytoplasmic ratio (40% marijuana-only smokers, 6% nonsmokers and 30% tobacco-only smokers) (32). The increased frequency of goblet cell hyperplasia (leading to increased mucus production) and of reserve cell hyperplasia and squamous metaplasia with the associated loss of cilia in the marijuana-only smokers would be expected to diminish their capacity to clear the airways of the excess mucus, consistent with their increased prevalence of symptoms of chronic bronchitis.

Effects on alveolar macrophages. Bronchial alveolar lavage conducted in 14 marijuana-only smokers, 13 tobacco-only smokers, 16 smokers of both marijuana and tobacco, and 19 nonsmokers from the Los Angeles cohort revealed a nearly threefold increase in the number of alveolar macrophages (AMs) per milliliter recovered from the marijuana-only smokers, a similar increase from the tobacco-only smokers, and a nearly sixfold increase from the smokers of both marijuana and tobacco (33). Increases in neutrophils were also observed in all smoking groups. Subsequent functional studies have demonstrated significant impairment in fungicidal activity of AMs from both marijuana-only and tobacco-only smokers (34, 35), as well as significant impairment in phagocytic and bactericidal activity of AMs from marijuana-only smokers (but not tobacco-only smokers) against *Staphylococcus aureus* (35). The defect in microbicidal activity of AMs from marijuana-only smokers may be related to an immunosuppressant effect of THC (mediated via cannabinoid type 2 [CB2] receptors, which are highly expressed on immune cells) manifested, in part, by THC-induced inhibition of production of inducible nitric oxide synthase (iNOS) during infection, leading, in turn, to impairment in production of reactive nitrogen intermediates that are important effector molecules in bacterial killing. The inhibition of iNOS production by marijuana appears to be caused by THC-related impairment in the production of key proinflammatory cytokines that

mediate the induction of iNOS (35, 36). Potential clinical implications of marijuana-related impairment in AM microbicidal activity are an increased susceptibility to lung infection (*see below*).

Is Regular Smoking of Marijuana a Risk Factor for Respiratory Cancer?

Several lines of evidence exist both for and against a link between marijuana use and respiratory cancer (Table 2).

Evidence for a Link

Marijuana smoke contains about 50% more benzopyrene and nearly 75% more benzanthracene, both polycyclic aromatic hydrocarbon procarcinogens, than the smoke from a comparable quantity of an unfiltered Kentucky reference tobacco cigarette, as well as other carcinogens and cocarcinogens found in tobacco smoke, including phenols, vinyl chlorides, nitrosamines, and reactive oxygen species (2, 3). Moreover, differences in the technique of smoking marijuana compared with tobacco, including deeper inhalation and much longer breath-holding time, in addition to the lower rod filtration offered by the more loosely packed marijuana in a "joint," result in a fourfold increase in deposition of the tar from marijuana than from a comparable amount of tobacco (27), thus amplifying exposure of the lung to the carcinogens within the smoke.

Endobronchial biopsies from habitual marijuana-only smokers reveal widespread histopathologic alterations, such as squamous cell metaplasia and cellular atypia, comparable to those observed in biopsies from tobacco-only smokers (32) and are recognized as precursors to the subsequent development of malignancy (37). In addition, immunohistology of bronchial tissue from the marijuana-only smokers revealed marked overexpression of the nuclear proliferation antigen Ki-67, and of epidermal growth factor receptor, both molecular markers of pretumor progression (38).

Although lung and upper airway cancer are relatively uncommon in young individuals (<40–45 yr), several small case series have identified an unusually high proportion of regular marijuana smokers among young persons with these respiratory cancers compared with the proportion of regular smokers of marijuana in the general population (39–43). However, case series represent uncontrolled observations from which causality cannot be inferred, indicating the need for well-designed epidemiologic studies.

A few small case–control studies have been performed demonstrating significantly positive associations between self-reported cannabis use and either upper airway cancer (44) or lung cancer (45, 46). The single study showing a positive association between marijuana smoking and upper airway cancer (RR, 2.6; 95% CI, 1.1–6.6) was flawed by inappropriate matching of control subjects to case subjects (44). Moreover, the two North African studies revealing significantly positive associations between cannabis and lung cancer (RR, 8.2; 95% CI, 1.3–15.5; and RR, 5.6; 95% CI, 1.6–20.5) were confounded by concomitant tobacco use for which no adjustment was possible because the two substances are typically mixed together in the form of a "kiff" and smoked (45, 46).

Table 2. Associations of marijuana use with lung or upper airway cancer: epidemiologic studies*

Lung Cancer
No positive association (57, 61)
Significantly increased risk only in heavy marijuana smokers (>10.5 joint-years), but numbers of heavy marijuana smokers among case and control subjects were small (62)
Significantly increased risk, but confounded by concomitant tobacco use (45, 46)
Upper Airway Cancer
No positive association (57–60)
Significantly increased risk, but control subjects not adequately matched with case subjects (44)

*Nonsmokers as reference; adjustments for tobacco smoking and other known potential confounders.

Evidence against a Link

Several investigators have demonstrated antitumoral effects of THC and other cannabinoids on a variety of malignancies, including lung cancer, in both cell culture systems and animal models (47–56). Such effects might be mediated by the antimitogenic, proapoptotic, and antiangiogenic properties of THC, which could counteract the protumoral effects of the carcinogens in marijuana smoke. However, epidemiologic (longitudinal cohort or case–control) studies are needed to assess the net effect of marijuana smoking on the risk for developing respiratory malignancy

A retrospective cohort study of nearly 65,000 members of the Kaiser Permanente health maintenance organization in northern California who were monitored for up to 8 years failed to find any increased risk for tobacco-related malignancies, including lung and upper airway cancer, in association with ever or current marijuana use, after adjustment for tobacco smoking (57). However, limitations of this study include the relatively young age (mean, 48 yr) of the members at the end of the follow-up period and the inclusion of few long-term or heavy smokers of marijuana.

A well-designed population-based case–control study in Washington State failed to find any increased risk for upper airway cancer in association with marijuana use (RR, 0.9; 95% CI, 0.6–1.3) or any trend toward a dose response in relation to frequency or duration of use (58). Two smaller case–control studies in the United Kingdom also failed to find a significant association between marijuana use and oral cancer (59, 60), although the small size of these studies probably reduced sensitivity for demonstrating increased risks. A large case–control study of 611 lung cancer cases, 601 cases of upper aerodigestive tract cancers and 1,040 matched control subjects conducted in Los Angeles county failed to find any significant associations between marijuana use and either lung or upper aerodigestive tract cancer irrespective of the

intensity/duration of marijuana use, after adjustment for demographic variables, educational level, tobacco, and alcohol (61). In fact, for all degrees of marijuana use, the estimated odds ratios were less than 1.0, without any suggestion of a dose–response. In contrast, the risks associated with tobacco use were highly significant with clear-cut dose–response relationships.

A subsequent, case–control study of marijuana use and lung cancer risk that included only 79 cancer case subjects and 324 matched control subjects was conducted in New Zealand (62). The latter study did not find a significant association between lung cancer and either any use of marijuana (RR, 1.2; 95% CI, 0.5–2.6) or use of marijuana among smokers in the first and second tertiles of marijuana use (RR, 0.3 and 0.9, respectively), after adjustment for other relevant factors, including tobacco use. However, an increased risk was noted among the 14 case subjects and 4 control subjects in the highest tertile of marijuana use (RR, 5.7; 95% CI, 1.5–21.6), corresponding to a life-time history of more than 10.5 joint-years (number of joints per day times number of years smoked). This study has been criticized because of the small number of case and control subjects in the third tertile (63). In contrast, the Los Angeles study, which notably failed to find any increased risk of even heavy marijuana use for respiratory cancer, included 115 control subjects with more than 10 joint-years of use. Therefore, it seems likely that the small sample size of the New Zealand study led to imprecise and vastly inflated estimates.

Epidemiologic studies for assessing the association between marijuana use and cancer risk are fraught with several limitations, including errors in subject recall regarding past marijuana use, dishonest reporting (because marijuana use is illegal), the relatively limited number of long-term heavy users, possible selection bias, and limited ability to control for all potential confounders. Therefore, even though population-based studies have generally failed to show increased risks, one cannot be entirely certain that some individuals (especially heavier marijuana users) may incur an elevated risk, although such risks appear to be small in relation to the well-known hazards of tobacco smoking. This issue is important for weighing the benefits and risks of medicinal marijuana.

Does Marijuana Smoking Increase the Risk of Lower Respiratory Tract Infection?

Biologic evidence suggests that smoking marijuana may increase the risk of lower respiratory tract infection (Table 3). The airway injury from marijuana smoking results in a loss of cilia and an increase in mucous secretions that likely lead to impairment in mucociliary clearance, compromising the lung's first line of defense against infection. In addition, the immunosuppressive effects of THC and other cannabinoids have been well documented (63), including marijuana-related impairment in alveolar macrophage phagocytic and microbicidal activity (34–36), which further compromises host defense against pulmonary infection. Moreover, marijuana has been reported to be contaminated with potentially pathogenic bacteria (65), as well as with *Aspergillus fumigatus* (66), thereby providing a vehicle for the introduction of pathogens into the lung. Isolated cases of invasive *Aspergillus* pneumonia in patients already immunocompromised due to AIDS, chronic granulomatous disease, bone marrow or renal transplantation, or cancer chemotherapy have been reported in marijuana smokers (67–71). More recently, sharing a marijuana water pipe (bong) with a patient with cavitary pulmonary tuberculosis has been associated with an increased risk of acquiring infection with tuberculosis (72); it is not clear, however, whether the acquisition of tuberculous infection was due to close contact with a case of active TB or marijuana-induced impairment in host defense. A few older epidemiologic studies appear to have demonstrated marijuana to be a significant independent risk factor for opportunistic pulmonary infection in patients seropositive for HIV (73–75). On the other hand, follow-up examination of a large cohort of gay men (the Multicenter AIDS Cohort Study) failed to find an increased risk from self-reported marijuana use for either HIV seroconversion, progression of AIDS, or the development of opportunistic infection (76). Therefore, whether or to what extent marijuana use might predispose to pulmonary infection remains unclear.

Possible Associations of Marijuana Use with Pulmonary Barotrauma and Bullous Lung Disease

Several cases of spontaneous pneumothorax or pneumomediastinum have been reported in association with marijuana smoking (77–84) (Table 3). Possible mechanisms for this association might involve either

Table 3. Miscellaneous effects

Possible Association of Marijuana Use with Lower Respiratory Tract Infection
Case reports of pulmonary aspergillosis in immunocompromised patients who smoked marijuana (67–71)
Case report of a cluster of pulmonary tuberculosis in smokers of marijuana who shared a water pipe with patients with cavitary tuberculosis (72)
Older epidemiologic study suggesting an increased risk of bacterial pneumonia in HIV-seropositive marijuana users (75)
Multicenter AIDS cohort study failing to find an association of marijuana use with progression of AIDS or acquisition of opportunistic pneumonia (76)
Association of Marijuana Use with Pulmonary Barotraumas or Bullous Lung Disease
Several reports of pneumothorax or pneumomediastinum in marijuana smokers (77–84)
Case reports of lung bullae associated with marijuana smoking (85–88)

repeated deep inhalations during the smoking of marijuana, a typical marijuana-smoking technique, followed by prolonged Valsalva maneuvers that pressurize the air in the lungs or successive deep inhalations through a high-resistance smoking apparatus simulating Muller maneuvers; in either case, rupture of subpleural blebs or alveoli might ensue with dissection of air to the pleural space or mediastinum (79, 84).

Several cases of large lung bullae have been reported in young to middle-aged, mostly heavy smokers of marijuana along with various amounts of tobacco (85–88). However, because the prevalence of bullous lung disease among marijuana smokers compared with that in the general population is unknown, no firm conclusions can be drawn as to whether or not bullous lung disease is causally linked to marijuana smoking (89).

Summary and Conclusions

Regular use of marijuana causes airway injury leading to symptoms of chronic bronchitis in some smokers but no physiological or high-resolution computed tomography evidence of emphysema. Despite the presence of procarcinogenic components in marijuana smoke, a limited number of appropriately performed and analyzed epidemiologic studies have failed to demonstrate an increased risk for either lung or upper airway cancer in association with marijuana smoking, although evidence is mixed regarding the risk of heavy, long-term use. The immunosuppressive effects of THC and reports of bacterial and fungal contamination of marijuana imply an increased risk of pneumonia. While this increased risk is also suggested by isolated case reports in immunocompromised patients and by older epidemiologic studies, it has not been confirmed in a large AIDS cohort study. Isolated case reports of pneumothorax/pneumomediastinum and bullous lung disease in heavy users of marijuana have implicated marijuana as an etiologic factor, but epidemiologic confirmation of a causal link is absent. Overall, the risks of pulmonary complications of regular use of marijuana appear to be relative small and far lower than those of tobacco smoking. However, such potential pulmonary risks need to be weighed against possible benefits in considerations regarding medicinal use of marijuana. ■

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