Opium Use and Risk of Lung Cancer: A Multi-center Case-Control Study in Iran

Hamideh Rashidian, PhD[1#]; Maryam Hadji, PhD student[2,1#]; Mahin Gholipour, PhD[3]; Ahmad Naghibzadeh-Tahami, PhD student[4,5]; Maryam Marzban, PhD[6,7]; Elham Mohebbi, PhD[1,8;] Roya Safari-Faramani, PhD[9]; Mahdieh Bakhshi, MsC[10]; Monireh Sadat Seyyedsalehi, MsC[1]; Bayan Hosseini, PhD student[1,11]; Reza Alizadeh-Navaei, PhD[12]; Habib Emami, MD[13]; Ali Akbar Haghdoost, PhD[4,14]; Abbas Rezaianzadeh, PhD[15]; Abdolvahab Moradi, MD[3]; Alireza Ansari-Moghaddam, PhD[10]; Azim Nejatizadeh, PhD[16]; Soodabeh ShahidSales, MD[17]; Alireza Rezvani, MD[18]; Mohammad Hasan Larizadeh, MD[19]; Farid Najafi, PhD[9,20]; Hossein Poustchi, PhD [21]; Mohammad Ali Mohagheghi, MD[1]; Paul Brennan, PhD[11;] Elisabete Weiderpass, PhD[11]; Joachim Schüz, PhD[11]; Eero Pukkala, PhD[2,22]; Neal D. Freedman, PhD[23]; Paolo Boffetta, PhD[24,25;] Reza Malekzadeh, MD [21,26]; Arash Etemadi, PhD[23,26]; Afarin Rahimi-Movaghar, MD[27]; Farin Kamangar, PhD[28]; Kazem Zendehdel, PhD[1,29 *]

1- Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences
2- Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland
3- Metabolic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran
4- Social Determinants of Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
5- Department of Biostatistics and Epidemiology, Kerman University of Medical Sciences, Kerman, Iran
6- Department of Public Health, School of Public Health, Bushehr University of Medical Science, Bushehr, Iran
7- Clinical Research Development Center, The Persian Gulf Martyrs, Bushehr University of Medical Science, Bushehr, Iran
8- Pathology and Stem Cell Research Center, Kerman University of Medical Sciences, Kerman
9- Research Center for Environmental Determinants of Health, School of Public Health, Kermanshah Medical Sciences University, Kermanshah, Iran.
10- Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
11- International Agency for Research on Cancer, Lyon, France
12- Gastrointestinal Cancer Research Center, Non-Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

13- National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

14- Regional Knowledge HUB for HIV/AIDS Surveillance, Research Centre for Modelling in Health, Institute for Future Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

15- Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

16- Tobacco and Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

17- Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

18- Hematology Research Center, Shiraz University of Medical Science, Fars, Iran

19- Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

20- Social Development and Health Promotion Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

21- Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

22- Finnish Cancer Registry - Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

23- Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

24- Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA

25- Department of Medical and Surgical Sciences, University of Bologna, Italy

26- Digestive Oncology Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

27- Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran

28- Department of Biology, School of Computer, Mathematical, and Natural Sciences, Morgan State University, Baltimore, USA

29- Cancer Biology Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences, Tehran, Iran

#Authors contributed to the manuscript equally

*Corresponding author:

Kazem Zendehdel, MD, PhD

Cancer Research Center, Cancer Institute of Iran

Tehran University of Medical Sciences, Tehran, I.R. Iran

Email: kzendeh@sina.tums.ac.ir

Tel : +98 21 66581542

Fax : +98 2166581638

“Novelty and Impact”

Results of this large multicenter case-control study on the association between opium use and risk of lung cancer showed a decreasing risk of lung cancer after opium cessation. There was a higher association among small cell carcinoma types than others. The association remained highly significant among never tobacco users and there was an additive interaction between tobacco and opium use. The provided evidence is in line with the carcinogenicity of opium use.

Abstract

Recently, opium use has been classified as a human carcinogen for lung cancer by International Agency for Research on Cancer. We conducted a large, multicenter case-control study evaluating the association between opium use and the risk of lung cancer. We recruited 627 cases and 3477 controls from May 2017 to July 2020. We used unconditional logistic regression analyses to estimate the odds ratios (OR) and 95% confidence intervals (CI) and measured the association between opium use and the risk of lung cancer. The ORs were adjusted for the residential place, age, sex, socioeconomic status, cigarettes, and waterpipe smoking. We found a 3.6-fold risk of lung cancer for regular opium users compared to never users (95% CI: 2.9, 4.6). There was a strong dose-response association between a cumulative count of opium use and lung cancer risk. The OR for regular opium use was higher for small cell carcinoma than in other histology (8.3, 95% CI: 4.8, 14.4). The OR of developing lung cancer among opium users was higher in females 7.4 (95% CI: 3.8, 14.5) than in males (OR 3.3, 95% CI: 2.6, 4.2). The OR for users of both opium and tobacco was 13.4 (95% CI: 10.2, 17.7) compared to non-users of anything. The risk of developing lung cancer is higher in regular opium users and these results strengthen the conclusions on the carcinogenicity of opium. The association is stronger for small cell carcinoma cases than in other histology.

Keywords: Small Cell, Lung Cancer, Adenocarcinoma, Opium, Opiate, Iran, Squamous cell

Abbreviations

CI: Confidence intervals
IROPICAN: The Iranian Study of Opium and Cancer
ORs: Odds ratios
RERI: Relative excess risk due to interaction

SES: Socioeconomic status

Introduction

Lung cancer is the leading cause of death due to cancer worldwide, with almost 1.8 million deaths per year and 18% of all deaths due to cancer.[1] Although lung cancer is more prevalent among males and the incidence and mortality due to lung cancer in men are more than two times higher than in women, lung cancer is the leading cause of death cancer in both sexes.[1]

Several risk factors have been proposed for lung cancer including tobacco smoke, secondhand smoke, exposure to environmental and occupational carcinogens, family history of lung cancer, and diet [2] Cigarette smoking is the most important risk factor and is responsible for 80% of lung cancers [3] Opium use was recently classified by the International Agency for Research on Cancer (IARC) as a human carcinogen with for lung cancer.[4] About 1100–1500 tons of opium are consumed each year globally and 76% of which pertains to Asian countries.[5]

About 10–25% of all lung cancers worldwide occur in never smokers, [6, 7] while this estimate in Southeast and East Asia is as high as 30–50% .[8, 9] Part of this variation may be explained by opium use in this region. Asian countries are the main producers of opium and, although opium consumption in this region is stabilizing, it remains a problematic drug group in many countries.[5]

There are some studies on the association between opium use and lung cancer.[10-13] but most of them did not have adequate sample size or requisite data to assess the dose-response relationship, the effect of route of opium use, type of opium, or the effect of opium cessation on lung cancer risk. Furthermore, the association between opium use and the risk of lung cancer in the previous studies was not evaluated by histology, sex, and tobacco smoking status.

We aimed to conduct a large multicenter case-control study with detailed information on opium consumption and give a comprehensive overview of the risk of lung cancer related to opium consumption. Moreover, we studied the effect of interaction between opium and tobacco use on the risk of lung cancer.

Materials and Methods

This study is based on the Iranian Study of Opium and Cancer (IROPICAN), a multicenter case-control study conducted in 10 provinces of Iran that investigates the association between opium use and the risk of lung, colorectal, bladder, and head and neck cancers. Detailed information about the study protocol is provided elsewhere.[14] In brief, cancer patients were referred to the referral hospitals in each province and healthy hospital visitor controls were recruited from May 2017 to July 2020.[15, 16] The controls were frequently matched by sex, age, and residential places with the cases of all studied cancer types combined.

In the current study, we included 627 pathologically confirmed cancer cases of the trachea, bronchus, and lung (codes C33-34 in the International Classification of Diseases for Oncology, third edition) and 3477 controls.

We used well-trained interviewers and standard data collection protocols to collect detailed information about the opium use history, including duration, amount, type [Teriak (crude opium), Sukhteh (opium dross), Shireh (condensed extract of smoked opium ashes)] and route (oral ingestion, smoking) of opium use.[17] In our study, we had very few Sukhteh users (n=4), therefore, we categorized them as Teriak (crude opium) users. We defined ever opium users as using any opium type at least once during their lifetime, and regular users as using opium at least once a week for at least six consecutive months in their life.

We also collected detailed information about cigarette smoking and waterpipe use, job history, and socioeconomic status of the participants. Using principal component analyses, we used years of education and ownership of some assets including vacuum, dress washing machine, the dishwashing machine, freezer, internet access, microwave, laptop, mobile phone, personal car, and shop to define the socioeconomic status (SES) of the participants.[18]

Statistical analyses

To assess the effect of opium use on lung cancer risk, we used different metrics of opium including an average daily dose of opium use during their addiction period (average frequency of opium use per day multiplied by the average amount at each time of use), cumulative count of opium use (average frequency of opium use per day multiplied by total opium use duration), and the cumulative amount of opium use (average daily amount multiplied by total opium use duration). In all analyses we considered a three years lag time of opium use and we excluded the opium use during the 3 last years before the interview date.

We used unconditional logistic regression to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI) and adjusted the ORs for age, gender, place of residence, water pipe smoking (head-years category), cigarette smoking (pack-years category), and SES (low/medium/high). In the final model, we dropped occupation, alcohol use, and exposure to secondhand smoke variables as they did not improve the fitness of the model ($p> 0.1$).

We conducted subgroup analyses by type of histology (small cell carcinoma, adenocarcinoma, squamous cell carcinoma, other), and by gender. We also assessed the association between opium use and the risk of lung cancer among non-users of tobacco.

We assessed the multiplicative interaction between tobacco and opium use using the Wald test of the interaction coefficient and additive interaction using relative excess risk due to interaction (RERI).

Results

The distribution of demographic characteristics and habits of cases and controls are presented in Table 1. About 76% of cases were male, and 66% were from the non-capital city with a median age of 60 (25^{th} centile 54 and 75^{th} centile 67 years). The response rates among cases and controls were 97% and 89%, respectively. There was no statistically significant difference in age, gender, marital status, and educational distribution between respondents and non-respondents.

The OR for regular opium use was 3.6 (95% CI: 2.9, 4.6). There was a strong dose-response association by the average count of opium uses per day. The OR for those who use opium two or more times a day was 9.3 (95% CI: 5.8, 14.7) and for those who used opium less than once a day 1.8 (95% CI: 1.3, 2.4). The strong effect of the daily count of opium use was further reflected in a strong dose-response association with the cumulative lifelong count of opium use; the OR for the highest category of the cumulative lifelong count of opium use was 7.2 (95% CI: 5.3, 10.0) and for the lowest category 1.6 (95% CI: 1.2, 2.3; Table 2).

A smaller amount of opium used at the time carries a significantly larger risk of lung cancer than larger amounts: the OR for using less than one gram per time was 4.9 (95% CI: 3.7, 6.5) and for using more than two grams per time 1.8 (95% CI: 1.1, 2.7). Consequently, we could not see dose-response associations by other metrics including the amount of opium, such as the cumulative amount of opium use.

We could not see a difference in the OR between categories starting age of opium use after controlling the results for the cumulative count of opium use. Those who had stopped opium use had a lower risk of developing lung cancer than those who had not sopped after controlling the results for the cumulative count of opium use (Table 2). In addition, we adjusted the results for stopping the age of cigarette use and the results were approximately the same (Results not shown).

The risk of developing lung cancer among those who used both types of opium (Teriak and Shireh) was significantly higher (OR 8.4, 95% CI: 4.7, 15.3) than those who used just one type of opium. Those who used opium only via ingestion had a significantly higher risk (OR 4.9, 95% CI: 2.7-8.9) of developing lung cancer than those who only smoked opium. We adjusted the results for types and routes of opium consumption by the cumulative count of opium use too (Table 2).

The association between regular opium use and the risk of small cell lung carcinoma was higher (OR 8.3, 95% CI: 4.8, 14.4) than the risk of adenocarcinoma (OR 2.9, 95% CI: 2, 4.1) and squamous cell carcinoma (OR 2.9, 95% CI: 2.0, 4.3; Table3).

The OR for the association between regular opium use and the risk of lung cancer was 3.9 (95% CI: 2.3, 6.4) among non-users of tobacco. The majority of non-tobacco users' lung cancer cases were female (59.8%) and were adenocarcinoma cases (57.9%; results are not shown). Results of the analyses among non-users of tobacco showed a comparable OR for the association between regular opium use and the risk of lung cancer for both males (OR 3.2, 95% CI: 1.7, 6.1) and females (OR 4.9, 95% CI: 2.1, 11.6). In the main analysis the OR for regular opium use among males was 3.3 (95% CI: 2.6, 4.2) and among females 7.4 (95% CI: 3.8, 14.5), however, the sex difference was not statistically significant (p=0.2).

We found a significant additive interaction between tobacco and opium use; the OR for using both opium and tobacco was 13.4 (95% CI: 10.2, 17.7) compared to using neither one. The OR for only regular opium users was 3.4 (95% CI: 2.1, 5.5) and 3.6 (95% CI: 2.8, 4.7) for only tobacco users and RERI was 7.4 (95% CI: 4.1-10.7; Table 4).

Discussion

This is the largest case-control study investigating the association between opium use and lung cancer. In this study, we found a more than 3-fold risk of developing lung cancer in regular opium users compared to never users. This relationship was similar among never tobacco smokers. There was a dose-response relationship considering the frequency of opium use. Using both types of opium including Teriak and Shireh increased the risk of lung cancer by about 4 times more than only crude opium use or only opium juice use, which was not explained by higher consumption among those using both types. The risk of developing lung cancer in those who use opium through only ingestion was more than 3 folds higher than only smoking opium and it was more similar to those using opium through both ingestion and smoking. The OR of lung cancer related to regular opium use was higher in women than among men but the difference was not statistically significant. The risk of developing small-cell carcinoma was near 3 folds higher than adenocarcinoma and squamous cell carcinoma. We found a strong additive interaction between the risk of lung cancer and using both tobacco and opium.

Our results demonstrated that opium is an important risk factor for lung cancer. A similar conclusion was reached by a recently published systematic review, which showed a summary OR of 4.2 (95% CI: 2.0, 8.6).[19] Our results strengthen the previous conclusions on the carcinogenicity of opium and it's being a risk factor for lung cancer[4] We found this significant association after controlling for age, sex, SES, residential place, and tobacco use. We used a three-year lag period

in our analyses to control for the possible reverse causality bias. In other words, opium use during the last three years before the interview date was not counted as some patients may start opium use to relieve their pain due to lung cancer symptoms. However, the effect of such bias would have been small because only 9 cases and 11 controls started their opium use less than 3 years before the interview date.

We showed a significant dose-response relationship between the frequency of opium use and the risk of developing lung cancer. A higher cumulative count of opium use increased the risk 4 times more compared to the lowest category. The dose-response relationship was not evident for other metrics of opium use, especially for those metrics including the amount of opium used. The present findings suggest that the reported amount of opium use might be inaccurate which is in line with the currently published study that explored the implication of reporting opium use units in epidemiologic studies.[20] Results of the mentioned study revealed that people may not be able to report the amount of their opium use accurately because opium is not packaged in a standard form. Despite using standard units in reporting, however, it is prone to misclassification because it is not reported based on packaging.[20] According to our study results, using the frequency of opium use is preferred to assess dose-response association than the amount of opium use.

The results provide evidence that lung cancer risk reduces after cessation of opium use. There is no earlier evidence on the effect of opium cessation on lung cancer risk.

This study suggested that mixed use of both crude opium and opium juice can have a synergistic effect on the carcinogenicity of opium for the lung, as dual opium type users had an odds ratio of about 4 times higher than only crude opium users and opium juice users. Those who used opium only through the ingestion route were at higher risk than those who only smoke opium, even after controlling the results for the cumulative count of opium use. These findings are in line with previous studies.[12, 13] and can shed light on the effect of opium alkaloid carcinogenicity.

All histologic types of lung cancer were significantly associated with opium use; however, small cell carcinoma was more strongly associated with opium use than squamous cell carcinoma and adenocarcinoma. This observation is similar to the findings related to cigarette smoking, as the risk of developing lung cancer is highest in small cell lung cancer.[21] Our study is the first one that assessed opium and lung cancer risk by histology and more investigations are needed to find the underlying cause of this phenomenon and confirm our study findings.

The association between opium use and the risk of developing lung cancer was stronger in females than in males, however, the difference was not statistically significant and the difference in the sex-specific ORs among non-users of tobacco. There is no earlier evidence about the effect of gender on opium carcinogenicity, but the gender effect of cigarette smoking has been assessed

in many studies. Some pieces of evidence showed that women are more susceptible to the carcinogenic effect of cigarette smoking, [22] however, the others found no difference.[23] or higher effect in men.[24] It seems that the differences in various tumor characteristics by gender could be an explanation for the tumor etiology.

Several potential mechanisms have been proposed to be responsible for the carcinogenicity of opium through smoking and ingestion. Heterocyclic and polycyclic aromatic hydrocarbons, produced as a result of smoking opium, have carcinogenic effects.[25, 26] Morphine and other alkaloids are alternate carcinogens that the body may be exposed to via ingesting opium. Genotoxic effects of opium including angiogenesis, proliferation, migration, and epithelial-mesenchymal transition are other potential mechanisms to increase the hazard of cancer.[27, 28]

Survival of lung cancer patients is poor and only about 15% of cases survive five years or more.[29] Therefore, primary prevention of lung cancer should be emphasized. Opium use is an important risk factor for lung cancer and has been classified as a human carcinogen by the IARC monograph group.[4] In populations with rather large opium use it has an important population attributable fraction. The current results primarily apply to minimally processed opium including crude opium, opium dross, and opium sap. The association between other opiates (e.g., heroin, morphine, and codeine) or opioids (e.g., fentanyl) and cancer need further attention and investigation as the illegal use of opioids and their potential to cause cancer is a global public health issue.[30]

Large sample size and high response rate are strengths of the current study. In this study, we used healthy visitor controls to overcome the potential underreporting bias as opium is an illicit drug use who more prone to report its use than population controls.[15] Healthy visitor controls are usually motivated to answer questions more accurately due to the relationship they build with their patient caregivers, and their exposure is more comparable to the general population than patient controls.[16] Detailed information about opium use allowed us to assess the dose-response relationship and the effect of opium use initiation and stopping age. Detailed information about tobacco use as the main confounder enables us to decline the chance of residual confounding. Moreover, we did the analyses among never tobacco users to completely remove the residual effect of tobacco use and the association between opium use and risk of lung cancer remained strong and significant. All of the cases in this study were histologically confirmed. This is the first study that assessed the effect of gender and histology on the carcinogenicity of opium and evaluated the interaction between opium and tobacco use on lung cancer.

Like in other case-control studies, information bias in the assessment of exposure is one of the concerns in this study. However, according to the result of the validation study underreporting of opium use was similar among cancer cases and healthy visitor controls.[14] We used well-trained

and experienced interviewers with continuous monitoring and evaluation to minimize other sources of information bias along with a standard data collection protocol.

Conclusions

We found a 3.6-fold risk of lung cancer among opium users compared to non-users, with a strong dose-response relationship with the frequency of opium use, and a suggestion of risk reduction after opium cessation. This association was strongest for small cell lung cancer cases. The additive interaction between opium and tobacco use observed in this study should be taken into account in cancer prevention programs. Our results strengthen the previous conclusions on the carcinogenicity of opium which is a risk factor for lung cancer.

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Author contributions

Conceptualization- AAH, RM, FK, KZ. Data curation- HR, MH, KZ. Formal analysis- HR, MH, AAH, JS, EP, PB, AE, FK, KZ. Funding acquisition- KZ. Investigation- HR, MH, ANT, MG, MM, EM, RSF, MB, MSS, BH, RAN, HE, AR, MHL. Methodology- AAH, AR, ARM, FK, KZ. Project administration- HR, MH, ANT, MG, MM, EM, RSF, MB, MSS, RAN, HE. Resources- RAN, HE, AAH, AR, AM, AAM, AN, SS, FN, MAM. Software- HR, MH, HP, KZ. Supervision- HR, MH, KZ. Validation- HR, MH, MG, MM, AAH, ARM, FK, KZ. Visualization- HR, MH, KZ. Writing- original draft- HR, MH, KZ. Writing- review & editing- all of the authors.

Conflicts of interest

All authors declare no conflict of interest.

Disclaimer

Where authors are identified as personnel of the IARC/ World Health Organization (WHO) /National Cancer Institute (NCI), the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the IARC/ WHO/ NCI.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author

Ethics statement

The study was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) of Iran (Code: IR.NIMAD.REC.1394.027). All participants signed written informed consent to participate in the study.

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Table 1: Distribution of demographic and characteristics of lung cancer cases and controls

	Cases N (%)	Controls N (%)
Total		
Age group	627	3,477
30-39	14 (2.2)	257 (7.4)
40-49	74 (11.8)	559 (16.1)
50-59	203 (32.4)	1070 (30.8)
60-69	218 (34.8)	1092 (31.4)
≥70	117 (18.7)	499 (14.3)
Gender		
Female	145 (23.1)	1077 (31.0)
Male	482 (76.9)	2400 (69.0)
Place of residence		
Capital city	413 (65.9)	2167 (62.3)
Non-capital city	214 (34.1)	1310 (37.7)
Province		
Tehran	130 (20.7)	816 (23.5)
Fars	191 (30.5)	943 (27.1)
Kerman	111 (17.7)	525 (15.1)
Golestan	48 (7.7)	374 (10.8)
Mazandaran	33 (5.3)	136 (3.9)
Kermanshah	38 (6.1)	251 (7.2)
Khorasan-Razavi	9 (1.4)	170 (4.9)
Bushehr	36 (5.7)	84 (2.4)
Hormozgan	16 (2.5)	78 (2.2)
Systan-Balouchestan	15 (2.4)	100 (2.9)
Socioeconomic status		
Low	271 (43.2)	974 (28.0)
Medium	225 (35.9)	1174 (33.8)
High	131 (20.9)	1329 (38.2)
Water pipe use (Head-years)		

Non/non-regular user [a]	555 (88.5)	3238 (93.1)
<14	16 (2.5)	119 (3.4)
14-55	16 (2.5)	60 (1.7)
>55	40 (6.4)	60 (1.7)
Cigarette use (Pack-years)		
Non/non-regular user [a]	235 (37.5)	2500 (72.0)
<15	71 (11.3)	493 (14.2)
15-31	94 (15.0)	255 (7.3)
>31	214 (34.1)	229 (6.6)
unknown	13 (2.1)	44 (1.3)

[a] Regular user was defined as using the substance once a week for at least 6-months.

Table2: The associations of opium use with lung cancer

	Cases N (%)	Controls N (%)	OR [a] (95% CI)
Opium use			
Non-user	308 (49.1)	2881 (82.9)	Ref.
Irregular	19 (3.0)	138 (4.0)	1 (0.6,1.7)
Regular [b]	300 (47.8)	458 (13.2)	3.6 (2.9,4.6)
Duration of opium use (years)			
<19	123 (19.6)	263 (7.6)	3 (2.2,4.0)
19-29	92 (14.7)	112 (3.2)	4.2 (3.0,6.0)
>29	85 (13.6)	83 (2.4)	4.6 (3.1,6.6)
Count per day			
<1	101 (16.1)	320 (9.2)	1.8 (1.3,2.4)
1- 2	129 (20.6)	101 (2.9)	7.5 (5.4,10.5)
>2	70 (11.2)	37 (1.0)	9.3 (5.8,14.7)
Average amount of opium use per time (g)			
<1	175 (27.9)	203 (5.8)	4.9 (3.7,6.5)
1-2	83 (13.2)	143 (4.1)	3.3 (2.4,4.7)
>2	42 (6.7)	112 (3.2)	1.8 (1.1,2.7)
Daily dose of opium use (g) [c]			
<1	149 (23.7)	246 (7.1)	3.6 (2.7,4.7)
1-2	67 (10.7)	87 (2.5)	4.3 (2.9,6.3)
>2	84 (13.4)	125 (3.6)	3.4 (2.4,4.8)
Cumulative count of opium use [d]			
<4900	57 (9.1)	224 (6.4)	1.6 (1.2,2.3)
4900-11000	84 (13.4)	130 (3.7)	3.9 (2.7,5.5)
>11000	159 (25.4)	104 (3.0)	7.2 (5.3,10.0)
Cumulative amount of opium (kg) [e]			
<4	81 (12.9)	220 (6.3)	2.3 (1.6,3.1)
4-14	116 (18.5)	121 (3.5)	5.8 (4.1,8.0)
>14	99 (15.8)	115 (3.3)	3.9 (2.8,5.5)

Unknown	4 (0.6)	2 (0.1)	-
Starting age of opium use [f]			
<20	19 (3.0)	53 (1.5)	0.8 (0.4-1.6)
20-29	98 (15.6)	142 (4.1)	1.6 (1.0-2.5)
30-39	99 (15.8)	112 (3.2)	2.6 (1.7-4.0)
>=40	84 (13.4)	151 (4.3)	2.2 (1.6-3.2)
Time since stopping [f] opiumuse			
Current	182 (29.0)	223 (6.4)	2.8 (2.0-3.9)
<10	83 (13.2)	138 (4.0)	1.6 (1.1-2.5)
>=10	34 (5.4)	90 (2.6)	1.4 (0.9-2.3)
Unknown	1 (0.2)	7 (0.2)	-
Type of opium used [f]			
Crude opium (Teriak)	216 (34.4)	402 (11.6)	1.9 (1.4-2.6)
Opium juice (Shireh)	20 (3.2)	32 (0.9)	2.2 (1.1-4.5)
Both types	64 (10.2)	24 (0.7)	8.4 (4.7-15.3)
Route of opium use [f]			
Only smoking	156 (24.9)	380 (10.9)	1.6 (1.1-2.1)
Only ingestion	34 (5.4)	30 (0.9)	4.9 (2.7-8.9)
Both routes	109 (17.4)	45 (1.3)	8.3 (5.1-13.5)
Unknown	1 (0.2)	3 (0.1)	-

[a] Adjusted for age, gender, province, socioeconomic status, cigarette and water pipe use.
[b] Regular user was defined as using the substance once a week for at least 6-months.
[c] Daily dose of opium (gram) : The average amount of opium use multiplied by the average count per day
[d] Cumulative count of opium use: The average count per day multiplied by total opium duration (years)
[e] Cumulative amount of opium use: The average amount of opium use multiplied by average count per day and total opium duration(years)
[f] To assess the independent effect of these metrics we adjusted the results for the cumulative count of opium use too as they are correlated with each other.

Table 3: The associations of opium use with lung cancer by histology

		Small cell carcinoma		Adenocarcinoma		Squamous cell carcinoma		Other	
	Controls N (%)	Cases N (%)	OR[a] (95% CI)	Cases N (%)	OR[a] (95% CI)	Cases N (%)	OR[a] (95% CI)	Cases N (%)	OR[a] (95% CI)
Opium use									
Non-user	2881 (82.9)	27 (25.7)	Ref.	144 (60.8)	Ref.	85 (49.1)	Ref.	52 (46.4)	Ref.
Irregular	138 (4.0)	4 (3.8)	2.0 (0.6-6.1)	5 (2.1)	0.7 (0.3-1.7)	6 (3.5)	0.9 (0.4-2.3)	4 (3.6)	1.3 (0.4-3.7)
Regular [b]	458 (13.2)	74 (70.5)	8.3 (4.8-14.4)	88 (37.1)	2.9 (2.0-4.1)	82 (47.4)	2.9 (2.0-4.3)	56 (50.0)	4.5 (2.7-7.5)
Duration of opium use (years)									
<19	263 (7.6)	35 (33.3)	3.0 (2.2-4.0)	31 (13.1)	2.0 (1.3-3.2)	34 (19.7)	2.6 (1.6-4.2)	23 (20.5)	3.8 (2.1-7.0)
19-29	112 (3.2)	21 (20.0)	4.2 (3.0-6.0)	28 (11.8)	3.7 (2.2-6.1)	22 (12.7)	3.2 (1.8-5.7)	21 (18.8)	6.2 (3.2-12.1)
>29	83 (2.4)	18 (17.1)	4.6 (3.1-6.6)	29 (12.2)	4.3 (2.6-7.3)	26 (15.0)	3.4 (2.0-6.0)	12 (10.7)	4.3 (2.0-9.3)
Count per day									
<1	320 (9.2)	25 (23.8)	1.8 (1.3-2.4)	29 (12.2)	1.4 (0.9-2.2)	30 (17.3)	1.6 (1.0-2.6)	17 (15.2)	2.2 (1.1-4.2)
1-2	101 (2.9)	30 (28.6)	7.5 (5.4-10.5)	46 (19.4)	7.1 (4.5-11.2)	28 (16.2)	4.8 (2.7-8.3)	25 (22.3)	8.9 (4.7-17.1)
>2	37 (1.1)	19 (18.1)	9.3 (5.8-14.7)	13 (5.5)	4.9 (2.4-10.0)	24 (13.9)	8.9 (4.7-16.9)	14 (12.5)	12.6 (5.7-27.8)
Average amount of opium use per time (g)									
<1	203 (5.8)	42 (40)	4.9 (3.7-6.5)	51 (21.5)	3.8 (2.6-5.8)	51 (29.5)	4.3 (2.7-6.7)	31 (27.7)	5.7 (3.2-10)
1-2	143 (4.1)	17 (16.2)	3.3 (2.4-4.7)	25 (10.6)	2.9 (1.7-4.8)	22 (12.7)	2.7 (1.5-4.7)	19 (17)	5.1 (2.7-9.9)
>2	112 (3.2)	15 (14.3)	1.8 (1.1-2.7)	12 (5.1)	1.3 (0.7-2.5)	9 (5.2)	1.1 (0.5-2.4)	6 (5.4)	1.6 (0.6-4.3)

Daily dose of opium use (g)[c]									
<1	246 (7.1)	38 (36.2)	3.6 (2.7-4.7)	46 (19.4)	2.9 (1.9-4.4)	41 (23.7)	3.0 (1.9-4.7)	24 (21.4)	3.9 (2.1-7)
1-2	87 (2.5)	10 (9.5)	4.3 (2.9-6.3)	17 (7.2)	3.1 (1.7-5.6)	24 (13.9)	4.3 (2.4-7.6)	16 (14.3)	6.7 (3.3-13.6)
>2	125 (3.6)	26 (24.8)	3.4 (2.4-4.8)	25 (10.6)	2.7 (1.6-4.5)	17 (9.8)	2.1 (1.1-3.8)	16 (14.3)	4.4 (2.2-8.8)
Cumulative count of opium use [d]									
<4900	224 (6.4)	18 (17.1)	1.0 (0.6-1.7)	17 (7.2)	1.3 (0.7-2.3)	14 (8.1)	1.3 (0.7-2.4)	8 (7.1)	1.7 (0.7-3.8)
4900-11000	130 (3.7)	19 (18.1)	1.6 (1.2-2.3)	23 (9.7)	2.9 (1.7-5)	26 (15)	3.2 (1.8-5.5)	16 (14.3)	4.9 (2.4-9.9)
>11000	104 (3.0)	37 (35.2)	3.9 (2.7-5.5)	48 (20.3)	6.2 (3.9-9.7)	42 (24.3)	5.2 (3.2-8.5)	32 (28.6)	9.5 (5.1-17.5)
Cumulative amount of opium (kg) [e]									
<4	220 (6.3)	22 (21.0)	2.3 (1.6-3.1)	27 (11.4)	2 (1.2-3.2)	19 (11)	1.6 (0.9-2.9)	13 (11.6)	2.5 (1.2-5.0)
4-14	121 (3.5)	24 (22.9)	5.8 (4.1-8.0)	31 (13.1)	4.3 (2.6-7.0)	41 (23.7)	6.0 (3.7-9.9)	20 (17.9)	6.6 (3.4-12.8)
>14	115 (3.3)	26 (24.8)	3.9 (2.8-5.5)	30 (12.7)	3.3 (2-5.4)	21 (12.1)	2.4 (1.3-4.3)	22 (19.6)	6.1 (3.2-11.8)
Unknown	2 (0.1)	2 (1.9)	-	0 (0)	-	1 (0.6)	-	1 (0.9)	-
Starting age of opium use [f]									
<20	53 (1.5)	2 (1.9)	0.8 (0.4-1.6)	7 (3)	1.2 (0.5-3.1)	4 (2.3)	0.6 (0.2-2.2)	6 (5.4)	2.5 (0.9-7.1)
20-29	142 (4.1)	18 (17.1)	1.6 (1.0-2.5)	33 (13.9)	2.1 (1.1-3.9)	27 (15.6)	1.3 (0.6-2.7)	20 (17.9)	3.1 (1.4-6.8)
30-39	112 (3.2)	31 (29.5)	2.6 (1.7-4)	28 (11.8)	2.6 (1.5-4.6)	26 (15)	2.3 (1.2-4.3)	14 (12.5)	3.5 (1.6-7.6)
>=40	151 (4.3)	23 (21.9)	2.2 (1.6-3.2)	20 (8.4)	1.7 (1.0-2.9)	25 (14.5)	2.1 (1.2-3.6)	16 (14.3)	3.6 (1.8-7.2)
Time since stopping opium use [f]									

Current	223 (6.4)	45 (42.9)	2.8 (2-3.9)	46 (19.4)	2.2 (1.4-3.6)	54 (31.2)	2.7 (1.6-4.5)	37 (33)	4.6 (2.5-8.5)
<10	138 (4.0)	18 (17.1)	1.6 (1.1-2.5)	28 (11.8)	1.9 (1-3.4)	24 (13.9)	1.8 (1.0-3.4)	13 (11.6)	2.1 (1.0-4.7)
>=10	90 (2.6)	10 (9.5)	1.4 (0.9-2.3)	14 (5.9)	1.6 (0.8-3.2)	4 (2.3)	0.4 (0.1-1.4)	6 (5.4)	2.0 (0.7-5.7)
Unknown	7 (0.2)	1 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)	-
Type of opium use [f]									
Crude opium (Teriak)	402 (11.6)	52 (49.5)	1.9 (1.4-2.6)	60 (25.3)	1.7 (1.1-2.6)	60 (34.7)	1.7 (1.0-2.7)	44 (39.3)	3.1 (1.7-5.5)
Opium juice (Shireh)	32 (0.1)	4 (3.8)	2.2 (1.1-4.5)	7 (3)	3.0 (1.2-7.6)	5 (2.9)	1.2 (0.3-4.1)	4 (3.6)	4.1 (1.2-14)
Both types	24 (0.7)	18 (17.1)	8.4 (4.7-15.3)	21 (8.9)	10.5 (4.9-22.5)	17 (9.8)	8.9 (3.8-20.7)	8 (7.1)	9.8 (3.4-28.5)
Route of opium use [f]									
Only smoking	380 (10.9)	42 (40.0)	1.6 (1.1-2.1)	38 (16)	1.2 (0.8-2)	43 (24.9)	1.4 (0.8-2.3)	33 (29.5)	2.6 (1.4-4.8)
Only ingestion	30 (0.9)	9 (8.6)	4.9 (2.7-8.9)	10 (4.2)	4.4 (1.9-10.2)	8 (4.6)	3.8 (1.4-10.3)	7 (6.3)	7.0 (2.4-19.9)
Both routes	45 (1.3)	22 (21.0)	8.3 (5.1-13.5)	40 (16.9)	10.7 (5.9-19.5)	31 (17.9)	7.8 (3.9-15.5)	16 (14.3)	10.0 (4.3-23.2)
Unknown	3 (0.1)	1 (0.95)	-	0 (0)	-	0 (0)	-	0 (0)	-

[a] Adjusted for age, gender, province, socioeconomic status, cigarette and water pipe use.
[b] Regular user was defined as using the substance once a week for at least 6-months.
[c] Daily dose of opium (gram) : The average amount of opium use multiplied by the average count per day
[d] Cumulative count of opium use: The average count per day multiplied by total opium duration (years)
[e] Cumulative amount of opium use: The average amount of opium use multiplied by average count per day and total opium duration(years)
[f] To assess the independent effect of these metrics we adjusted the results for the cumulative count of opium use too as they are correlated with each other

Table 4: Effect modification of tobacco smoking on the association between lung cancer and opium use

Tobacco use [a]	Opium use [a]			
	Never		Regular	
	Cases/Controls	OR (95% CI)[b]	Cases/Controls	OR (95% CI)[b]
Never	136/1951	Ref.	24/101	3.4 (2.1,5.5)
Regular	157/706	3.6 (2.8,4.7)	267/345	13.4 (10.2,17.7)[c]

[a] The results for irregular opium and tobacco use not shown.

[b] Adjusted for age, gender, province, socioeconomic status, cigarette and water pipe use.

[c] Relative excess risk due to interaction (RERI) is equal to OR (AB) - OR (Only A)-OR (Only B) +1 in the absence of interaction, RERI is equal to zero. RERI was 7.4 (4.1-10.7).