Cannabis Smoking and Risk of Lung Cancer in Men

A Pooled Analysis of Three Studies in Maghreb

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Background: Cannabis is the most widely consumed illicit drug worldwide and the relation between cannabis smoking and lung cancer is suggestive, albeit inconclusive.

Method: We conducted three hospital based case-control studies in Tunisia, Morocco, and Algeria, three areas of high prevalence of cannabis consumption as well as production. This paper presents the pooled analysis of these three studies restricted to men with a total of 430 cases and 778 controls.

Results: Ninety-six percent of the cases and 67.8% of the controls were tobacco smokers and 15.3% of the cases and 5% of the controls were ever cannabis smokers. All cannabis smokers were tobacco users. Adjusting for country, age, tobacco smoking, and occupational exposure, the odds ratio (OR) for lung cancer was 2.4 (95% confidence interval [CI]: 1.6–3.8) for ever cannabis smoking. This association remained after adjustment for lifetime tobacco packyears as continuous variable, OR = 2.3 (95% CI: 1.5–3.6). The OR adjusted for intensity of tobacco smoking (cigarette/d) among current tobacco smokers and never cannabis smokers was 10.9 (95% CI: 6.0–19.7) and the OR among current tobacco users and ever cannabis smokers was 18.2 (95% CI: 8.0–41.0). The risk of lung cancer increased with increasing joint-years, but not with increasing dose or duration of cannabis smoking.

Conclusion: Our results suggest that cannabis smoking may be a risk factor for lung cancer. However, residual confounding by tobacco smoking or other potential confounders may explain part of the increased risk.

Key Words: Cannabis, Lung cancer, Maghreb, Tobacco, Pooled case-control study.

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With 1.18 million deaths in 2002, lung cancer is the leading cause of cancer deaths among men.[1] In 2002, more persons died of lung cancer in the developing countries than in the developed countries.[1] In Northern Africa, the lung cancer incidence rate was 12.0 per 100,000 men-years in 2002 after adjustment for the age structure of the world population, where particularly high rates were observed among men in the Maghreb (Algeria, Morocco, and Tunisia), with 16.9, 20.1 and 27.8/100,000 men-years, respectively.[1]

Tobacco smoking is the major cause of lung cancer[2] although other factors such as exposure to asbestos and radon have also been established as risk factors of lung cancer.[3] The role of other smoked products (such as pipe, cigar or narghile) is recognized[4] and some studies have suggested an association between cannabis smoking and lung cancer.[5–7] Two published studies conducted by our team suggested that consumption of hashish/kiff with snuff in Morocco[8] and cannabis smoking in Tunisia[9] are associated with lung cancer risk (kiff is a mixture of black tobacco and sieved resin of cannabis).

To further evaluate this association, particularly with more powerful means of control for potential confounding by tobacco smoking we pooled the data from the studies conducted in Morocco[8] and Tunisia[9] with the data from a third, yet unpublished study conducted in Algeria. The objective of this pooled analysis was to estimate the risk of lung cancer associated with cannabis smoking in Maghreb.

PATIENTS AND METHODS

Study Design

Three hospital-based case-control studies conducted in Morocco,[8] Tunisia,[9] and Algeria were pooled. The protocols of the three studies were similar and are briefly presented below. Except for the unpublished study from Algeria the detailed methodology is described in the published papers[8,9];

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and only briefly summarized here. All studies were approved by both the local and the International Agency for Research on Cancer ethical committees.

Morocco

A hospital based case-control study included 118 cases and 235 controls that were enrolled in the Ibn Rochd Hospital of Casablanca, Morocco, between January 1996 and January 1998. Cases were defined as subjects diagnosed with primary incident lung cancer. All cases were diagnosed radiologically and 77 cases (68%) were histologically confirmed. Two controls were matched to each case on age (±2 years for 62% and ±5 years for 99% of the study population), sex, and place of residence. Controls were selected in the same hospital and during the same period as cases and had a diagnosis not related to tobacco consumption. They were hospitalized with the following conditions: diabetes ($n = 54$), acute and chronic gastrointestinal illnesses ($n = 48$), acute or chronic urinary tract diseases ($n = 21$), liver and biliary tract diseases ($n = 33$), inguinal and abdominal hernias ($n = 13$), ocular symptoms and diseases ($n = 27$), prostatic disease ($n = 9$), endocrine diseases ($n = 6$), other infectious diseases ($n = 7$), circulatory diseases, such as hypertension ($n = 12$), anemia ($n = 2$), and osteoarticular diseases ($n = 3$). Women from this study were excluded from the pooled analysis because of the small number (four cases and eight controls).

Tunisia

A hospital based case-control study was conducted among men only, in Tunis, Tunisia between March 2000 and February 2003 and included 149 cases and 188 controls. Cases were enrolled in the Salah Azaiz Institute (the National Cancer Institute) and the Ariana hospital. Cases were defined as patients with primary incident lung cancer with histologic or cytologic confirmed diagnosis except for two cases with only a radiologic diagnosis. Controls were men recruited in the same period in the Salah Azaiz Institute, the Ariana hospital and the Charles Nicolle hospital. Hospitalization was for nonmalignant diseases of the genitourinary system ($n = 112$), endocrine, nutritional, or metabolic diseases ($n = 28$), blood or circulatory system disease ($n = 10$), muscular or osteoarticular disease ($n = 18$), pneumothorax, pleurisy or infectious pneumopathy ($n = 10$) or other infectious disease ($n = 9$). The diagnosis for one control is missing. Controls were matched to each case on age and place of residence.

Algeria

A hospital based case-control study was conducted in the Wilaya of Setif, Algeria between March 2003 and December 2004 and included 167 cases and 340 controls. Cases and controls were enrolled in the University Hospital of Setif. Cases were defined as men with primary incident lung cancer and diagnosis was confirmed by histologic or cytologic examination. Two controls were matched with each case on age and place of residence. Controls were men recruited in the same hospital and during the same period as cases, with the following conditions: cardiovascular disease ($n = 118$), diabetes ($n = 71$), chronic or acute disease of the genito-urinary track ($n = 49$), healthy controls (visitors from patient's family) ($n = 33$), chronic or acute gastrointestinal disease ($n = 31$), infectious disease ($n = 16$) osteoarticular disease, fracture or trauma ($n = 12$), dermatological disease ($n = 9$), and various other diseases ($n = 24$).

Instruments

For the three studies, a questionnaire was used to obtain information about demographic factors, tobacco and cannabis smoking and occupational exposures (asbestos, nickel, arsenic). The questionnaire was administrated by a trained physician in Arabic language after informed consent was obtained from each individual. The first questionnaire was initially designed for the study in Morocco. It was further improved and questions on quantitative information on cannabis smoking were added for the two studies conducted in Tunisia and Algeria.

Cannabis Smoking

In the study in Morocco the question on cannabis was an open question: "Have you ever used other smoked products?" The question was amended for the studies in Tunisia and Algeria and allowed the definition of three categories of cannabis smokers: non smoker, former smoker, and current smoker (see Appendix). Further information on intensity and duration of cannabis smoke was also collected. Due to the very low number of self-reports on current cannabis smoking (one control and three cases from the study in Algeria), cannabis smoking was defined as never or ever smoking cannabis in lifetime. For the pooled analyses the information on cannabis smoking was missing for 27 cases and 23 controls. Based on a conservative recoding strategy, these subjects were assigned to the never smokers of cannabis.

The cumulative consumption was assessed in the studies from Tunisia and Algeria using the variable 'joint-years.' It was defined as the number of joints per day multiplied by the duration of smoking cannabis in years.

Tobacco Smoking

Smoking status was defined using categories of never, former (stopped smoking at least 1 year before diagnosis for cases and equivalent period for controls) (see Appendix) and current smoker. In 3 cases and 6 controls among current smokers, and 26 cases and 14 controls among former smokers, the numbers of cigarettes per day were not available. The missing values were recoded using the median value of 20, estimated from the number of cigarettes smoked per day among former and current smokers in controls. For 7 cases and 21 controls, the duration of smoking exposure could not be calculated due to missing values for age at initiation and was replaced with a minimum value of 1 year. To estimate the odds ratio (OR) for different levels of tobacco smoking, we constructed a five-category variable with the never exposed individuals as the reference category. The other categories were former smokers, current smokers with the duration of use less than 25, 25 to ≤35 and more than 35 years. Pack-years of tobacco smoking were estimated for former and current smokers as the product of number of cigarettes per day divided by 20 and multiplied by the number of years exposed. When considering pack-years as a continuous variable, a value of zero pack-years was assigned to never smokers.

Occupational exposure was determined using an ever/never-exposed variable. Any individual with a history of occupational exposure to nickel or asbestos or arsenic was considered as ever exposed.

Statistical Analysis

Differences in distributions of qualitative variables between lung cancer cases and controls were tested using the Fisher's exact test. The *t* test was used to compare means of continuous variables (age only) and the Kruskal-Wallis test to compare between countries pack-years of tobacco smoked, and duration and dose of cannabis smoking. Unconditional logistic regression was performed to estimate the OR of lung cancer in the separate studies and in the pooled data. Multivariate analyses were adjusted for age (as a continuous variable), tobacco smoking status in five categories and occupational exposure; in addition, pooled analyses were adjusted for country. In addition, all analyses were carried out using complete sets of cases and controls instead of recoding of missing variables.

Analyses were carried out using SAS version 9.1. Relative risks of lung cancer were assessed by estimating ORs and 95% confidence intervals (CI) based on unconditional logistic regression models.

RESULTS

A total of 430 cases and 755 controls were included in the pooled analysis. No difference was observed between the controls of the 3 countries for tobacco smoking duration and number of pack-years smoked (Table 1). Similarly, no difference was observed between the controls for duration or intensity of cannabis smoking in Tunisia and Algeria ($p = 0.21$ and $p = 0.75$, respectively) (Table 2). Tobacco smoking was strongly associated with lung cancer risk in a dose dependant fashion in all three studies (Table 3).

Cannabis smoking was associated with lung cancer risk with an age-adjusted pooled OR of 3.3 (95% CI: 2.2–5.1). This association remained with an OR of 2.4 (95% CI: 1.5–3.7) after further adjustment for country, occupational exposures and tobacco smoking (Table 4). Conducting the previous analysis with adjustment for tobacco exposure expressed in lifetime pack-years and entered in the model as a continuous variable resulted in an adjusted OR of lung cancer of 2.3 (95% CI: 1.5–3.6) among ever smokers of cannabis compared with non smokers, with estimates of 2.6 (95% CI: 1.3–5.2) in Morocco, 2.5 (95% CI: 1.2–5.5) in Tunisia, and 2.4 (95% CI: 0.9–6.5) in Algeria.

We conducted a multivariate analysis stratified by tobacco and cannabis smoking status and adjusted for age, occupational exposure, country, and lifetime packyears of tobacco smoking. Cannabis smoking was associated with lung cancer risk among former tobacco smokers (OR = 11.9; 95% CI: 5.3–26.8) and among current tobacco smokers (18.4

TABLE 1. Description of Case-Control Studies in Morocco, Tunisia and Algeria

	Morocco		Tunisia		Algeria	
	Cases ($n = 114$)	**Controls ($n = 227$)**	**Cases ($n = 149$)**	**Controls ($n = 188$)**	**Cases ($n = 167$)**	**Controls ($n = 340$)**
Study period	January 1996–January 1998		March 2000–February 2003		March 2003–December 2004	
Mean age (std) (yr)	59.6 (11.1)	59.2 (10.9)	57 (11.6)	57 (11.7)	64.9 (11.1)	63.8 (11.5)
Occupational exposures[a]	6 (5%)	2 (1%)	12 (8%)	16 (9%)	4 (2%)	16 (5%)
Tobacco smoking						
Never	4 (3%)	87 (38%)	7 (4%)	46 (24%)	4 (2%)	112 (33%)
Former	33 (29%)	86 (37%)	31 (20%)	57 (30%)	82 (49%)	156 (46%)
Current (duration)						
<25 yr	14 (12%)	16 (7%)	12 (8%)	21 (11%)	4 (2%)	10 (3%)
25–35 yr	20 (18%)	16 (7%)	32 (21%)	32 (17%)	16 (10%)	15 (4%)
>35 yr	43 (38%)	22 (10%)	67 (45%)	32 (17%)	61 (37%)	47 (14%)
Pack years ever smoked, median (interquartile range)	40 (26–56)	24 (11–43)	47 (31–64)	28 (13–45)	32 (19–50)	22 (9–42)

Std, standard deviation.
[a]Ever being exposed to asbestos, nickel, or arsenic.

TABLE 2. Cannabis Smoking By Case-Control Status in Morocco, Tunisia and Algeria

	Morocco		Tunisia		Algeria	
	Cases ($n = 114$)	**Controls ($n = 227$)**	**Cases ($n = 149$)**	**Controls ($n = 188$)**	**Cases ($n = 167$)**	**Controls ($n = 340$)**
Ever cannabis	26 (23%)	18 (8%)	30 (20%)	12 (6%)	10 (6%)	9 (3%)
Duration in yr; median (interquartile range)	n/a	n/a	4 (2–6)	4.5 (3–6)	12.5 (9–30)	6 (4–13)
Number of joints per month; median (interquartile range)	n/a	n/a	5 (1–30)	4.5 (1–76)	9 (8–13)	9 (4–60)

n/a, not applicable.

TABLE 3. Age Adjusted Odds Ratios[a] and 95% CI for Tobacco and Cannabis Smoking and Lung Cancer in Case Control Studies in Morocco, Tunisia and Algeria

	Morocco (114 Cases, 227 Controls)		Tunisia (149 Cases, 188 Controls)		Algeria (167 Cases, 340 Controls)		Overall (430 Cases, 755 Controls)	
Tobacco exposure								
Tobacco smoking								
Never	1	(Reference)	1	(Reference)	1.	(Reference)	1	(Reference)
Former	8.2	2.8, 24.2	4.9	1.8, 13.1	14.6	5.2, 41.1	8.0	4.6, 14.0
Current (duration)								
<25 yr	28.8	7.2, 115.3	2.9	1.0, 8.8	12.5	2.6, 59.6	10.1	4.9, 21.1
25–35 yr	33.3	9.6, 115.6	6.3	2.5, 16.2	32.6	9.4, 113.1	17.4	9.2, 32.8
>35 yr	39.6	12.8, 122.7	18.0	6.8, 47.5	35.4	12.1, 103.1	27.9	15.6, 49.8
Pack years[b]	1.036	1.026, 1.047	1.029	1.020, 1.039	1.022	1.015, 1.030	1.028	1.023, 1.033
Cannabis exposure								
Never	1	(Reference)	1	(Reference)	1	(Reference)	1	(Reference)
Ever	3.4	1.8, 6.6	4.0	1.9, 8.3	2.9	1.1, 7.7	3.3	2.2, 5.1

OR, odds ratio; CI, confidence interval.
[a]OR and corresponding 95% CI were derived from a logistic regression adjusting for age.
[b]OR for the increase in risk of lung cancer per additional pack year smoked.

TABLE 4. Adjusted Odds Ratios and 95% CI for Cannabis Smoking and Lung Cancer, and Interaction with Tobacco Smoking Status in Case Control Studies in Morocco, Tunisia and Algeria

		Morocco (114 Cases, 227 Controls)		Tunisia (149 cases, 188 controls)		Algeria (167 Cases, 340 Controls)		Overall (430 Cases, 755 Controls)	
Cannabis exposure[a]									
Never		1	(Reference)	1	(Reference)	1	(Reference)	1	(Reference)
Ever		2.2	1.1, 4.5	4.1	1.8, 9.0	2.0	0.7, 5.3	2.4	1.5, 3.7
Combined exposure[b]									
Tobacco	Cannabis								
Never	Never	1	(Reference)	1	(Reference)	1.	(Reference)	1	(Reference)
Former	Never	2.9	0.9, 9.9	1.4	0.5, 4.2	10.6	3.7, 30.9	4.1	2.3, 7.5
Former	Ever	15.5	3.7, 65.1	2.1	0.5, 8.1	65.3	11.6, 367.5	11.9	5.3, 26.8
Current	Never	15.5	4.7, 51.5	3.2	1.3, 8.2	24.5	8.2, 73.6	11.3	6.2, 20.5
Current	Ever	16.3	4.0, 67.1	26.3	4.6, 149.7	12.2	2.0. 73.9	18.4	8.2. 41.6

OR, odds ratio; CI, confidence interval.
[a]OR were derived from a logistic regression adjusting for age, occupational exposure, country (in pooled analysis) and tobacco in categories of duration of exposure (never, former, <25 yr, 25–35 yr, >35 yr).
[b]OR were adjusted for age, occupational exposure, country (in pooled analysis) and lifetime pack-years tobacco smoking.

[95% CI: 8.2–41.6]) compared with never tobacco and never cannabis smokers (Table 4).

Compared with never cannabis smokers, the ORs for cumulative smoking of cannabis was 1.76 (95% CI: 0.81–3.82) for less than 2 joint-years and 3.44 (95% CI: 1.51–7.86) for 2 or more than 2 joint-years, respectively. No increased risk of lung cancer was observed with increasing intensity or duration of cannabis smoking (OR = 0.9 with $p = 0.29$ and OR = 1.1 with $p = 0.19$, respectively).

Using complete sets of cases and controls, the results were in general very similar to the results above derived from the dataset with recoding missing data on tobacco and cannabis smoking. Additional adjustment for socio economic status, involuntary smoking or indoor air pollution were conducted and the pooled ever/never estimates for cannabis smoking did not change substantially (data not shown). Because of the small number of never tobacco users, the analysis was also conducted among tobacco smokers, and the risk estimate of ever compared with never cannabis smoking was again similar (OR = 2.4; 95% CI: 1.6–3.8).

DISCUSSION

The results of this pooled analysis of three hospital based case-control studies conducted in Morocco, Tunisia, and Algeria support a positive association between cannabis smoking and lung cancer. A 2.4-fold increase in the risk of lung cancer among men was estimated for ever cannabis smokers compared with never users after adjustment for age, tobacco smoking, occupational exposures, and country.

Only the two more recent studies (Tunisia and Algeria) collected information about frequency and duration of cannabis smoking and the variability of cannabis smoking was low, both factors limiting the possibility to detect a statistically significant exposure-response relationship. Nevertheless, our results for joint-years suggest (albeit not statistically significant) a positive exposure-response relationship. However, no dose response relationship for duration or intensity of cannabis smoking was observed. Additional adjustment for indoor air pollution, involuntary smoking and socio economic status did not change the estimates. Information to conduct analyses by lung cancer histology was not available.

The country profiles of Morocco, Tunisia, and Algeria are similar with regard to their cultural and historical use of cannabis,[10] as well as their tobacco use. The prevalence of cannabis smoking in 2000 was 7.4% in Morocco according to the United Nations Office on Drugs and Crime (UNODC) report[11] and was 8% among the controls from Morocco. Data on cannabis smoking in Algeria and Tunisia were not available from the UNODC report.

In Morocco, subjects answering "hashish/kiff" to the following open question: "Have you ever used other smoked products?" were considered as cannabis smokers. Although the approach for assessing cannabis exposure was less specific and less detailed in Morocco compared with the two other studies, the prevalence of cannabis smoking reported from our study is in agreement with the UNODC figures for Morocco. There was no evidence that the questionnaire design of the Moroccan study could have led to serious misclassification of the individuals with regard to their cannabis smoking.

None of the cases and controls from Morocco and Tunisia and only three cases and one control in Algeria reported current cannabis smoking. In Maghreb, cannabis smoking has been legal and culturally accepted for almost four centuries, before recently becoming illegal. Therefore, given the age of the subjects, past consumption of cannabis mostly referred to a legal use and therefore, we do not expect substantial or differential underreporting. Recent legislation making cannabis illegal probably resulted in underreporting of current cannabis smoking. Although Maghreb is like a subcontinent, in our studies Morocco, Algeria, and Tunisia differed with regard to cannabis smoking. The lower Algerian consumption of cannabis compared with Tunisia and Morocco may be explained by the lowest cultivation of cannabis as well as cultural, political, and religious differences.

The prevalence of tobacco smoking among men in 2000 was 34.5% in Morocco, 46% in Tunisia, and 43.8% in Algeria according to the World Health Organization Surveillance of Risk Factors Report and the Tobacco Control Country Profiles.[12] It was similar to the prevalence observed in our studies during the same period in Tunisia (45%) and Morocco (24%), except for Algeria where it was much lower (22%) than reported by Surveillance of Risk Factors Report.

In agreement with the literature,[2] a higher risk of lung cancer for tobacco smokers compared with nonsmokers and a strong dose-response relationship between cumulative smoking habits and duration of smoking and the risk of lung cancer was observed. The dose-response relationship for duration of smoking was somewhat weaker in Tunisia. This may be due to some misclassification of duration of smoking, particularly age at start of smoking. However, the risk estimate for pack-years of smoking for Tunisia was similar to those for Morocco and Algeria.

In the three studies, all cannabis smokers were tobacco smokers and in Maghreb, cannabis is usually smoked mixed with tobacco or kiff. The mixing of tobacco with cannabis and the high proportion of tobacco smokers make it difficult to assess whether the increased lung cancer risk was related to the effect of cannabis rather than to the effect of the tobacco smoked with cannabis or tobacco smoking habits.

To explore the role of potential confounding by tobacco smoking, we conducted several analyses, using different approaches to adjust for tobacco smoking and the results were stable across the different analyses. The differences in changes of risk estimates observed between Morocco and Algeria versus Tunisia, between the age-adjusted OR for cannabis smoking (Table 3) and the OR adjusted for age, occupational exposures and duration of tobacco exposure (Table 4) (3.4–2.2 and 2.9–2.0 versus 4.0–4.1, respectively) may indicate residual confounding by duration of tobacco smoking in Tunisia, which might be due to an underestimation of the dose-response relationship for duration of tobacco smoking and lung cancer in Tunisia. This difference was no longer observed when we adjusted for pack-years instead of duration of tobacco smoking (data not shown).

Our analyses stratified by smoking status were additionally adjusted for duration and intensity of tobacco use. For smokers of cannabis compared with nonsmokers of cannabis these results show increased risks for lung cancer among former and among current tobacco smokers (Table 4). Therefore, we believe that confounding by tobacco smoking cannot explain the increased risk of cannabis smoking. The effect of tobacco mixed and smoked with cannabis, however, cannot be easily disentangled. At least, we can state that the quantity of tobacco mixed with cannabis in a joint is generally small.

All three studies were hospital based and a potential selection bias, particularly for controls can not be excluded. In Algeria the control group included subjects with cardiovascular disease entities not related to tobacco and other were ill defined cardiovascular disease entities where it was not possible to clearly rule out tobacco-related diseases. We decided to perform a sensitivity analysis with and without those controls with ill-defined cardiovascular disease possibly related to tobacco smoking. Since effect estimates did not change considerably, we decided to include these controls in the final analysis. Further, the wide variety of diagnoses among controls, exclusion of other tobacco-related diseases from controls, the plausible results for tobacco smoking and lung cancer, and the consistency of effects of cannabis smoking observed across all three studies argue against a serious selection bias.

Another potential bias may arise from the absence of histologic confirmation for 43 cases out of 430. However, most of the cases were histologically confirmed; only 10% (43 of 430) were radiologically diagnosed without histologic confirmation, and most of these cases were from Morocco (41 of 43). Our results for cannabis smoking and lung cancer from Morocco are very similar to the overall results of the pooled analyses (Tables 3 and 4). Therefore, we do not

believe that the small percentage of cases without histologic confirmation could have seriously biased our results. Further, a sensitivity analysis was conducted using histologically confirmed cases only and the results did not differ (data not shown).

We also conducted analyses using complete case and control data only, i.e., without assigning the missing values for cannabis user to never cannabis users and the estimates were similar.

Some recent reviews report more frequent abnormal histopathologic findings among cannabis smokers[13] but few epidemiological studies have investigated the association between cannabis smoking and the risk of lung cancer. Hsairi et al.,[5] reported on a hospital based case-control study in Tunisia that the OR of bronchial cancer for cannabis smokers compared with nonusers, adjusted for age, sex, cigarettes per day, snuff tobacco and water pipe use was 8.2 (95% CI: 1.3–15.5). In contrast, two large cohort studies in California did not find a positive association between marijuana smoking and lung cancer;[7,14] however, the assessment of marijuana smoking relied on self-administrated questionnaires, the cohort was relatively young and there were no cases of lung cancer among marijuana smoker who did not smoke tobacco. Further, marijuana smoking in California was probably less intense than in Maghreb.[15,16]

Mechanistically, there is little evidence that Δ^9-tetrahydrocannabinol (Δ^9-THC) which is the main active ingredient of cannabis, or other cannabinoids have carcinogenic effects.[17] Δ^9-THC seems to induce an increase of the enzymatic activity of the cytochrome CYP1A1 in vitro.[18] Moreover, several studies showed that Δ^9-THC and cannabinoids may have anticarcinogenic effects.[19,20] However, products of combustion of organic matter are known to be the carcinogenic. Furthermore, it has been demonstrated that the tar level and the pH of marijuana smoke was much higher than that of tobacco smoke.[21]

In conclusion, despite the difficulty to completely exclude residual confounding from tobacco, especially that coming from the cannabis-tobacco mixture in the joint, our results suggest an association between cannabis smoking and increased risk of lung cancer in an area of high level of consumption of cannabis. Future studies, especially among heavy and long-term smokers of cannabis and among nonsmokers of tobacco would be desirable to further corroborate our results, but such populations may be difficult to find. Experimental studies investigating mutagenic and carcinogenic effects of cannabis smoke may further strengthen the biologic plausibility of our results.

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APPENDIX. Questions Used to Set the Tobacco and Cannabis Smoking Status in the Three Studies (Original Questionnaire in French Translated to English)

Morocco
- Tobacco:
  - Are you currently smoking tobacco cigarette, even only from time to time?
  - If yes, are you smoking tobacco cigarette daily or less than that?
  - Have you ever smoked tobacco cigarette regularly in the past?
- Cannabis
  - Have you ever smoke something else than tobacco cigarette?
  - If yes, can you specify what type of product were you smoking?

Tunisia
- Tobacco
  - Are you currently smoking tobacco cigarette, even only from time to time?
  - If yes, are you smoking tobacco cigarette daily or less than that?
  - Have you ever smoked tobacco cigarette regularly in the past?
- Cannabis
  - Are you smoking cannabis (herb, resin or oil)?
  - In the past, were you smoking cannabis (herb, resin, oil)?

Morocco
- Tobacco
  - Are you currently smoking tobacco cigarette, even only from time to time?
  - If yes, are you smoking tobacco cigarette daily or less than that?
  - Have you ever smoked tobacco cigarette regularly in the past?
- Cannabis
  - Are you smoking cannabis (herb, resin or oil)?
  - In the past, did you smoke cannabis (herb, resin, oil)?

