Risk of Lung Cancer and Past Use of Cannabis in Tunisia

Nicolas Voirin, MSc, Julien Berthiller, MSc,* Véronique Benhaïm-Luzon,* Mathieu Boniol, PhD,† Kurt Straif, MD, PhD,‡ Wided Ben Ayoub, MD,§ Fahrat Ben Ayed, MD, PhD,¶ and Annie J. Sasco, MD, PhD||*

Abstract: The association between the use of cannabis and the risk of lung cancer is unclear. A hospital-based case-control study was conducted among men in Tunisia and included 149 incident lung cancer cases and 188 controls. Tobacco smoking was significantly associated with an increased risk of lung cancer with odds ratios increasing linearly (p for trend < 0.0001) from 3.9 (95% confidence interval [CI], 1.4–10.9) for former smokers to 17.1 (95% CI: 6.3–46.3) among current smokers who had smoked for >35 years. The odds ratio for the past use of cannabis and lung cancer was 4.1 (95% CI: 1.9–9.0) after adjustment for age, tobacco use, and occupational exposures. No clear dose-response relationship was observed between the risk of lung cancer and the intensity or duration of cannabis use. This study suggests that smoking cannabis may be a risk factor for lung cancer.

Key Words: Lung cancer, Cannabis, Tobacco, Case-control study, Tunisia.

(*J Thorac Oncol.* 2006;1: 577–579)

Little is known about the association between the use of cannabis and the risk of lung cancer.[1–3] Morocco is an important producer of cannabis in North Africa; the prevalence of cannabis use in the Moroccan population is around 8% according to the United Nations Office on Drugs and Crime. Few statistics are available on the use of cannabis in other North African countries, but it is reasonable to assume that its prevalence in this region is relatively high. A previous study conducted in Morocco[2] concluded that, when consumed alone or with snuff (tobacco powder), hashish/kiff, a mixture of cannabis and tobacco, was associated with lung cancer, which suggests a possible etiologic role of cannabis in lung cancer. Therefore, a case-control study was conducted in Tunisia to investigate the effect of cannabis use on the etiology of lung cancer.

METHODS

A hospital-based case-control study was conducted among men in Tunis, Tunisia, and included 149 cases of lung cancer and 188 controls who were enrolled between March of 2000 and February of 2003. Cases were defined as patients who had been diagnosed with primary incident lung cancer and who were enrolled at the Salah Azaïz Institut (the national cancer institute) and the Ariana Hospital. The diagnosis of lung cancer was confirmed by histologic or cytologic examination except for two cases that were diagnosed only radiographically. Controls were men hospitalized at the same time as cases and recruited at the Salah Azaïz Institut, the Ariana Hospital, and the Charles Nicole Hospital; hospitalization was mainly for nonmalignant diseases of the genitourinary system (110 controls) and endocrine, nutritional, or metabolic diseases (28 controls). The Salah Azaïz Institut, the Ariana Hospital, and the Charles Nicole Hospital cover both urban and rural areas in Tunisia and therefore ensure a wide recruitment of patients.

A questionnaire was used to obtain information on sociodemographic status, tobacco and cannabis smoking habits, and self-reported occupational exposures (asbestos, nickel, arsenic). After informed consent was obtained from each individual, the questionnaire was administered in Arabic by a trained physician.

Tobacco smoking status was defined as never smoker, former smoker, and current smoker of <25 years, 25–35 years, and >35 years. To avoid small numbers of patients in cells of stratified analyses, former smoking and current smoking were merged and a single cutoff of 35 years was used to explore the effect of cannabis according to duration of tobacco smoking. In this study, no patients declared current use of cannabis. Therefore, cannabis use was categorized as never and past use. For past users, self-reported duration of cannabis use and the number of cannabis cigarettes smoked per day were available. Occupational exposure was determined using an ever-/never-exposed variable. Any individual with a history of self-reported occupational exposure to nickel and/or asbestos and/or arsenic was considered to be ever exposed.

Unconditional logistic regression models were used to estimate the odds ratio for lung cancer. Different models including continuous or categorical variables for tobacco smoking and cannabis smoking were compared using likeli-

*Tobacco and Cancer Group, International Agency for Research on Cancer, Lyon, France; †Biostatistics Group, International Agency for Research on Cancer, Lyon, France; ‡Carcinogen Identification and Evaluation Group, International Agency for Research on Cancer, Lyon, France; §Institut Salah Azaiz, Tunis, Tunisia, ¶Association Tunisienne de Lutte contre le Cancer, Tunisia; and ||INSERM, French National Institute of Health and Medical Research, Bordeaux, France.

Address for correspondence: Annie J. Sasco, M.D., Ph.D., INSERM, Unité de Recherché U 593, Université Victor Segalen Bordeaux 2, 146 rue Léo-Saignat, Case 11, 33076 Bordeaux Cedex, France. E-mail: annie.sasco@isped.u-bordeaux2.fr

ISSN: 1556-0864/06/0106-0577

TABLE 1. Description of the Study Population

	Cases (n = 149)	Controls (n = 188)
Mean age at interview (SD)	57 (12)	57 (12)
Marital status		
Single	23 (15%)	10 (5%)
Married	123 (83%)	170 (90%)
Separated (divorced or widow)	3 (2%)	8 (4%)
Level of education		
No education	73 (49%)	80 (43%)
First level	43 (29%)	52 (28%)
Secondary level	26 (17%)	42 (22%)
University level	7 (5%)	14 (7%)
Living area		
Urban	95 (64%)	133 (71%)
Rural	54 (36%)	55 (29%)
Occupational status		
Active	71 (48%)	90 (48%)
Unemployed or retired	78 (52%)	98 (52%)
Occupational exposure to		
Asbestos	6 (4%)	3 (2%)
Nickel	9 (6%)	6 (3%)
Arsenic	4 (3%)	10 (5%)

hood ratio tests and models were selected based on goodness of fit. In the multivariate analysis, results were adjusted for age as a continuous variable, tobacco smoking status, and occupational exposure. Tests for trend were used to assess dose-response relationships. Analyses were carried out using SAS version 8.2. Two-sided p values that were <5% were considered to be statistically significant.

RESULTS

The description of the study population is presented in Table 1. Controls were more frequently married than cases ($p = 0.01$), but no difference was observed between cases and controls for age at interview ($p = 0.64$), level of education ($p = 0.44$), area of residence ($p = 0.20$), or occupational activity ($p = 0.99$). Tobacco smoking status was significantly associated with an increased risk of lung cancer (Table 2), with odds ratios that increased linearly (p for trend < 0.0001) from 3.9 for former smokers to 17.1 among current smokers who had smoked for >35 years. Thirty cases and 12 controls reported having smoked cannabis in the past, which corresponded to an age-adjusted odds ratio of 3.7 (95% confidence interval [CI]: 1.8–7.5). This association between past use of cannabis and lung cancer remained statistically significant after adjustment for age, tobacco smoking, and occupational exposure (Table 2). The analysis to explore the effect of past cannabis use according to different strata of duration of tobacco smoking (Table 3) showed an increase in the risk of lung cancer associated with past cannabis use among men who had smoked for ≤35 years as well as among men who had smoked for >35 years. No clear dose-response relationship with the daily dose of cannabis used and the duration of cannabis use after adjustment for age, occupational exposure and tobacco smoking duration was observed. The odds ratios for lung cancer for men who had smoked less than one cannabis cigarette per day or one or more cigarettes per day compared with never smokers were 4.0 (95% CI: 1.6–10.2) and 4.2 (95% CI: 1.2–15.0), respectively. The odds ratios for lung cancer for smokers who had smoked cannabis cigarettes for <5 years or ≥5 years were 4.7 (95% CI: 1.7–13.2) and 3.4 (95% CI: 1.1–10.1), respectively, when compared with never smokers of cannabis.

DISCUSSION

In agreement with the well-confirmed relationship between tobacco smoking and lung cancer,[4,5] this study conducted among Tunisian men showed that current smokers were at higher risk of lung cancer than former smokers and that the risk of lung cancer increased with duration of smoking.

TABLE 2. Risk of Lung Cancer According to Duration of Tobacco Smoking and Past Cannabis Use among Tunisian Men

	Cases (n = 149)	Controls (n =188)	OR[a]	95% CI
Age, y (mean)	57	57	1.0	0.9–1.0
Occupational exposure				
Never	137 (92%)	172 (91%)	1	Reference
Ever	12 (8%)	16 (9%)	0.7	0.3–1.7
Duration of tobacco smoking				
Never	7 (5%)	46 (24%)	1	Reference
Former	31 (21%)	57 (30%)	3.9	1.4–10.9
Current				
<25 y	12 (8%)	21 (11%)	2.7	0.9–8.2
25–35 y	32 (21%)	32 (17%)	5.9	2.7–15.3
>35 y	67 (45%)	32 (17%)	17.1	6.3–46.3
Cannabis use				
Never	119 (80%)	176 (94%)	1	Reference
Past use	30 (20%)	12 (6%)	4.1	1.9–9.0

OR, odds ratio; CI, confidence interval. [a] OR and 95% CI were estimated using an unconditional logistic regression adjusted on all categorical variables presented in the table as well as age entered as a continuous variable.

TABLE 3. Risk of Lung Cancer by Strata of Duration of Tobacco Smoking and Past Cannabis Use among Tunisian Men

		Cases (n = 149)	Controls (n = 188)	OR[a]	95% CI
Tobacco[b]	Cannabis				
Never	Never	7 (5%)	46 (24%)	1	Reference
≤35	Never	49 (33%)	77 (41%)	4.2	1.7–10.4
≤35	Past use	6 (4%)	6 (3%)	8.9	2.1–38.0
>35	Never	63 (42%)	53 (28%)	15.3	5.6–42.3
>35	Past use	24 (16%)	6 (3%)	65.0	16.7–253.1

OR, odds ratio; CI, confidence interval. [a] OR and 95% CI were estimated using an unconditional logistic regression adjusted on age entered as continuous variable and occupational exposure. [b] Lifetime duration of tobacco use in years.

Few epidemiologic studies have evaluated the association between the use of cannabis and lung cancer.[1–3] We found a positive association between smoking cannabis cigarettes and lung cancer, and this finding is consistent with the results of Sasco et al.[2] and of Hsairi et al.[3] who reported higher risks of lung cancer among marijuana users compared with nonusers. In our study, no clear dose-response relationship was observed with intensity or duration of cannabis use. Reasons for the absence of a dose-response relationship may include measurement error of cannabis consumption, residual confounding by tobacco smoking, and imprecise point estimates due to the small number of cannabis users.

One limitation of the current study was the use of hospital-based cases and controls. Incomplete recruitment of cases or the recruitment of controls who were possibly not representative of the source population of cases may have introduced a selection bias, and it would be difficult to quantify such a potential bias or to qualify its direction. However, the hospitals enrolled in this study are the major centers for the treatment of cancer patients in Tunisia, and a spectrum of diagnoses was ensured for controls.

In addition, in the present study, no patient declared that he currently used cannabis, and this might be explained by the current strict narcotic legislation concerning the use of cannabis in Tunisia. In future studies, the detection of urinary metabolites of Δ9-tetrahydrocannabinol (Δ9-THC), such as COOH-THC and 11-hydroxy-THC, may be considered as a validation of current cannabis use.

There is little evidence that Δ9-THC is mutagenic, but there is some evidence that cannabis smoke rather than Δ9-THC is carcinogenic.[6] In a study that compared tar, carbon monoxide, and pH levels in smoke from marijuana and tobacco cigarettes, higher pH and tar levels were found in marijuana cigarettes than in tobacco cigarettes.[7] Further, cannabis cigarettes are usually composed of a mixture of tobacco and cannabis, and the strong effects of cannabis consumption might in part be explained by exposure to the high levels of tar that are usually found in Tunisian tobacco as well as possible deeper inhalation of the smoke among cannabis users.[7]

In conclusion, this study suggests that the use of cannabis may be a risk factor for lung cancer. However, in our study population, it was difficult to separate fully the effects of tobacco and cannabis. Larger studies that include subjects who smoked cannabis cigarettes without tobacco and pooled analysis of published data are needed to evaluate the association between use of cannabis and lung cancer.

ACKNOWLEDGMENTS

The authors declare that they have no conflict of interest. They thank the following persons for their help in the recruitment of the cases and controls: Dr. Tarek Kilani, Service de Chirurgie Cardio-vasculaire, Mami Ariana Hospital, Dr. Hédi Ben Maiz, Service de Médecine Interne, and Dr. Zouari, Service de Rhumatologie, Charles Nicolle Hospital, Tunis. They also thank Jane Mitchell for excellent editorial assistance.

REFERENCES

1. Hashibe M, Straif K, Tashkin DP, et al. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 2006;35:265–275.
2. 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.
3. Hsairi M, Achour N, Zouari B, et al. Etiologic factors in primary bronchial carcinoma in Tunisia. *Tunis Med* 1993;71:265–268.
4. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328:1519.–
5. IARC. *Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 83, Tobacco Smoke and Involuntary Smoking.* Lyon: IARC Press, 2004.
6. Hall W, MacPhee D. Cannabis use and cancer. *Addiction* 2002;97:243–247.
7. Rickert WS, Robinson JC, Rogers B. A comparison of tar, carbon monoxide and pH levels in smoke from marijuana and tobacco cigarettes. *Can J Public Health* 1982;73:386–391.

