REVIEW ARTICLE

The Association Between Marijuana Smoking and Lung Cancer

A Systematic Review

Reena Mehra, MD, MS; Brent A. Moore, PhD; Kristina Crothers, MD; Jeanette Tetrault, MD; David A. Fiellin, MD

Background: The association between marijuana smoking and lung cancer is unclear, and a systematic appraisal of this relationship has yet to be performed. Our objective was to assess the impact of marijuana smoking on the development of premalignant lung changes and lung cancer.

Methods: Studies assessing the impact of marijuana smoking on lung premalignant findings and lung cancer were selected from MEDLINE, PSYCHLIT, and EMBASE databases according to the following predefined criteria: English-language studies of persons 18 years or older identified from 1966 to the second week of October 2005 were included if they were research studies (ie, not letters, reviews, editorials, or limited case studies), involved persons who smoked marijuana, and examined premalignant or cancerous changes in the lung.

Results: Nineteen studies met selection criteria. Studies that examined lung cancer risk factors or premalignant changes in the lung found an association of marijuana smoking with increased tar exposure, alveolar macrophage tumoricidal dysfunction, increased oxidative stress, and bronchial mucosal histopathologic abnormalities compared with tobacco smokers or nonsmoking controls. Observational studies of subjects with marijuana exposure failed to demonstrate significant associations between marijuana smoking and lung cancer after adjusting for tobacco use. The primary methodologic deficiencies noted include selection bias, small sample size, limited generalizability, overall young participant age precluding sufficient lag time for lung cancer outcome identification, and lack of adjustment for tobacco smoking.

Conclusion: Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions.

Arch Intern Med. 2006;166:1359-1367

Author Affiliations:
Departments of Medicine, Case Western Reserve University, Cleveland, Ohio (Dr Mehra), and West Haven Veterans Administration Hospital, West Haven, Conn (Dr Tetrault); and Departments of Medicine (Drs Crothers, Tetrault, and Fiellin) and Psychiatry (Dr Moore), Yale University School of Medicine, New Haven, Conn.

MARIJUANA IS THE MOST commonly used illicit drug in the United States.[1] According to the 2003 National Survey on Drug Use and Health, more than 94 million Americans, or 40% of Americans aged 12 years or older have tried marijuana at least once.[2] Recent data indicate that past-year prevalence of marijuana abuse or dependence increased significantly in the population from 1.2% in 1991-1992 to 1.5% in 2001-2002, which translates into an increase from 2.2 million persons to 3.0 million.[3] Given the widespread use of marijuana, its use for what are believed to be medicinal purposes, and the increasing abuse and dependence on this substance, it is important to examine potential adverse clinical consequences.

Marijuana smoking, like tobacco smoking, may be associated with increased risk of lung cancer. Marijuana smoke contains cannabinoid compounds in addition to many of the same components as tobacco smoke. For instance, benzopyrene, a carcinogenic polycyclic aromatic hydrocarbon, is found in both tobacco and marijuana smoke and has been implicated in mutations related to lung cancer.[4-7] Furthermore, experimental studies support an association between marijuana smoke exposure and lung cancer, with lung cancer cell lines demonstrating tetrahydrocannabinol (THC)-induced malignant cell proliferation[8,9] and a murine model suggesting that THC promotes tumor growth by inhibiting antitumor immunity by a cannibinoid-2 receptor mediated pathway.[10] Although the preponderance of in vitro data supports a biologically plausible association, limited research exists that suggests anticarcinogenic cannabinoid effects.[11-13] Given these contrasting data, we chose to systematically evaluate the association between smoking marijuana and lung cancer.

©2006 American Medical Association. All rights reserved.

Table 1. Specific Medical Subject Headings Terms, Main Terms, and Text Words in MEDLINE, EMBASE, and PSYCHLIT

Concept	Terms	Text Words
MEDLINE		
Marijuana use	Cannabis, cannabinoids, marijuana abuse, marijuana smoking	marijuana or marihuana or cannabis or hashish or hash or ganja or ganga or bhang or hemp or pot
Pulmonary disorders	Neoplasms/or exp carcinoma/or pathology/or smoking/pathology or tars/respiratory tract diseases/, exp respiratory physiology/or lung	cance$ or carcinom$ or squamous$ or adenocarcinom$ or metaplasi$ or hyperplasi$ or dysplasia$ or pathology or tar or tars pulmonary or respirat$ or airway$ or lung$ or bronch$ or inhale$
EMBASE		
Marijuana use	Cannabis, cannabinoids	marijuana or marihuana or cannabis or hashish or hash or ganja or ganga or bhang or hemp or pot
Pulmonary disorders	Respiratory tract tumor/or neoplasm/or carcinoma/or pathology/or tar/respiratory tract diseases/. respiratory tract infections/respiratory system/respiratory physiology	cance$ or carcinom$ or squamous$ or adenocarcinom$ or metaplasi$ or hyperplasi$ or pathology or tar or tars pulmonary or respirat$ or airway$ or lung$ or bronch$ or inhale$
PSYCHLIT		
Marijuana use	Cannabis, cannabinoids/or marijuana/or exp marijuana usage	marijuana or marihuana or cannabis or hashish or hash or ganja or ganga or bhang or hemp or pot
Pulmonary disorders	Neoplasms/neoplasms/or pathology/respiratory system/or exp respiratory distress/or exp respiratory tract disorders	Pulmonary, respirat$, airway$, lung$, wheez$, cough$, dyspnea, pulmonary or respirat$ or airway$ or lung$ or bronch$ or inhale$

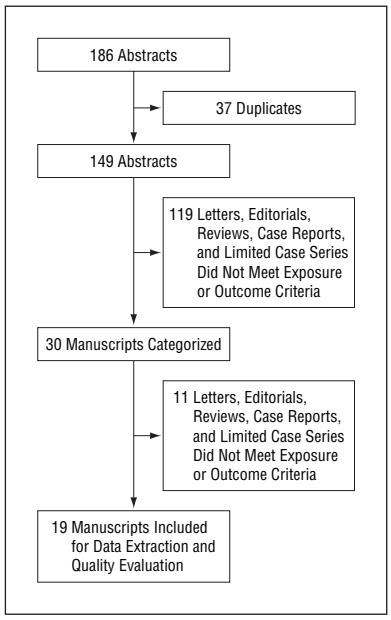

Figure. Literature search results.

The purpose of the current review is to determine whether (1) marijuana smoking is associated with lung cancer risk factors or premalignant changes assessed by known or potential mediators of lung carcinogenesis and (2) marijuana smoking is associated with increased incidence of lung cancer.

METHODS

SEARCH STRATEGIES

English-language studies in persons aged 18 years or older were identified from the OVID, MEDLINE, PSYCHLIT, and EMBASE databases from 1966 to the second week of October 2005, using the medical subject headings and text words shown in **Table 1**.

Retrieval of studies was performed by 2 reviewers (R.M. and B.A.M.) who examined the titles and abstracts obtained from the initial electronic search. We excluded letters, reviews, editorials (ie, nonresearch studies), and case series involving fewer than 10 patients, as well as studies that did not involve humans with direct, intentional marijuana smoking (eg, studies of hemp exposure in occupational settings) or did not examine lung functioning or lung conditions related to premalignant or cancerous changes. Studies involving cannabis, hashish, and/or kif (Moroccan hashish) were included owing to content overlap. Abstracts that could not be categorized based on the information provided were reviewed in manuscript form to allow a final decision regarding classification. Studies with discrepant categorizations by the 2 reviewers were resolved by a third member (D.A.F.) of the research team using consensus.

ABSTRACTION AND VALIDITY ASSESSMENT

Data regarding methods were extracted using a custom-designed data collection form. Data were collected on (1) amount, frequency, mode, and methods of marijuana smoking; lung cancer risk factors or premalignant changes and lung cancer outcomes; (2) assessment of tobacco or illicit substance use; (3) evaluation of preexisting lung disorders; (4) study setting; (5) subject selection; and (6) subject characteristics.

Two reviewers independently assigned a quality index score according to a 31-point scale that assesses reporting, external validity, bias (internal validity), confounding (external validity), and power.[14] Based on these quality components, we graded articles as good (a score ≥ 12) or fair to poor (a score < 12) based on an established cutoff.[14] Differences between reviewers were resolved by consensus with input from the third reviewer. Interrater reliability was high ($r = 0.77$).

SELECTION AND DATA SYNTHESIS

We identified 186 abstracts through the literature search as described in the "Search Strategies" subsection (107 from MEDLINE, 67 from EMBASE, and 12 from PSYCHLIT); 37 were duplicates, leaving 149 unique abstracts. Of these, we categorized 119 based on abstract review and evaluated full manuscripts for the remaining 30 citations. The level of agreement regarding inclusion of potential manuscripts based on abstract review between the 2 reviewers was high ($\kappa = 0.95$). Of the 149 articles, 56 were excluded because they were not research studies (ie, they were letters, reviews, or editorials); 8 were case series of fewer than 10 cases; 51 did not involve humans with direct, intentional marijuana smoking; and 15 did not include measures related to lung cancer. Thus, 19 studies that examined the association between marijuana use and lung cancer were included in this systematic review (**Figure**).

©2006 American Medical Association. All rights reserved.

Table 2. Studies Reporting Marijuana (MJ) Use Exposure and Tar Exposure

Source; Study Type	Male Participants, No. (%)	Age (SD), y	Setting	Outcome
Matthias et al[15]; experimental	10 (100)	23.2 (.3)	Metropolitan Los Angeles	Tar delivery
Tashkin et al[16]; experimental	10 (NP)	NP	NP	Amount of inhaled tar deposition of inhaled tar, CO boost; THC delivered to lung
Tashkin et al[17]; experimental	10 (NP)	NP	NP	Amount of inhaled tar, percentage deposition of inhaled tar, CO boost, THC delivered to lung
Wu et al[18]; experimental	15 (100)	31.5 (7.1)	NP	Blood CO, inhaled tar retention in the respiratory tract

Source; Study Type	Cannabis Exposure	Results	Confounders Controlled	Mean Study Quality Score
Matthias et al[15]; experimental	Habitual MJ smokers	Tar delivered and deposited in the lung in the most potent compared with the least potent MJ preparation	NA	11
Tashkin et al[16]; experimental	Daily or near daily MJ use over ≥5 y	Longer breath-holding time significantly increased retention of inhaled tar in the lungs ($P<.001$)	NA	11
Tashkin et al[17]; experimental	Daily or near daily MJ use over ≥5 y	More tar was inhaled from the second half of the MJ cigarette than the first half ($P<.05$)	MJ exposure compared with tobacco exposure	9.5
Wu et al[18]; experimental	Habitual smokers	Compared with smoking tobacco, smoking MJ resulted in 3-fold increase in amount of tar inhaled ($P<.001$)	MJ exposure compared with tobacco exposure	11.5

Abbreviations: CO, carbon monoxide; NA, not applicable; NP, not provided; THC, tetrahydrocannibinol.

Table 3. Studies Reporting Marijuana (MJ) Use Exposure and Cytomorphologic Changes in Sputum Specimens

Source; Study Type	Male Participants, No. (%)	Age (SD), y	Characteristic	Outcome
Roby et al[27]; case-control	75 (100)	28 (17-38)	Surfers from north coast of California	Sputum samples
Starr and Renneker[26]; case control	75 (100)	27.5 (15-38)	Surfers from California and Hawaii	Cytologic evaluation of sputum

Source; Study Type	Cannabis Exposure	Results	Confounders Controlled	Mean Study Quality Score
Roby et al[27]; case-control	Smoking MJ regularly for ≥2 y without tobacco use	Cytologic changes in habitual MJ smokers similar to tobacco smokers and different from nonsmokers; MJ smokers had more of the following compared with nonsmokers: columnar cells ($P<.01$), metaplastic cells ($P<.01$), reactive columnar cells ($P = .03$), and purse cells ($P = .01$)	MJ smokers compared with tobacco smokers	9.5
Starr and Renneker[26]; case-control	Regular MJ smokers (smoked at least twice weekly) for >2 y	MJ (n = 75) smokers show higher levels of metaplastic cells, macrophages, pigmented macrophages, and columnar cells ($P<.05$) compared with nonsmokers and lower levels of neutrophils ($P = .005$) and pigmented macrophages ($P<.001$) compared with tobacco smokers; dysplasia noted in 2 tobacco smokers, 1 MJ smoker, and no nonsmokers	Non–tobacco smoking MJ smokers compared with tobacco smokers	10.5

The 19 studies on marijuana smoking and lung cancer that met our criteria for inclusion had diverse study designs that included 4 experimental studies,[15-18] 5 prospective cohort studies (all involving a similar cohort),[19-23] 2 retrospective cohort studies,[24,25] 6 case-control studies,[26-31] and 2 case series.[32,33]

Study subjects included those who responded to newspaper advertisements and radio announcements,[19-23,29] army volunteers presenting with respiratory tract symptoms at a clinic,[30,33] volunteer surfers,[26,27] and patients recruited at hospital admission or outpatient clinic visits.[24,25,31,32] Five studies[15-18,34] did not specify recruitment procedures. Approximately 50% of these studies reported the ages of subjects (mean age, 32.5 years [range, 20.4-63 years]). Roughly 75% of the studies reported the subject's sex (male, 43.9%; range, 43%-100%).

Studies described marijuana exposure using a variety of methods, including frequency, duration, and quantity (**Tables 2**, **3**, **4**, **5**, and **6**). Most studies defined marijuana use as current smoking of marijuana, with an average of more than 10 marijuana cigarettes per week for 5 or more years.[19-23,29]

Premalignant and lung cancer outcomes included those with (1) premalignant associated changes such as tar

©2006 American Medical Association. All rights reserved.

Table 4. Studies Reporting Marijuana (MJ) Use Exposure and Alveolar Macrophage Effects

Source; Study Type	Male Participants, No. (%)	Age (SD), Range, y	Setting	Outcome
Baldwin et al[19]; cohort	56 (71.4)	34.4 (8.4), 21-49	Metropolitan Los Angeles	Alveolar macrophage tumor cytotoxicity assays
Sarafian et al[34]; case-control	20 (NP)	NP	NM (assumed Los Angeles metropolitan area)	BAL alveolar macrophage oxidative stress
Sherman et al[29]; case-control	52 (NP)	26.8-41.4	Newly recruited or from existing cohort	DNA damage, superoxide anion production, nitrite production

Source; Study Type	Cannabis Exposure	Results	Confounders Controlled	Mean Study Quality Score
Baldwin et al[19]; cohort	Smoked MJ for at least 5 d/wk for 5 y	Alveolar macrophages from MJ smokers were limited in their tumoricidal ability ($P<.01$) compared with nonsmokers	Non–tobacco-smoking MJ smokers	11.5
Sarafian et al[34]; case-control	>10 MJ cigarettes/wk for ≥5 y	BAL from habitual MJ smokers revealed GSH levels that were 31% lower than cells from nonsmokers ($P<.03$)	Non–tobacco-smoking MJ smokers and controls	7
Sherman et al[29]; case-control	ND	Alveolar macrophages recovered from MJ smokers, either alone or in combination with tobacco smoking, show a trend toward DNA damage	MJ smokers compared with MJ + tobacco smokers	7.5

Abbreviations: BAL, bronchoalveolar lavage; GSH, glutathione; ND, not defined; NM, not mentioned; NP, not provided.

delivery[15-18]; (2) cytomorphologic abnormalities in sputum[26,27]; (3) alveolar macrophage tumoricidal activity, DNA damage, and oxidative stress[19,29,34]; (4) histopathologic and molecular alterations in bronchial biopsy specimens[20-23,30,33]; and (5) lung or respiratory tract cancer diagnosed radiographically or histopathologically.[24,25,31,32]

The heterogeneous nature of the studies and their outcomes precluded quantitative synthesis (eg, a meta-analysis); therefore, this review focuses on a qualitative synthesis of the data.

RESULTS

MARIJUANA SMOKING AND TAR EXPOSURE

Tar is particulate matter residue from smoke and includes carcinogens. Tar exposure results from marijuana smoking and may serve as a potential mediator of lung carcinogenesis. In general, 4 experimental studies demonstrate that marijuana smoking is associated with increased tar delivery to the lungs compared with cigarette smoking; furthermore, there are several factors that affect the degree of tar exposure from smoking marijuana[13] (Table 2). A study[17] examining the association between marijuana smoking and tar exposure indicated that the longer breath-holding time typical of marijuana users significantly increased the percentage of retention of inhaled tar in the lungs compared with shorter breath-holding time in tobacco smokers ($P<.001$). In a study of 15 male participants, smoking marijuana resulted in a 3-fold increase in amount of tar inhaled ($P<.001$) compared with smoking tobacco.[18] The amount of tar delivered and deposited in the lung was reduced in the most potent marijuana compared with the less potent marijuana preparation, which suggests that there is reduced exposure to carcinogenic components in the tar phase of marijuana with higher THC content.[15] Increased tar exposure in the proximal half of the marijuana cigarette compared with the distal half ($P<.05$) was also noted, which suggests that smoking fewer marijuana cigarettes to a shorter length results in a greater delivery of tar to the respiratory tract relative to a comparable amount of marijuana from more cigarettes smoked to a longer butt length.[16]

This literature supports an increased exposure to tar in marijuana smoke compared with tobacco smoke based on comparable amounts of smoked contents and increased tar exposure associated with decreased marijuana potency in the proximal portion of a marijuana cigarette compared with the distal portion.

MARIJUANA SMOKING AND CYTOMORPHOLOGIC CHANGES IN SPUTUM SPECIMENS

Two case-control studies[26,27] examined marijuana smoking and sputum cytomorphologic changes in habitual marijuana smokers without current or prior use of tobacco (Table 3). These studies[26,27] noted that non–tobacco-smoking marijuana smokers had more metaplastic cells, macrophages, pigmented macrophages, and columnar cells compared with nonsmokers. In another study,[17] dysplasia was observed in 3 of 25 tobacco smokers, 1 of 25 marijuana smokers, and none of the 25 nonsmokers. Conversely, lower mean levels of neutrophils and pigmented macrophages were observed in marijuana smokers compared with tobacco smokers.

These studies suggest overall increased pathologic changes, in particular metaplastic changes, in select populations of marijuana smokers compared with tobacco smokers and nonsmokers.

MARIJUANA SMOKING AND ALVEOLAR MACROPHAGE EFFECTS

Studies evaluating the associations between marijuana smoking and alveo-

©2006 American Medical Association. All rights reserved.

Table 5. Studies Reporting Marijuana (MJ) Use Exposure and Bronchial Biopsy Histopathologic and Molecular Alterations

Source; Study Type	Male Participants, No. (%)	Age, y	Setting	Outcome
Barsky et al[20]; cohort	104 (77.9)	Range, 21-50	Metropolitan Los Angeles	Histopathologic and molecular alteration in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco (bronchial biopsy and brush specimens)
Fligiel et al[22]; cohort	70 (NP)	NP	Metropolitan Los Angeles	Bronchial biopsy specimens, examining for epithelial changes and basement membrane changes
Fligiel et al[21]; cohort	241 (83)	NP	Metropolitan Los Angeles	Bronchial biopsy specimens, light microscopic evaluation
Gong et al[23]; cohort	37 (85)	NP	Metropolitan Los Angeles	Bronchial biopsy specimens, examining for epithelial changes, basement membrane changes, and submucosal inflammation
Henderson et al[33]; case-control	n = 200, 6 of whom underwent bronchoscopy, 100%	NP	Army medical facility. Came to facility with respiratory complaint related to high-dose hashish use	Bronchial biopsy specimens
Tennant[30]; case-control	36 (100)	Mean, 20.4 (range, 17-22)	US soldiers stationed in West Germany	Bronchial biopsy specimens showing atypical cells, basal cell hyperplasia, squamous metaplasia

Source; Study Type	Cannabis Exposure	Results	Confounders Controlled	Mean Study Quality Score
Barsky et al[20]; cohort	Current smoking of MJ with an average of >10 MJ cigarettes/wk for ≥5 y	MJ-only smokers (n = 12) had more frequent histopathologic abnormalities than nonsmokers: squamous metaplasia ($P<.001$), cell disorganization ($P<.001$), nuclear variation ($P<.001$), mitotic figures ($P<.001$), increased nuclear-cytoplasmic ratio ($P<.001$), MJ smokers had more abnormal expression of Ki-67 ($P<.01$) and EGFR ($P<.01$) compared with nonsmokers	MJ smokers non–tobacco smokers and compared with a tobacco smoking group	11
Fligiel et al[22]; cohort	Smoking of MJ with an average of >10 MJ cigarettes/wk for ≥5 y	Tobacco, cocaine, and marijuana smokes had severe effects on histopathologic alterations; abnormalities were more commonly seen in MJ-tobacco smokers as opposed to tobacco smokers; compared with nonsmokers, MJ and tobacco smokers more often had squamous metaplasia ($P<.001$)	MJ smokers non–tobacco smokers and compared with a tobacco smoking group	10
Fligiel et al[21]; cohort	Current smoking of MJ with an average of >10 MJ cigarettes/wk for ≥5 y	Effects of MJ and tobacco on bronchial histopathologic findings is additive; those who smoked MJ only had more frequent histopathologic abnormalities than nonsmokers: squamous metaplasia ($P<.001$), stratification ($P<.001$), cell disorganization ($P<.05$), mitotic figures ($P<.001$), increased nuclear-cytoplasmic ratio ($P<.001$)	MJ smokers non–tobacco smokers and compared with a tobacco smoking group	11.5
Gong et al[23]; cohort	Current smoking of MJ with an average of >10 MJ cigarettes/wk for ≥5 y	MJ smokers have more abnormal airway appearance and histopathologic alterations irrespective of tobacco use; MJ smokers had more basal cell hyperplasia ($P<.009$) compared with nonsmokers; MJ smokers had more cellular disorganization ($P<.03$) compared with tobacco smokers	MJ smokers (non–tobacco smokers) compared with tobacco only smokers	9.5
Henderson et al[33]; case-control	Heavy hashish smokers	All 6 MJ smokers who underwent bronchoscopy had mucosal injection, and all biopsy specimens had epithelial abnormalities	Tobacco smoking not taken into account	1.5

Abbreviations: EGFR, epidermal growth factor receptor; NP, not provided.

lar macrophage function, DNA damage, and oxidative stress consisted of 1 cohort study[19] and 2 case-control studies[29,34] (Table 4). A study involving a prospective cohort revealed that alveolar macrophages recovered from marijuana smokers were severely limited in their ability to kill tumor cells ($P<.01$) compared with nonsmokers.[19] Alveolar macrophages recovered from marijuana smokers with and without tobacco exposure were more likely to show DNA damage; however, results were not statistically significant.[29] In a separate

©2006 American Medical Association. All rights reserved.

Table 6. Studies Reporting Marijuana (MJ) Use Exposure and Other Lung Cancer Outcomes

Source; Study Type	Male Participants, No. (%)	Mean Age (Range), y	Setting	Outcome
Sasco et al[24]; case-control	353 (97)	59.3	Hospital-based, Morocco	Lung cancer diagnosed radiographically and/or by lung biopsy, other diagnostic biopsy, or exfoliated cells
Sidney et al[25]; cohort	64 855 (43)	33 (15-49)	Health plan, early 1980s, Northern California	Incident smoking-related cancers (upper aerodigestive, lung, pancreas, kidney, bladder)
Sridhar et al[31]; case-control	110 (54)	60.5 (27-87)	Oncology clinic, University of Miami Medical Center	Lung cancer
Taylor[32]; case series	10 (60)	(28-39)	Hospital; no exclusion criteria; no control for tobacco	Respiratory tract malignancy

Source; Study Type	Cannabis Exposure	Results	Confounders Controlled	Mean Study Quality Score
Sasco et al[24]; case-control	Use of hashish/kiff (Moroccan hashish)	Lung cancer OR with hashish/kiff use as relevant exposure: 1.93, (95% CI, 0.57-6.58) after controlling for tobacco use, with hashish/kiff/snuff use the lung cancer: OR: 6.67 (95% CI,1.65-26.90)	Statistical adjustment for tobacco smoke	14
Sidney et al[25]; cohort	Smoked MJ >6 times ever or current MJ smoker	Past and current use of MJ was not associated with an increased risk for cancer of all sites: male OR, 0.9 (95% CI, 0.5-1.7); female OR, 1.1 (95% CI, 0.5-2.6)	Controlled for tobacco use	11
Sridhar et al[31]; case-control	Smoked MJ sometime in their life	13 (100%) of 13 patients with lung cancer >45 y reported ever smoking marijuana vs 6 (6%) of 97 >45 y; $P<001$; self-report	Tobacco use not taken into account	6
Taylor[32]; case series	Defined as heavy use (daily use) and regular use (frequent but less than daily use)	Surgical pathologic specimens collected; 7 of 10 patients with respiratory tract malignancy had a history of regular to heavy MJ use	Tobacco use not taken into account	3

Abbreviations: CI, confidence interval; OR, odds ratio.

study,[34] bronchoalveolar lavage from habitual marijuana smokers revealed glutathione levels that were 31% lower than cells from nonsmokers ($P<.03$), as well as a dose-dependent relationship between THC content and reactive oxygen species generation.

These studies demonstrate that alveolar macrophages from marijuana smokers had less tumoricidal ability, increased likelihood of DNA damage, lower glutathione levels (enhanced oxidative stress), and a dose-dependent relationship between THC and reactive oxygen species when compared with nonsmokers.

MARIJUANA SMOKING AND HISTOPATHOLOGIC AND MOLECULAR ALTERATIONS ON BRONCHIAL BIOPSY FINDINGS

There were 6 studies evaluating histopathologic and/or molecular alterations from bronchial biopsy findings associated with marijuana smoking; 4 were cohort-based studies[20-23] and 2 were case series[30,33] (Table 5). All reported an increase in abnormal and precancerous findings in marijuana smokers compared with controls who smoked tobacco[20-23,30] or controls with unspecified tobacco exposure.[33] Observational cohort studies demonstrated a relationship between marijuana use and abnormal bronchial disease.[20-23] One study demonstrated that marijuana-only smokers had more frequent abnormal histopathologic findings than nonsmokers with a significant association between marijuana use and pathologic changes, including squamous cell metaplasia and increased mitotic figures.[20] Compared with nonsmokers, marijuana smokers were noted to more commonly have abnormal expression of Ki-67, a proliferation marker. Epidermal growth factor receptor, a surrogate marker for lung malignancy and a potential cause for the histopathologic alterations, was also noted more frequently in marijuana smokers compared with nonsmokers.[20] A separate study concluded that all types of smokers (those who smoked tobacco, cocaine, and marijuana) had abnormal histopathologic findings; specifically, marijuana smokers were more likely to have pathologic bronchial mucosal alterations compared with nonsmokers.[21] In this study, mucosal and basement membrane changes were observed with a greater frequency in the marijuana-smoking group than the tobacco-smoking group. Marijuana smokers demonstrated more frequent histopathologic alterations compared with nonsmokers in 8 of the 11 pathologic categories, and the effects of marijuana and tobacco smoking seemed to be additive.[21]

This literature supports the conclusion that marijuana smokers were more likely to have basal, goblet, and squamous cell hyperplasia; stratification; cell disorganization; nuclear variation; an increased nuclear-cytoplasmic ratio; basement mem-

©2006 American Medical Association. All rights reserved.

brane thickening; squamous cell metaplasia; mitotic figures; abnormal expression of a proliferation marker, Ki-67; and increased epidermal growth factor receptor compared with nonsmokers.[20-23,30,33] The effects of marijuana and tobacco smoking seemed to be additive according to 1 study.[21]

MARIJUANA SMOKING AND LUNG CANCER

Studies examining the association of marijuana smoking and diagnoses of lung cancer included 1 large retrospective cohort study (n=64855),[25] 2 case-control studies,[24,31] and 1 case series[32] (Table 6). The cohort study demonstrated that past and current use of marijuana was not associated with an increased odds of lung cancer, after adjusting for tobacco use in men (odds ratio [OR], 0.9; 95% confidence interval [CI], 0.5-1.7) or women (OR, 1.1; 95% CI, 0.5-2.6).[25] A case-control study (n=353) found the odds of lung cancer in users of hashish or kiff to be 1.93 (95% CI, 0.57-6.58) after controlling for tobacco use.[24] Among patients younger than 45 years with lung cancer, marijuana smoking was reported in 13 (13.4%) of 97 compared with 6 (6.2%) of 97 among patients older than 45 years ($P<.001$), demonstrating an uncharacteristic presentation of lung cancer in young marijuana smokers compared with older marijuana smokers, which suggests that marijuana exposure may accelerate the malignancy latency period.[31] However, most subjects in this cohort were also tobacco smokers, and the investigators did not account for this. A small case series (n=10) reported respiratory tract malignancy in association with marijuana smoking; however, this report did not control for tobacco smoking.[32]

These studies were not able to demonstrate a relationship between marijuana smoking and a diagnosis of lung cancer.

STUDY QUALITY

Overall, the mean quality score was 9.5 (range, 1.5-14) on a 31-point scale.[14] The mean quality score for the 4 experimental studies was 10.75 (range, 9-12); for the 5 prospective cohort studies, 10.75 (range, 9.5-11.5); for the 2 retrospective cohort studies, 8.5 (range, 6-11); for the 6 case-control studies, 9.0 (range, 3.5-14); and for the 2 case series, 2.25 (range, 1.5-3).

COMMENT

These 19 diverse studies offer biological evidence for the potential association between marijuana smoking and lung cancer. Most studies support an association between marijuana smoking and premalignant lung cancer findings, although small observational studies fail to demonstrate such an association. In particular, all of the studies that measure tar exposure support increased tar retention with marijuana smoking compared with tobacco smoking. The higher lung tar burden associated with the longer breath-holding characteristic of marijuana smoking may enhance carcinogenic risk based on prior studies that have demonstrated an association between tar exposure from tobacco smoking and lung cancer.[35-37]

In addition, there were more cytomorphologic changes, in particular metaplasia, alveolar macrophage tumoricidal dysfunction, enhanced oxidative stress, and histopathologic/molecular alterations associated with marijuana smoking compared with controls or those who smoked tobacco. These findings offer biological evidence that marijuana smoking could be associated with the development of lung cancer in humans, as has been suggested by animal studies and cell line experiments. Specifically, metaplastic cellular changes may lead to malignant transformation. Abnormal macrophage tumoricidal function may result in unchecked cellular proliferation, and enhanced oxidative stress has been described as a mechanistic link in carcinogenesis presumably via mutagenic oxidative DNA damage.[38-41] Bronchial histopathologic and molecular alterations, such as those involving Ki-67 and epidermal growth factor receptor, may represent a harbinger of malignant conversion. Despite these findings, the small number of observational studies fail to demonstrate a clear association between marijuana smoking and diagnoses of lung cancer. Therefore, we must conclude that no convincing evidence exists for an association between marijuana smoking and lung cancer based on existing data.

Nonetheless, certain logistic properties of marijuana smoking may increase the risk of carcinogenic exposure compared with conventional tobacco smoking, raising questions as to why observational studies have not demonstrated an association with lung cancer. These properties include the association of marijuana smoking with a deeper inhalation technique in conjunction with greater puff volume and length of inhalation, which presents an increased likelihood of enhanced exposure. Marijuana smoke also contains similar carcinogens as tobacco smoke, such as nitrosamines; phenols; aldehydes; polyvinyl chlorides; and polyaromatic hydrocarbons, such as benzopyrene, which occurs in higher concentrations in marijuana smoke compared with tobacco smoke.[4,13] The biological plausibility of an association of marijuana smoking and lung cancer is supported by experimental studies, including induction of pathways known to be key steps in the development of tobacco-related cancers.[28,42-44] Furthermore, unlike most tobacco cigarettes, marijuana is typically smoked without a filter. Experimental studies support a marijuana exposure–lung cancer association; a study involving lung cancer cell lines demonstrated THC-induced proliferation of cancer cells,[9] and a murine model suggested that THC promotes tumor growth.[10]

Given this biological plausibility for the enhanced risk of lung cancer associated with marijuana, the observational studies reported thus far may have failed to find such an association owing to methodologic limitations. Most studies defined marijuana exposure dichotomously, precluding determination of relevant threshold effects or dose-response relationships. Limitations of the studies reviewed overall include the following: selection bias, small sample sizes, lack of adjustment for tobacco smoking, lack of blinding, inconsistent measurement of marijuana exposure, lack of standardized

©2006 American Medical Association. All rights reserved.

surveillance of lung cancer diagnosis, young age of study participants, and concerns regarding generalizibility owing to the use of similar cohort in 9 (47.4%) of 19 of the reviewed studies. Of the 6 studies examining the association between marijuana use and histopathologic findings, 4 involved a similar prospective cohort.[20-23] These 4 studies revealed a positive association between marijuana use and premalignant bronchial disease; however, given the similar cohort involved, the external validity of these findings is uncertain. In addition, the case-control study evaluating marijuana smoking with lung cancer outcomes may be limited by the definition of lung cancer because some diagnoses were made radiographically rather than by tissue diagnosis, which may have led to misclassification bias.[24] In this study, an OR of 1.93 (95% CI, 0.57-6.58) assessing the strength of the relationship of marijuana use and lung cancer was observed, and lack of a statistically significant relationship may have been secondary to limited power to detect an effect as well as a potential outcome misclassification.[24] The large cohort study (n=64 855) involving a retrospective review may be subject to recall bias because data were not prospectively collected to evaluate the exposure and outcome variables of interest.[25] In addition, the overall young age of the participants (mean age, 33 years) poses a serious overall limitation of these studies because this may have precluded an adequate period of follow-up for the development of a malignancy. Finally, despite performing an extensive literature search in 3 electronic databases, there is the possibility that relevant studies that were not published or not included in databases were missed.

The findings of this systematic review have implications for research and clinical practice. Our assessment of study quality reveals that future research directions should include increased adherence to methodologic standards, more detailed assessment of marijuana exposure, larger sample sizes, adjustment for tobacco smoking, uniform surveillance for lung cancer diagnoses, multicenter evaluation, evaluation of dose-response relationships, and involvement of study participants who represent a wider spectrum of ages with longer follow-up periods. Continued research on the pathophysiologic mechanisms by which marijuana smoking may lead to development of malignancy should provide insight into shared and convergent pathways with tobacco-related lung cancer. The potential for additive or synergistic effects between marijuana and tobacco smoking, as suggested from this literature, deserves rigorous evaluation, especially given the significant comorbid prevalence of these 2 behaviors. Large, prospective studies with detailed assessment of marijuana exposure and definitive pathologic diagnosis of lung cancer are also needed. A population-based case-control trial that started in 1999 and recently concluded has assessed the association of marijuana smoking and lung cancer involving cases identified via the Los Angeles Surveillance Epidemiology and End Results registry and matched controls. This study[45,46] with results forthcoming has incorporated marijuana exposure data collection in joint years obtained via trained interviewers in the home setting.

Although observational studies have not shown a substantive marijuana smoking–lung cancer association, these studies are fraught with serious methodologic limitations. Therefore, the combination of the widespread use of marijuana, potential marijuana-related health implications outlined in this review, and studies evaluating lung premalignant alterations supporting a biologically plausible association between marijuana smoking–lung cancer association, in addition to compelling in vitro data not included in this review, provide support for physician advice regarding the potential adverse effects, including the potential for premalignant lung changes, to their patients that use marijuana.

Accepted for Publication: April 9, 2006.
Correspondence: Reena Mehra, MD, MS, Case Western Reserve University, 11100 Euclid Ave, Cleveland, OH 44106-6003 (mehrar@ameritech.net).
Financial Disclosure: None reported.

Funding/Support: This study was funded by grants from the Robert Wood Johnson Foundation's Program of Research Integrating Substance Use in Mainstream Healthcare (PRISM), the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism administered by the Treatment Research Institute. Dr Fiellin is a Robert Wood Johnson Foundation Generalist Physician Faculty Scholar. Dr Moore is supported by NIDA R21 DA019246-02. Dr Mehra is supported by an American Heart Association National Scientist Development Award (0530188N) and an Association of Subspecialty Professors and CHEST Foundation of the American College of Chest Physicians T. Franklin Williams Geriatric Development Research Award. Dr Crothers is supported by the Yale Mentored Clinical Scholar Program (NIH/NCRR K12 RR0117594-01).

REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Results From the 2003 National Survey on Drug Use and Health: National Findings.* Rockville, Md: SAMHSA; 2004. National Survey on Drug Use and Health Series H-25. DHHS publication (SMA) 04-3964.
2. National Cancer Institute. Cancer Progress Report 2003. http://progressreport.cancer.gov/doc.asp?pid=1&did=21&chid=13&coid=33&mid=vpco. Accessed September 12, 2005.
3. Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS. 2004. Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. *JAMA.* 2004;291:2114-2121.
4. Denissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. *Science.* 1996;274:430-432.
5. Hoffman D, Brunnemann KD, Gori GB, et al. On the carcinogenicity of marijuana smoke. In: Runeckles VC, ed. *Recent Advances in Phytochemistry.* New York, NY: Plenum;1975: 63-81.
6. Novotny M, Merli F, Weisler D, Fencl M, Saeed T. Fractionation and capillary gas chromatographic mass spectrometric characterization of the neutral components in marijuana and tobacco smoke concentrates. *J Chromatogr.* 1982;238: 141-150.
7. Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis.* 2005;63:93-100.
8. Galve-Roperh I, Sanchez C, Cortes ML, del Pulgar TG, Izquierdo M, Guzman M. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nat Med.* 2000;6: 313-319.
9. Hart S, Fischer OM, Ullrich A. Cannabinoids induce cancer cell proliferation via tumor necrosis factor alpha-converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor. *Cancer Res.* 2004;64:1943-1950.

©2006 American Medical Association. All rights reserved.

10. Zhu LX, Sharma S, Stolina M, et al. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. *J Immunol*. 2000;165:373-380.
11. Kogan NM. Cannabinoids and cancer. *Mini Rev Med Chem*. 2005;5:941-952.
12. Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. *Harm Reduct J*. 2005; 2:21.
13. Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. *J Natl Cancer Inst*. 1975;55:597-602.
14. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377-384.
15. Matthias P, Tashkin DP, Marques-Magallanes JA, Wilkins JN, Simmons MS. Effects of varying marijuana potency on deposition of tar and delta9-THC in the lung during smoking. *Pharmacol Biochem Behav*. 1997;58:1145-1150.
16. Tashkin DP, Gliederer F, Rose J, et al. Tar, CO and Delta9THC delivery from the 1st and 2nd halves of a marijuana cigarette. *Pharmacol Biochem Behav*. 1991;40:657-661.
17. Tashkin DP, Gliederer F, Rose J, et al. Effects of varying marijuana smoking profile on deposition of tar and absorption of CO and delta-9-THC. *Pharmacol Biochem Behav*. 1991;40:651-656.
18. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med*. 1988;318:347-351.
19. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *Am J Respir Crit Care Med*. 1997; 156:1606-1613.
20. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *J Natl Cancer Inst*. 1998;90:1198-1205.
21. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest*. 1997;112:319-326.
22. Fligiel SE, Venkat H, Gong H Jr, Tashkin DP. Bronchial pathology in chronic marijuana smokers: a light and electron microscopic study. *J Psychoactive Drugs*. 1988;20:33-42.
23. Gong H Jr, Fligiel S, Tashkin DP, Barbers RG. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *Am Rev Respir Dis*. 1987;136:142-149.
24. Sasco AJ, Merrill RM, Dari I, et al. A case-control study of lung cancer in Casablanca, Morocco. *Cancer Causes Control*. 2002;13:609-616.
25. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). *Cancer Causes Control*. 1997; 8:722-728.
26. Starr K, Renneker M. A cytologic evaluation of sputum in marijuana smokers. *J Fam Pract*. 1994; 39:359-363.
27. Roby TJ, Hubbard G, Swan GE. Cytomorphologic features of sputum samples from marijuana smokers. *Diagn Cytopathol*. 1991;7:229-234.
28. Sarafian TA, Tashkin DP, Roth MD. Marijuana smoke and Delta(9)-tetrahydrocannabinol promote necrotic cell death but inhibit Fas-mediated apoptosis. *Toxicol Appl Pharmacol*. 2001;174: 264-272.
29. Sherman MP, Aeberhard EE, Wong VZ, Simmons MS, Roth MD, Tashkin DP. Effects of smoking marijuana, tobacco or cocaine alone or in combination on DNA damage in human alveolar macrophages. *Life Sci*. 1995;56:2201-2207.
30. Tennant FS Jr. Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Subst Alcohol Actions Misuse*. 1980;1:93-100.
31. Sridhar KS, Raub WA Jr, Weatherby NL, et al. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *J Psychoactive Drugs*. 1994;26:285-288.
32. Taylor FM III. Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. *South Med J*. 1988;81:1213-1216.
33. Henderson RL, Tennant FS, Guerry R. Respiratory manifestations of hashish smoking. *Arch Otolaryngol*. 1972;95:248-251.
34. Sarafian TA, Magallanes JA, Shau H, Tashkin D, Roth MD. Oxidative stress produced by marijuana smoke: an adverse effect enhanced by cannabinoids. *Am J Respir Cell Mol Biol*. 1999; 20:1286-1293.
35. Kaufman DW, Palmer JR, Rosenberg L, Stolley P, Warshauer E, Shapiro S. Tar content of cigarettes in relation to lung cancer. *Am J Epidemiol*. 1989;129:703-711.
36. Yoshie Y, Ohshima H. Synergistic induction of DNA strand breakage by cigarette tar and nitric oxide. *Carcinogenesis*. 1997;18:1359-1363.
37. Zang EA, Wynder EL. Cumulative tar exposure: a new index for estimating lung cancer risk among cigarette smokers. *Cancer*. 1992;70:69-76.
38. An Y, Kato K, Nakano M, Otsu H, Okada S, Yamanaka K. Specific induction of oxidative stress in terminal bronchiolar Clara cells during dimethylarsenic-induced lung tumor promoting process in mice. *Cancer Lett*. 2005;230:57-64.
39. Kaynar H, Meral M, Turhan H, Keles M, Celik G, Akcay F. Glutathione peroxidase, glutathione-S-transferase, catalase, xanthine oxidase, Cu-Zn superoxide dismutase activities, total glutathione, nitric oxide, and malondialdehyde levels in erythrocytes of patients with small cell and non-small cell lung cancer. *Cancer Lett*. 2005;227: 133-139.
40. Masri FA, Comhair SA, Koeck T, et al. Abnormalities in nitric oxide and its derivatives in lung cancer. *Am J Respir Crit Care Med*. 2005;172:597-605.
41. Stringer B, Kobzik L. Environmental particulate-mediated cytokine production in lung epithelial cells (A549): role of preexisting inflammation and oxidant stress. *J Toxicol Environ Health A*. 1998; 55:31-44.
42. Ammenheuser MM, Berenson AB, Babiak AE, Singleton CR, Whorton EB Jr. Frequencies of hprt mutant lymphocytes in marijuana-smoking mothers and their newborns. *Mutat Res*. 1998;403:55-64.
43. Roth MD, Marques-Magallanes JA, Yuan M, Sun W, Tashkin DP, Hankinson O. Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta (9)-tetrahydrocannabinol. *Am J Respir Cell Mol Biol*. 2001; 24:339-344.
44. Sarafian TA, Kouyoumjian S, Khoshaghideh F, Tashkin DP, Roth MD. Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics. *Am J Physiol Lung Cell Mol Physiol*. 2003;284:L298-L306.
45. Morgenstern HM. Marijuana use and the risks of lung and other cancers. National Institute of Drug Abuse on Computer Retrieval of Information on Scientific Projects Web site. http://crisp.cit.nih.gov/crisp/CRISP_LIB.getdoc?textkey=2761718&p_grant_num=1R01DA01138601A1&p_query=&ticket=20721777&p_audit_session_id=92963459&p_keywords=. Accessed February 20, 2006.
46. Tashkin DP, Zhang ZF, Greenland S, Cozen W, Mack TM, Morgenstern H. Marijuana use and lung cancer: results of a case-control study. American Thoracic Society web site. http://www.abstracts2view.com/ats06/. Accessed May 30, 2006.

©2006 American Medical Association. All rights reserved.