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## CANNABIS USE AND RISK OF LUNG CANCER: A CASE-CONTROL STUDY

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### Abstract

**Aim:** To determine the risk of lung cancer associated with cannabis smoking.

**Methods:** A case-control study of lung cancer in adults  $\geq 55$  years of age was conducted in eight district health boards in New Zealand. Cases were identified from the New Zealand Cancer Registry and hospital databases. Controls were randomly selected from the electoral roll, with frequency matching to cases in 5-year age groups and district health boards. Interviewer administered questionnaires were used to assess possible risk factors including cannabis use. The relative risk of lung cancer associated with cannabis smoking was estimated by logistic regression.

**Results:** There were 79 cases of lung cancer and 324 controls. The risk of lung cancer increased 8% (95% CI 2% to 15%) for each joint-year of cannabis smoking, after adjustment for confounding variables including cigarette smoking, and 7% (95% CI 5% to 9%) for each pack-year of cigarette smoking, after adjustment for confounding variables including cannabis smoking. The highest tertile of cannabis use was associated with an increased risk of lung cancer RR=5.7 (95% CI 1.5 to 21.6), after adjustment for confounding variables including cigarette smoking.

**Conclusions:** Long term cannabis use increases the risk of lung cancer in young adults.

### Keywords

Cannabis; tobacco; lung cancer; case-control

## INTRODUCTION

Cannabis smoking may have a greater potential than tobacco smoking to cause lung cancer. [1-4] Cannabis smoke is qualitatively similar to tobacco smoke, although it contains up to twice the concentration of the carcinogenic polyaromatic hydrocarbons.[1] Cannabis is less densely packed than tobacco cigarettes, and tends to be smoked without filters [2] to a smaller butt size,[3] leading to higher concentrations of smoke inhaled. Furthermore, smokers of cannabis inhale more deeply and hold their breath for longer,[4] facilitating the deposition of the carcinogenic products in the lower respiratory tract. These factors are likely to be responsible for the five-fold greater absorption of carbon monoxide from a

cannabis joint, compared with a tobacco cigarette of similar size despite similar carbon monoxide concentrations in the smoke inhaled.[4] Several studies have demonstrated pre-cancerous histological [5,6] and molecular [7] abnormalities in the respiratory tracts of cannabis smokers, and the carcinogenic effects of cannabis smoke have been demonstrated in vitro [8] and in different in vivo animal models.[1,9,10] Conversely, there is also evidence that delta-9-tetrahydrocannabinol may have anti-carcinogenic effects.[11-13]

Epidemiological evidence for an association between cannabis and lung cancer is limited and conflicting. Case series have suggested a causative role for cannabis in lung cancer in young adults.[14,15] The few published case-control studies have shown both the presence [16-18] and absence [19] of an association, but have been limited by the inability to quantify use,[16-18] confounding with combined cannabis and tobacco use,[16-18] studies being undertaken in populations in which use may have serious legal consequences resulting in potential information bias [16-19] and poor response rates.[19]

New Zealand represents an ideal country in which to study the association between cannabis and respiratory tract cancer. New Zealand has a high rate of cannabis use,[20] and it is rarely mixed with tobacco within the joint [21] as is the custom in the United Kingdom.[22] New Zealand has among the highest rates of lung cancer worldwide with the indigenous Maori population having the highest incidence of any ethnic group.[23] These circumstances provided the opportunity to undertake a case-control study to investigate the association between lung cancer and cannabis use in young people.

## METHODS

### Study participants

Cases were patients with confirmed lung cancer aged 55 years and under at the time of diagnosis, identified from hospital databases and the New Zealand Cancer Registry between January 2001 and July 2005. Cases were a mixture of prevalent and incident cases of lung cancer. Subjects were excluded if they had lung metastasis from a distant primary other than lung, or a histological diagnosis of carcinoid or melanoma. Age at diagnosis, anatomical location of their malignancy and histological type were collected for cases. Controls without lung cancer were randomly selected from the electoral roll and frequency matched in 5-year age groups and district health boards. Subjects came from eight district health board regions, serving both urban and rural populations. The eight District Health Boards together serve approximately 1.8 million people, representing just under half of the total New Zealand population. The study was approved by the regional ethics committees and each participant gave written informed consent. Patients with cancers of the head and neck were also interviewed, but will be reported separately.

### Methods

Questionnaires were administered face-to-face by trained interviewers, usually at the home of the participant. Information on demographics (including ethnic group), smoking history, passive smoking exposure, recreational drug use, diet, occupation, income, education, alcohol consumption and family history of malignancy was collected. A family history of lung cancer was defined as having a sibling or parent with lung cancer. Occupations associated with a higher risk of lung cancer were identified from the literature and subjects were assigned a 'duration at risk' value in years. Ethnicity was derived by priority coding of the responses into three groups; Maori, Pacific Islander and 'other'. The highest level of educational attainment was recorded, as was income at diagnosis (or reference age). Alcohol consumption was calculated using a semi-quantitative score based on amount and frequency of consumption.

Subjects who reported having ever smoked 20 or more joint of cannabis were then asked to complete a more detailed exposure questionnaire regarding their cannabis smoking. This questionnaire obtained information about the age of starting cannabis use, the amount, frequency and duration of use, and the characteristics of their smoking. This information was collected for each period of their lives when pattern of use changed and was then summed to give an estimate of total lifetime use. If subjects smoked cannabis in a form other than a joint, e.g. pipes or bongs, they were asked to estimate the number of cannabis joints to which that would equate. This conversion allowed cannabis use for all participants to be quantified in joint-years of use, with 1 joint-year being equivalent to 1 joint per day for 1 year. Subjects who had smoked <20 and 20 cannabis joints in their lifetime were classified as non-smokers and smokers of cannabis respectively. A similar approach of determining lifetime use of cigarettes was employed to enable pack-years of cigarette smoking to be calculated, with 1 pack-year equivalent to 20 cigarettes per day for 1 year. Subjects who reported smoking tobacco cigarettes occasionally but never daily, or daily at some stage in their life, were classified as non-smokers and smokers of cigarettes, respectively. The questionnaire was piloted among ex-cannabis smokers.

## Analysis

Standard methods for analysis of case-control studies were used. The mean delay from diagnosis to interview was subtracted from the date of interview to calculate a reference date for duration of exposure for each control. Tertiles of cannabis use were determined by the marginal distribution of use for all subjects to reduce the chance of zero cell counts if just the control group was used. Relative risks were estimated by calculating odds ratios by logistic regression using SPSS version 11.0 for Mac OSX (SPSS Inc, Chicago, Ill) and adjusted for confounding variables. Adjustment for age, joint-years of cannabis smoking and pack-years of cigarette smoking was made by including them as continuous variables in the regression models. The effects of categories of pack-years of cigarette smoking (quintiles of smoking for all subjects interviewed) and joint-years of cannabis smoking (tertiles of use for all subjects interviewed) were also assessed. The relative risks were also calculated based on cannabis use up to 5 years prior to diagnosis or reference date in the controls, on the basis that exposure after that time was unlikely to have caused the malignancy. The age at which cannabis smoking started was categorised, and the relative risk associated with starting <16 years of age, compared with 21 years was estimated. Various logistic regression models were fitted with potential confounders as continuous and categorical variables, and the estimates of relative risk and the confidence intervals were not appreciably different from the results presented.

## Power calculation

Assuming that 15% of the population smokes cannabis, a sample size of 75 cases and 300 controls had 80% and 90% power at a type 1 error rate of 5% to detect an odds ratio of lung cancer of 2.4 and 2.7, respectively.

## RESULTS

A total of 102 eligible cases were contacted and invited for interview of whom 79 (77%) agreed to participate. There were 493 controls contacted and invited for interview of whom 324 (66%) agreed to participate.

The 79 cases of lung cancer included 16 (20%) small-cell and 63 (80%) non-small-cell cancers. This is consistent with the established distribution of histological type seen in the general population.[24] There were 39 (49%) female cases of lung cancer, similar to the female proportion (50%) of all lung cancer cases aged <55 years in New Zealand between

1998 and 2003.[25] The risk of lung cancer did not vary with age, due to cases and controls being frequency matched on 5-year age group to improve the efficiency of the study. A family history of lung cancer was associated with an increased risk of lung cancer (RR=3.9, 95% CI 1.8 to 8.4). There was no significant association between lung cancer risk and passive smoking, diet, occupation, income, educational level, and alcohol use after adjustment for age, sex, ethnicity, cigarette smoking and a family history of lung cancer. The proportion of controls (aged 35 to 55 years) who had ever smoked cannabis, with age-adjustment for the age distribution of the general population was 36%, similar to the 40-52% reported amongst the younger 15 to 45 year age group, in New Zealand population surveys undertaken between 1990 and 2001.[20]

While cannabis smoking (defined as lifetime use of  $\geq 20$  joints) was not associated with a significantly increased risk of lung cancer (Table 3), those with the highest tertile of use ( $>10.5$  joint-years of exposure) had a significantly increased risk, RR=5.7 (95% CI 1.5 to 21.6), after adjustment for age, sex, ethnicity, pack-years of cigarette smoking and a family history of lung cancer. Using the prevalence of the highest tertile of cannabis smoking of the controls we estimated that about 5% of lung cancer in those aged 55 years and under in New Zealand may be attributable to cannabis smoking.

When joint-years of use were fitted as a continuous variable, thus providing greater statistical power than the assessment by tertile of use, a significant increasing risk, 8%, with each joint-year of use was found (RR=1.08, 95% CI 1.02 to 1.15) (Table 2). The strength of the association was maintained when cannabis use in the 5 years prior to diagnosis, or reference date for controls, was excluded (RR=1.10, 95% CI 1.02 to 1.18). (Table 2). A significant increase in the risk was also observed with increasing cigarette smoking, with a 7% increase in risk for each pack-year of exposure (RR=1.07, 95% CI 1.05 to 1.09), after adjustment for confounding variables including cannabis smoking. Therefore, the increased risk for each pack-year of cigarette smoking was similar to that for each joint-year of cannabis use.

Among users of cannabis no significant correlation between joint-years of use and age of onset of use was found (Pearson correlation coefficient 0.077, P=0.56). Compared with subjects who started smoking cannabis aged 21 or older, those that started under the age of 16 had a relative risk of lung cancer of 10.3 (95% CI 0.8 to 132) after adjustment for joint-years of cannabis use, pack-years of cigarette smoking, age, sex, ethnicity, and a family history of lung cancer.

## DISCUSSION

This population-based case-control study provides evidence of a relationship between smoking cannabis and lung cancer in young adults. For each joint-year of cannabis exposure the risk of lung cancer was estimated to increase by 8%.

There are a number of methodological considerations relevant to the interpretation of these findings. We studied subjects aged 55 years or younger due to published case series,[14,15] which suggested a strong association between cannabis use and lung cancer in young adults. Additionally, the lifetime exposure of older individuals would be expected to be much lower as they would have been older than the typical age for onset of use when the “epidemic” of cannabis use began in the 1960's. Due to the low incidence of lung cancer in this age group, representing less than 10% of all lung cancers,[23] cases diagnosed up to 5 years before interview were included. If survival after diagnosis was different for users compared to non-users of cannabis, this may have influenced the results obtained. Cases were identified from

both the National Cancer Registry and from hospital outpatient and discharge databases to ensure case ascertainment was as complete as possible.

In the initial approach no mention was made of the primary risk factor of interest to avoid recruitment bias with either the cases or the controls. To minimize response bias the interviewer did not state the specific research hypothesis and took a detailed history of all well known risk factors. Cannabis exposure was measured as joint-years of cannabis use, which combines both the intensity (amount and frequency) and duration of use. This approach follows the current convention for quantifying life long cannabis consumption and recognizes the evidence that the risk of lung cancer with cigarette smoking is related to both intensity and duration of use.[26] Recall of the amount of cannabis smoked over a long period of time may have been difficult for some subjects, however, this is likely to have been similar for both cases and controls as subjects were not aware of the study hypothesis.

We used a population-based control group rather than a hospital-based control group as the latter is susceptible to significant bias due to the many medical conditions associated with cannabis use.[27,28] In recognition of the low incidence of lung cancer in the age group studied, we studied four controls for each case to increase the power of the study.

The major finding from this study was that for each joint-year of cannabis exposure, the risk of lung cancer increased by 8%, after adjustment for confounding variables including tobacco smoking. A major differential risk between cannabis and cigarette smoking was observed, with 1 joint of cannabis similar to about 20 cigarettes for risk of lung cancer. This is consistent with the observation that smoking 'a few' cannabis joints a day causes similar histological changes in the tracheobronchial epithelium as smoking 20-30 tobacco cigarettes a day.[29] It has also been reported that smoking 2 joints per day results in cytomorphological abnormalities in the sputum, similar to about 30 cigarettes per day. [30,31] These differential risks are greater than the 1:5 dose ratio between cannabis and tobacco for carbon monoxide levels and the 1:3 dose ratio for amount of tar inhaled,[4]. This suggests that as well as differences in smoking topography, in which cannabis joints are usually smoked without a filter,[2] to a smaller butt size,[3] using deeper and longer inhalation techniques,[4] differences in chemical composition of cannabis and cigarette smoke may also be responsible for the differences in their lung cancer risks. In this regard, cannabis smoke has been shown to have greater concentrations of the carcinogenic polyaromatic hydrocarbons benz[a]pyrene and benz[a]anthracene than cigarette smoke.[1]

The risk of lung cancer from cannabis use was restricted to the upper tertile of joint-years of use, with a 5.7-fold greater risk in those with more than 10.5 joint-years of cannabis use. However, it is unlikely that this represents a threshold effect, as a linear relationship has been clearly demonstrated between tobacco cigarette consumption and risk of lung cancer. [32] The lack of an association in the lower tertiles may be due to the relatively small number of cannabis users in the study and the young age of subjects reducing the time available for high numbers of joint-years to accumulate, resulting in low levels of exposure (up to 1.39 joint-years for the lower tertile).

Further analysis was undertaken in which the risk of lung cancer was assessed for cannabis use up to 5 years prior to the diagnosis. This approach was based on evidence that in most cases with lung cancer, the duration between malignant change and diagnosis is greater than 5 years.[33] When cannabis use in the 5 years prior to diagnosis for the cases (and prior to the reference date for the controls) was excluded from the analysis the strength of the association was maintained, as would be expected if a causal association existed, with a 10% increase in risk for each joint-year of exposure.

There was some suggestion that the risk of lung cancer may increase with earlier onset of cannabis use but the small number of subjects prevented more detailed assessment of this potential risk factor. However, such an association would be consistent with the evidence that the age of onset of tobacco smoking is a determinant of lung cancer risk.[34,35] Further case-control studies are needed to quantify the lung cancer risk associated with cannabis use, including the influence of the age of starting cannabis smoking, the dose-response relationship, and the dose equivalence with cigarette smoking.

In the young adults we studied, the population attributable risk for cancer of the lung with cannabis smoking was estimated to be 5%. If any increased risk was maintained as these young people age, then a considerable burden from lung cancer due to cannabis smoking may occur in the future.

Our findings are consistent with the three North African case-control studies [16-18] which have reported a six to eight-fold increased risk of lung cancer with cannabis smoking, although the lack of detailed smoking histories and the custom of mixing cannabis with tobacco may have contributed to the risks observed. In contrast, a large case-control study from California with an estimated participation rate in cases of only 39% reported no association between cannabis use and lung cancer.[19] The controls in the Californian study were matched for neighbourhood which may have made detection of an association less likely, as cannabis use is likely to be similar within distinct neighbourhoods. This may have contributed to the higher rates of cannabis use in the controls than previously reported from California.[36] Also, African-American people were less likely to have participated than other ethnic groups, suggesting significant selection bias may have occurred. A positive relationship between cannabis use and cigarette smoking was observed in the controls, but the opposite relationship was present in the lung cancer cases, which also suggests selection bias or differential reporting between cases and controls.

These studies, and our own, highlight the difficulties inherent in undertaking epidemiological research of the effects of cannabis. While it is important to interpret the findings in the context of these limitations, the balance of evidence would suggest a positive association between cannabis and lung cancer. This issue is of major public health importance, due to the prevalent use of cannabis globally and lung cancer being responsible for over a million deaths each year.[37,38] With the prevalence and mortality from lung cancer increasing, prevention by risk factor modification is of paramount importance. Major efforts are being made to reduce the prevalence of tobacco smoking.[39] The findings of this study suggest that these public health programmes may need to include greater initiatives to reduce cannabis smoking and should be directed particularly at young people.

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TABLE 1

The frequency distribution of cases and controls for selected variables

Variable	Category	Cases (n=79)		Controls (n=324)		Total (n=403)	
		No.	%	No.	%	No.	%
Age group	35-39	6	7.6	9	2.8	15	3.7
	40-44	13	16.5	24	7.4	37	9.2
	45-49	18	22.8	121	37.3	139	34.5
	50-54	36	45.6	146	45.1	182	45.2
	55 years	6	7.6	24	7.4	30	7.4
Gender	Male	40	50.6	147	45.4	187	46.4
	Female	39	49.4	177	54.6	216	53.6
Ethnic group	Maori	18	22.8	25	7.7	43	10.7
	Pac. Islander	1	1.3	3	0.9	4	1.0
	Other	60	75.9	296	91.4	356	88.3
Cigarettes	Never	9	11.4	172	53.1	181	44.9
	Ever	70	88.6	152	46.9	222	55.1
Pack-years*	Non-smoker	9	11.4	172	53.1	181	44.9
	1st quintile (<4.7)	7	8.9	44	13.6	51	12.7
	2nd quintile (4.7-14)	5	6.3	41	12.7	46	11.4
	3rd quintile (14.1-23.8)	13	16.5	28	8.6	41	10.2
	4th quintile (23.9-34.5)	23	29.1	22	6.8	45	11.2
	5th quintile (>34.5)	22	27.8	17	5.2	39	9.7
Cannabis	Non-smoker	58	73.4	285	88.0	343	85.1
	Smoker	21	26.6	39	12.0	60	14.9
Joint-years**	Non-smoker	58	73.4	285	88.0	343	85.1

Variable	Category	Cases (n=79)		Controls (n=324)		Total (n=403)	
		No.	%	No.	%	No.	%
	1 <sup>st</sup> tertile (<1.39)	3	3.8	20	6.2	23	5.7
	2 <sup>nd</sup> tertile (1.39-10.5)	4	5.1	15	4.6	19	4.7
	3 <sup>rd</sup> tertile (>10.5)	14	17.1	4	1.2	18	4.5
Joint-years of use up to 5 years before reference date	Non-smoker	58	73.4	285	88.0	343	85.1
	<1.39	3	3.8	21	6.5	24	6.0
	1.39-10.5	6	7.6	14	4.3	20	5.0
	>10.5	12	15.2	4	1.2	16	4.0
Age at onset of cannabis use	Non-smoker	58	73.4	285	88.0	343	85.1
	12-16 years	8	10.1	12	3.7	20	5.0
	17-20 years	7	8.9	18	5.6	25	6.2
	21+ years	6	7.6	9	2.8	15	3.7
Income \$NZ	0-25,000	31	39.2	46	14.2	77	19.1
	25,001-40,000	13	16.5	57	17.6	70	17.4
	40,001-70,000	19	24.1	106	32.7	125	31.0
	>70,000	16	20.3	110	34.0	126	31.3
	Not provided	0	0	5	1.5	5	1.2
Education <sup>§</sup>	Pre Sch. Cert	13	16.5	25	7.7	38	9.4
	School Cert	29	36.7	76	23.5	105	26.1
	Year 12,13	11	13.9	57	17.6	68	16.9
	Tertiary	26	32.9	166	51.2	192	47.6

\* Pack-year: 1 pack of 20 tobacco cigarettes smoked per day for one year

\*\* Joint-year: 1 cannabis joint smoked per day for one year

<sup>§</sup>School Cert: New Zealand Secondary School Certificate Examination (age 15,16), Year 12, 13 (age 17, 18) were previously Forms 6 and 7

**TABLE 2**

Cannabis use, tobacco use and age of onset of cannabis use as continuous variables

Characteristic	RR of lung cancer	95% CI
Pack-year of cigarette smoking <sup>*</sup>	1.07	(1.05 to 1.09)
Joint-year of cannabis smoking <sup>**</sup>	1.08	(1.02 to 1.15)
Joint-years to 5 yrs prior to diagnosis <sup>§</sup>	1.10	(1.02 to 1.18)

<sup>\*</sup> Adjusted for age, sex, ethnicity, family history of lung cancer and joint-years of cannabis use

<sup>\*\*</sup> Adjusted for age, sex, ethnicity, family history of lung cancer and pack-years

<sup>§</sup> Adjusted for age, sex, ethnicity, family history of lung cancer, pack-years and age of onset of cannabis use

TABLE 3

Tobacco use, cannabis use and alcohol consumption and risk of lung cancer

Characteristic	Number of cases	Number of controls	RR of lung cancer	95% Confidence Interval
<b><i>Cigarette smoking</i></b> *				
Never	9	172	1.0	
Ever	70	152	6.7	(3.1 to 14.0)
<b><i>Pack-years</i></b> *				
Non-smoker	9	172	1.0	
1 <sup>st</sup> quintile	7	44	2.6	(0.9 to 7.7)
2 <sup>nd</sup> quintile	5	41	2.5	(0.8 to 7.9)
3 <sup>rd</sup> quintile	13	28	6.1	(2.2 to 16.4)
4 <sup>th</sup> quintile	23	22	12.3	(4.7 to 32.7)
5 <sup>th</sup> quintile	22	17	23.9	(8.7 to 65.5)
<b><i>Cannabis use</i></b> †				
Non-smoker	58	285	1.0	
Smoker	21	39	1.2	(0.5 to 2.6)
<b><i>Joint-years</i></b> †				
Non-smoker	58	285	1.0	
1st tertile	3	20	0.3	(0.1 to 1.7)
2nd tertile	4	15	0.5	(0.1 to 2.0)
3rd tertile	14	4	5.7	(1.5 to 21.6)
<b><i>Joint-years up to 5 years prior to reference date</i></b> †				
Non-smoker	58	285	1.0	
1st tertile	3	21	0.3	(0.1 to 1.3)
2nd tertile	6	14	0.9	(0.3 to 2.9)
3rd tertile	12	4	5.2	(1.3 to 20.4)
<b><i>Alcohol consumption</i></b> **				
None	5	22	1.0	
Light	30	126	0.6	(0.2 to 2.1)
Moderate	39	161	0.7	(0.2 to 2.6)
Heavy	5	15	0.8	(0.1 to 4.0)

Cigarette use (pack-years) quintiles were; <4.7, 4.7-14, 14.1-23.8, 23.81-34.5, >34.5.

Cannabis use (joint-years) tertiles were: <1.39, 1.39 -10.5, >10.5.

\* Adjusted for age, sex, ethnicity, family history of lung cancer, and joint-years of cannabis use.

† Adjusted for age, sex, ethnicity, family history of lung cancer and pack-years of cigarette smoking.

\*\* Adjusted for age, sex, ethnicity, family history of lung cancer, pack-years of cigarette smoking and joint-years of cannabis use. Alcohol consumption was measured using a semi-quantitative scale.