

Cannabis Use and Risk of Lung Cancer: A Case-Control study

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Abstract- Purpose

Cannabis smoke and tobacco smoke contain many of the same potent carcinogens, but a critical—yet unresolved—medical and public-health issue is whether cannabis smoking might facilitate the development of lung cancer. The current study aimed to assess the risk of lung cancer among cannabis users.

Methods

A case-control study of lung cancer in adults aged 18 and over at the time of diagnosis was conducted at the National Institute of Oncology in Rabat, Morocco between January 2011 and December 2015.

The relative risk of lung cancer associated with cannabis smoking was estimated by logistic regression.

The risk factors that were statistically significant associated with lung cancer on univariate analysis were introduced into the multivariate model.

Results

There were 200 cases of lung cancer and 200 controls. Cannabis smoking was associated with a significantly increased risk of lung cancer ($p=0,01$ and 95% CI: 1,140 to 2,593). Cannabis increases then the risk of developing lung cancer by 1,719. In multivariate analysis, in two different subjects of our series having the same age, the same alcoholic and smoking status, whether or not they have the same geographical origin, the addition of cannabis in one of them multiplies the risk of cancer by 2.3

Conclusion

Our results suggest that Long term cannabis use 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.

Index Terms— Cannabis use, Case-control study, Lung cancer

I. INTRODUCTION

The cannabis plant and its derivatives have been exploited for centuries for recreational and medicinal purposes, with millions of regular users around the world. The use of cannabis is explained by its neuropsychiatric effects, such as anxiolysis and euphoria.

Cannabis smoke is qualitatively similar to tobacco smoke,

although it contains up to twice the concentration of the carcinogenic polyaromatic hydrocarbons. [1]

Although much is known about the association between tobacco smoke and cancer, less is known about the association between marijuana smoke and cancer.

It is the most widely used illicit drug in the world [2,3], the question of the cause and effect between cannabis and lung cancer is still not resolved because data are limited by small studies, misclassification due to self-reporting of use, cannabis is often smoked-mixed with tobacco (“joint”) and cannabis smokers often also smoke tobacco cigarettes.

Morocco is ranked the world's largest producer of cannabis resin [4], according to the 2020 annual report of the United Nations Office on Drugs and Crime, with a high rate of cannabis use, which makes it an ideal country to study the association between cannabis and respiratory tract cancer. On May 2021, Moroccan law authorized the therapeutic use of cannabis

These circumstances provided the opportunity to undertake a case-control study to investigate the association between lung cancer and cannabis use.

II. METHODS

A. Study participants

A hospital-based case-control study was conducted among men at the National Institute of Oncology in Rabat, Morocco and included 200 cases of lung cancer and 200 controls that were enrolled between January 2011 and December 2015. Cases were defined as patients aged 18 and over at the time of diagnosis, with histologically confirmed lung cancer regardless of the histological type.

Subjects were excluded if they had missing data in their medical records, or if they refused to participate in the study.

Controls without lung cancer were randomly selected especially from the patient's entourage and family.

Written informed consent was obtained from all study subjects.

B. Methods

Data were based on a questionnaire used to obtain information then was administered face-to-face in Arabic by a medical oncologist usually at the hospital or by phone calls.

The questionnaire includes information on

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sociodemographic status (age, gender, origin and profession), tobacco and cannabis smoking habits : age at starting smoking tobacco and cannabis, smoking cessation age (if applicable), duration of smoking, number of cigarette packs per day, how cannabis is prepared and consumed , type of tobacco (snuff, light, pipe), passive smoking exposure.

This questionnaire also obtained information about occupational exposures (asbestos, nickel, arsenic) and alcohol consumption.

C. Statistical analysis

Data collected from cases and controls in our study series were entered and processed in Excel and analyzed on SPSS Software.

The quantitative variables were presented as mean and standard deviation, and qualitative variables were presented as number and percentage. The chi-squared test (χ^2 test) and the p-value were used to determine whether a difference between certain variables is statistically significant. The analysis of the association of cannabis and lung cancer, by adjusting it for other risk factors, was carried out by univariate and then multivariate binary logistic regression.

The risk factors that were statistically significant associated with lung cancer on univariate analysis were introduced into the multivariate model.

D. Results

Descriptive phase

There were only 4 (2%) female cases of lung cancer versus 196 males (98%).

According to our inclusion criteria, females were not included in the study; therefore they have been voluntarily removed from cases and controls. Thus, the predominance is exclusively male in our study.

The mean age of our patients is 58 years with a standard deviation of 9.7 years ($58 \pm 9,7$), while in controls, it is 50,7 with a standard deviation of 10 years ($50,7 \pm 10$).

The majority of our patients (61,5%) were from Rabat-Salé- Kenitra, followed by the region of Tangier-Tétouan-Al Hoceima (16,8%).

In the series of cases, there is an increase in cannabis consumption in Kenitra with a percentage of 22%, followed by Rabat with 17%, then Tangier (16%), then Khemissat, Salé and Chaouen with 15%, 12% and 9% respectively.

In controls, the highest rate of cannabis use is found in Tangier (23%), then in Rabat (18%), followed by Salé and Kenitra.

Concerning the histological type, there is a clear predominance of adenocarcinomas with a percentage of 70% (140 patients), then squamous cell carcinoma with a percentage of 26% (53 patients).

50% of our patients had an advanced stage of the disease (stage IV), 36% had a stage III disease, 11% had a stage II disease and only 3% had a stage I.

In the series of cases, the number of cannabis consumers is 86 patients (43%), compared to 114 patients (57%) who don't

smoke it. In controls, total of cannabis users amounts to 61 subjects (30,5%) compared to 139 (69,5%) among non-cannabis users.

The average age of onset of cannabis use in cases is 23.7 years with a standard deviation of 5.4 years ($23,7 \pm 5,4$), while it is 21,3 in controls with a standard deviation of 3,3 years ($21,3 \pm 3,3$).

Tobacco consumption is found in the majority of patients (89,5%) , while it is 58% in controls.

According to the data taken from smoking patients and controls, we note that the simultaneous consumption of tobacco and cannabis is found in the vast majority (87% in cases and 85% in controls). Only 13% in cases were using cannabis alone.

Occupational exposure to asbestos was found respectively in 20.5% and 18.5% of our cases and controls.

For alcoholism, 16.5% of our patients are regular alcohol drinkers, 19,5% of them are occasional alcohol drinkers, while the majority (64%) do not consume it at all. The percentages are approximately the same as in controls.

Analytical phase

According to our study, the risk of lung cancer increases with age, the more the population age increases by one year, the more the risk of lung cancer increases by 1.07 (RR=1,07 ; 95% CI: 1,05 to 1,09).

Cannabis smoking was associated with a significantly increased risk of lung cancer ($p=0,01$ and 95% CI: 1,140 to 2,593). Cannabis increases then the risk of developing lung cancer by 1,719.

Among cannabis users, a significant correlation was found between the age of onset of cannabis use and the risk of lung cancer.

A significant increase in risk was obviously also observed with the increase in smoking, the difference is highly significant with a $p < 0.0001$; 95% CI: 3,625 to 10,510. Smoking then increases the risk of cancer by 6.172.

In terms of alcoholism, the difference between the two groups is statistically significant with a $p = 0.004$.

There was no significant association between lung cancer risk and the origin of the subjects, the age of withdrawal from cannabis or exposure to asbestos.

In multivariate analysis, in two different subjects of our series having the same age, the same alcoholic and smoking status, whether or not they have the same geographical origin, the addition of cannabis in one of them multiplies the risk of cancer by 2.3.

independent variables	Univariate analysis			Multivariate analysis		
	OR	IC (95%)	P value	OR	IC (95%)	P value
Age	1,07	1,05 – 1,09	0,0001	1,078	1,031-1,127	0,0001
Origin						
Rabat- Salé- Kenitra	0,89	0,483-1,301	0,576	-	-	-
Tanger- Tetouan- Hoceïma	0,78	0,491-1,447	0,535	-	-	-
Autres	1,08	0,481-1,281	0,332	-	-	-
Cannabis use	1,71	1,140-2,593	0,01	2,305	1,351-3,933	0,01
Age of onset of cannabis use	1,13	1,041-1,237	0,004	1,095	0,993-1,207	0,003
Tobacco use	6,17	3,625-10,510	<0,0001	5,693	3,098-10,460	<0,0001
Exposure to asbestos	1,13	0,692-1,864	0,614	-	-	-
Alcohol consumption	0,48	0,303-0,792	0,004	0,280	0,148-0,471	0,001

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.

III. DISCUSSION

The current body of epidemiological evidence linking marijuana smoking and lung cancer is sparse and contradictory [5,6], and these inconsistencies might be due to methodological issues in the area.

There is little evidence that Delta-9-tetrahydrocannabinol (Δ -9-THC) is mutagenic, but there is some evidence that cannabis smoke rather than Δ -9-THC is carcinogenic. 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.

The results of epidemiological studies on the links between cannabis use and lung cancer are discordant [7]. Eight studies published between 1997 and 2015, have attempted to study the impact of cannabis use on the development of lung cancer (table:1)

The smallest was a case-control study with 33 lung cancer cases [11], and the largest was a retrospective cohort study with 64 855 participants [12] in 1997 that didn't show an association between cannabis use and lung cancer. A 2015 case-control study based on studies from the Lung International Cancer Consortium did not show a direct link between exposure to cannabis smoke and lung cancer risk [13]. In contrast, another cohort study noted an increased risk of lung cancer in cannabis users when the duration of use was \geq 11 years [14].

A Pooled Analysis of Three Studies in Maghreb [15] suggests that cannabis smoking may be a risk factor for lung cancer.

A previous study conducted in Casablanca, Morocco [16] 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.

However, associated smoking mixed with cannabis in the joint or as a co-addiction, makes it difficult to demonstrate the risk specifically linked to cannabis. Thus, in a recent systematic review investigating the association between cannabis and lung cancer, all studies were at moderate to high (ROB) risk of bias, were limited by the low number of exclusive cannabis smokers, low cannabis exposure, and

inadequate adjustments for confounding factors including smoking. The authors were unable to draw any conclusions regarding a possible association between cannabis and lung cancer because the evidence of the association was insufficient [17]. Cohort studies of subjects who regularly smoke cannabis (exclusive or not) over periods of more than 20 years are necessary to definitively or not demonstrate a link between cannabis and lung cancer [18].

Table 1. Studies of Marijuana Use and Lung Cancer [17]

Source	Population or Data Source	Study Design	Sample Size	Adjusted Risk for Lung Cancer With Marijuana Use	Risk of Bias	Comments
Callaghan et al. [8] 2013	Swedish population based	Prospective cohort	49 321 Men	RR, 2.12 (95% CI, 1.08-4.14) with >50 lifetime episodes	High	1-Time use assessment, no results for marijuana-only smokers, 40-y follow-up period
Sidney et al. [12] 1997	Kaiser Permanente, California	Retrospective cohort	64 855	RR, 0.9 (95% CI, 0.5-1.7) in men; RR, 1.1 (95% CI, 0.5-2.6) in women	Moderate	Minimal exposure, short follow-up period of 8.6 y
Han et al. [14] 2010	National US sample	Cross-sectional	29 195	OR, 7.87 (95% CI, 1.28-48.40) with >11 y of marijuana use	High	Unclear marijuana use assessment, no results for marijuana-only smokers, inadequate adjustment
Zhang et al. [13] 2015	Multiple countries (United States, Canada, United Kingdom, and New Zealand)	Case-control	2159 Cases	OR, 0.64 (0.12-2.55) (0 joint-years)	High	Limited number of marijuana-only smokers (2 cases and 20 controls), inadequate adjustment
Aldington et al. [9] 2008	New Zealand registry	Case-control	79 Cases	RR, 5.7 (95% CI, 1.5-21.6) with >10.5 joint-years	Moderate	Small sample of heavy users, no results for marijuana-only smokers
Hashibe et al. [11] 2006	Los Angeles, California	Case-control	33 Cases	OR, 0.63 (95% CI, 0.32-1.2) with \geq 60 joint-years	Moderate	Young participants, no results for marijuana-only smokers
Berthiller et al. [15] 2008	Tunisia, Morocco, and Algeria	Case-control	430 Cases	OR, 2.3 (95% CI, 1.5-3.6)	High	Inadequate adjustment for confounders, unusual exposure form, no dose-response association seen
Naïm et al. [10] 2006	Tunisia	Case-control	149 Cases	OR, 4.1 (95% CI, 1.9-9.0)	High	Inadequate adjustment for confounders, unusual exposure form, no dose-response association seen

In agreement with the well-confirmed relationship between tobacco smoking and lung cancer, this study conducted among Moroccan men reported higher risks of lung cancer among marijuana users compared with nonusers. Our finding is consistent with the results of the study conducted in Casablanca, Morocco [16] and another study conducted in Tunisia [19].

One limitation of the current study was the use of hospital-based cases and controls only; this may have caused a selection bias. We also expected that the fact that the majority of control cases who smoke cannabis and are also tobacco smokers could lead to confusion and that this would be a source of overestimation of the causal link between cannabis and lung cancer.

IV. CONCLUSION

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 long term cannabis users. Future studies, especially among heavy and long-term smokers of cannabis and among non-smokers 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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