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Lung cancer risk in relation to jobs held in a nationwide case–control study in Iran

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ABSTRACT

Background Globally, lung cancer is the most frequent occupational cancer, but the risk associated with the occupations or occupational environment in Iran is not clear. We aimed to assess occupations with the risk of lung cancer.

Methods We used the IROPICAN nationwide case–control study data including 658 incident lung cancer cases and 3477 controls. We assessed the risk of lung cancer in relation to ever working in major groups of International Standard Classification of Occupations, high-risk occupations for lung cancer and duration of employment and lung cancer subtype among construction workers and farmers while controlling for cigarette smoking and opium consumption. We used unconditional regression logistic models to estimate ORs for the association between increased lung cancer risk and occupations.

Results We observed elevated ORs for lung cancer in male construction workers (OR=1.4; 95% CI: 1.0 to 1.8), petroleum industry workers (OR=3.2; 95% CI: 1.1 to 9.8), female farmers (OR=2.6; 95% CI: 1.3 to 5.3) and female bakers (OR=5.5; 95% CI: 1.0 to 29.8). A positive trend by the duration of employment was observed for male construction workers ($p< 0.001$). Increased risk of squamous cell carcinoma was observed in male construction workers (OR=1.9; 95% CI: 1.2 to 3.0) and female farmers (OR=4.3; 95% CI: 1.1 to 17.2), who also experienced an increased risk of adenocarcinoma (OR=3.8; 95% CI: 1.4 to 9.9).

Discussion Although we observed associations between some occupations and lung cancer consistent with the literature, further studies with larger samples focusing on exposures are needed to better understand the occupational lung cancer burden in Iran.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Most evidence regarding occupational lung cancer derives from industry-based and community-based epidemiological studies conducted in high-income countries.
⇒ While the industrial structure in Iran is developing in an opposite direction compared with what we observe in western countries, our understanding of the risk of lung cancer in occupational settings in Iran is limited.

WHAT THIS STUDY ADDS?

⇒ This is the largest case–control study on lung cancer in Iran holding occupational information to date.
⇒ So far, occupational epidemiological studies have considered smoking as the most important confounding factor.
⇒ In this study, we discovered that opium consumption also is a confounding factor to be accounted for, and opium consumption varies across economical activities.
⇒ In several major International Standard Classification of Occupations groups, lung cancer risk was reduced when adjusting for opium consumption.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ The current study is a very first step in advancing occupational cancer epidemiology research in Iran, with emphasis on conducting further studies to more accurately determine the risk of lung cancer arising from occupational exposures in workplaces in Iran.

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INTRODUCTION

In Iran, lung cancer is one of the leading causes of incident cancer in both men and women.[1] Globally, it has been estimated that approximately 15% of lung cancers can be attributed to occupational environment exposures, but the evidence for this estimate is derived mostly from the epidemiological studies carried out in high-income countries (HIC). Estimation of lung cancer attributable to occupational environment exposure to silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium and asbestos in Iran was 12%. However, this estimation is based on industrial and occupational statistics reported to the International Labour Organisation, in which the estimated proportions of exposed workers in those industries came from the European CARcinogen Exposure databases, and relative risk estimates from the international literature,[2 3] resulting in large uncertainties.

Tobacco smoking is by far the leading risk factor for lung cancer. Nevertheless, we must also focus on occupational environment risk factors, which are among the most preventable risk factors for lung cancer when eliminating or lowering exposure to hazardous agents.[4] According to the international STEP survey, the prevalence of ever cigarette smoking in Iran is 28.6% in men and 1.8% in women,[5] The prevalence of environmental tobacco smoke, whether it originates from home or work, is 35.7% in (men) and 27.7% (women). Opium consumption is another relevant lifestyle-related risk factor for lung cancer that recently was classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC) monographs.[6] Iran has the highest opium consumption in the world accounting for 42% of the global consumption, with the prevalence of 7.9% (men) and 0.8% (women) in the last 12 months.[7]

The industrial evolution in many of low-income and middle-income countries (LMICs) following economic development and shifting large industrial sectors from HICs to LMICs[8] may increase the risk of lung cancer due to exposure in the workplace environment. This field of research needs to be extended and has just started in Iran.[9] For this reason, we are faced with a lack of data that could directly affect cancer prevention programmes within the country and may lead to an increase in cancer prevention disparities compared with HICs.

In the present study, we investigate the risk of lung cancer in relation to major International Standard Classification of Occupations (ISCO-68) and specific high-risk occupations with sufficient evidence of increased lung cancer risk in a large nationwide case–control study (IROPICAN) in Iran.[10] For the selected occupations, we further analysed risk of lung cancer by duration of employment and by histological subtype when the number of exposed study participants allowed.

MATERIALS AND METHODS

The IROPICAN study is an Iranian nationwide multicentre hospital-based case–control study of various cancers (lung, urinary bladder, colorectal and head and neck), with a total of 3299 cancer cases. The study was conducted in 27 participating centres in 10 provinces across Iran between 2016 and 2020, with a response rate of 99% among cases and 89% in controls (virtually all patients, irrespective of their socioeconomical background, go to the same referral hospital in each province due to their diagnostic and treatment facilities for patients with cancer). The provinces were however chosen in a way to represent various geographical and cultural areas of the country, including the capital of Iran, so we assume they are highly representative of all lung cancer cases in Iran. The main objective of IROPICAN study was to investigate the cancer risks associated with opium consumption.

More details on the design and study objectives have been described elsewhere.[10]

Study population

We recruited eligible cases in referral cancer care hospitals who were diagnosed <1 year before enrolling into the study, patients with histologically confirmed lung cancer (ICD-O: C33/34) according to the International Classification of Diseases for Oncology (ICD-O-3) and >18 years of age. We classified the histopathology subtypes of all lung cancer cases according to the fifth edition of WHO Classification of Tumours series, thoracic tumour volume; into two major groups of epithelial (including adenocarcinoma, squamous cell carcinoma, neuroendocrine tumours and other epithelial tumours) and non-epithelial tumours.[11] Second primary cancers, and those without a confirmed pathology report were excluded.

Controls were hospital visitors who were relatives or friends of hospitalised patients in non-oncology wards in the hospital, that is, cardiology, neurology, ophthalmology, orthopaedic, general surgery, obstetrics and gynaecology, haematology, ear/nose/throat, rheumatology, neurosurgery and endocrinology, but not emergency rooms and maternity wards. For each lung cancer case, a cancer-free control was enrolled in the same hospital and frequency-matched by sex, 5-year age group and place of residence. In the current analysis, we included all controls that initially were recruited for the other cancer sites (bladder, head and neck and colorectal cancer) from the main study.

Data collection

Information was gathered by trained interviewers via a semi-structured questionnaire during a face-to-face interview. Participants reported up to three occupations (<5% of participants held a third occupation in their lifetime career) or other types of work circumstance held >1 year in their lifetime, including occupation title, industry or company title, occupation tasks, starting and finishing age for each occupation. Housewives were named as such and included as an occupation.

Data on demographics (age, sex, place of residence), personal history of respiratory diseases (including asthma, bronchitis, pneumonia and tuberculosis), environmental tobacco smoke, individual history of tobacco smoking, opium consumption, waterpipe smoking, including questions on the status of consumption, duration, frequency and amount for each individual substance used were also collected.

All occupation titles were coded using ISCO-68 at the 5-digit level.[12] A binary variable (never vs ever) was created for each ISCO-68 major group (nine major groups including military forces and housewives) and each selected high-risk occupation (ever/never) in the workers' lifetime career. The selected occupations were either previously evaluated by the IARC-WHO monograph working groups and classified as a high-risk occupations for lung cancer risk,[13] or reported increased risks in previous studies.[14–18] The list of specific occupations and the associated ISCO-68 codes are available in online supplemental table S1.

The selected specific occupations were construction workers (including bricklayers, stonemasons and tile setters, concreters, cement finishers, terrazzo workers, plasterers and their corresponding foremen and construction labourers), textile industry workers, painters, welders, workers in the petroleum industry and rubber industry workers. We also selected occupations with a large sample size and adequate power including farmers (field farmers, animal farmers) and drivers (road drivers, heavy vehicle drivers). In addition, we included bakers in our analyses since there is inconclusive results regarding a potential association between being a baker and the risk of lung cancer.[19 20] Working conditions of Iranian bakers and the environment of bakeries are different compared with in the western countries. For example, bakers are exposed to biomass fuel combustion from open ovens without chimneys,[21] in which they may be exposed to high levels of carcinogens in addition to flour dust.

Statistical analysis

As the distribution of occupations and individual substance use differed by sex, results were reported by sex in view of potential sex differences.

We compared the distributions of age groups, individual substance consumption (eg, tobacco, opium, waterpipe), personal history of respiratory diseases and environmental tobacco smoke between cases and controls by sex, using the χ^2 test for categorical variables. Two-sided p values were used with a 5% nominal statistical significance.

To investigate the association between occupation held—defined by ISCO-68 major groups or selected occupations—and lung cancer risk, ORs and 95% CIs were computed using unconditional logistic regression models.

Three models were fitted to assess the risk of lung cancer associated with ISCO-68 major groups and selected occupations (based on 5-digit codes). The first model was minimally adjusted for age (5 years categories) and residential areas (10 provinces), hereafter referred as model 0 (baseline adjustment). Cigarette smoking status (never/former/current) and intensity (never smokers/<10/10–20/>20 pack-years) were then added to the baseline model (model 1), and the last model (model 2) was adjusted for the baseline model variables plus cigarette smoking-related variables and opium consumption (never users; <1 time day; 1–2/day; >2/day). In the text, we refer to the fully adjusted model (model 2) unless otherwise mentioned. We explored waterpipe smoking (never/ever), environmental tobacco smoke either at home or workplace (never/ever) and respiratory disease history (never/ever) as covariates in the model but they did not change the fit of the models, so we did not retain them in the final analyses (data not shown).

Subsequently, for selected occupations known to be associated with lung cancer, for which sufficient numbers of cases were available (95 cases and 318 controls of male construction workers, 18/69 female farmers and 159/664 male farmers), we examined duration of employment. The median duration of employment among the controls was chosen as cut-off to reach enough subjects in each category. For male construction workers a cut-off was 28 years, and in female farmers the cut-off was 35 years, and in male farmers 36 years. Linear trends in ORs across categories of duration of employment, starting from never being employed as a construction worker/farmer, were examined by treating categories as equally spaced ordinal variables in the logistic regression models.

Since an interaction between construction work and tobacco smoking has been reported previously,[22] we also examined the interaction on a multiplicative scale using an interaction term between occupation as a construction worker (never vs ever) and smoking status (never vs ever smoker) in logistic regression models. We also evaluated the interaction on the additive scale by calculating the relative excess risk due to interaction.[23] We also did the same with opium consumption (never vs ever) instead of smoking to test for potential interaction between construction work and opium consumption.

Finally, we evaluated if working as a male construction worker and farming are associated with lung cancer by the major histopathology subtypes adenocarcinoma, squamous cell carcinoma and neuroendocrine tumours.

Statistical analyses were conducted using the statistical package STATA V.15.1 (StataCorp, College Station, Texas, USA).

RESULTS

Table 1 shows the study population's main characteristics, including 658 incident lung cancer cases and 3477 controls. The mean age of male cases was 60.6 years while 57.9 years among controls, while the corresponding ages in female study subjects were 60.2 and 56.2 years. The ratio of male/female in cases were 6.9 and in controls 4.8. As expected, cigarette smoking, waterpipe smoking and opium use was more frequent among cases than controls, and cigarette smoking and opium use were more frequent in men than in women. However, a larger proportion of female cases compared with male cases smoked waterpipe, had been exposed to environmental tobacco smoke and had a history of respiratory diseases. The predominant histopathological type of lung cancer in male and female cases was adenocarcinoma (33.5% and 51.6%, respectively), followed by squamous cell carcinoma (29.5%, and 17.8%, respectively).

Lung cancer risk estimated by major occupation groups of ISCO-68 are shown in table 2. Male workers in the first two major occupational groups (professional, technical and related workers; administrative and managerial workers) experienced a reduced lung cancer risk (OR=0.6; 95% CI: 0.4 to 0.9); (OR=0.4; 95% CI: 0.2 to 0.7) when compared with all others and after adjustment for smoking, which became less pronounced in model 2 adjusting in addition for opium consumption. The risk of lung cancer in the military service group remained reversely associated (OR=0.5; 95% CI: 0.2 to 0.9) even after full adjustment. Having ever worked in 'elementary occupations' or in 'plant and machine operators and assemblers' were associated with an increased lung cancer risk in model 0, which diminished or disappeared when adjusting for cigarette smoking and opium consumption.

Among females, ever having worked in the major group 'agricultural, animal husbandry and forest' was associated with a twofold lung cancer risk, which somewhat increased (OR=2.6; 95% CI: 1.3 to 5.3) when adjusting for cigarette smoking and opium consumption. Remaining major groups showed varying ORs with wide CIs due to small numbers.

Table 3 shows the risk of lung cancer associated with ever having worked in preselected occupations. In males, borderline statistically significant elevated risks of lung cancer were observed among construction workers (OR=1.4; 95% CI: 1.0 to 1.8) and petroleum industry workers (OR=3.2; 95% CI: 1.1 to 9.8), although the latter was based on small numbers. An increased risk of lung cancer was also observed in rubber industry workers (OR=2.7; 95% CI: 0.6 to 12.6) based on few exposed subjects (three cases and nine controls) leading to reduced statistical power to detect potential associations. In females, increased risks of lung cancer were observed among farmers (OR=2.6; 95% CI: 1.3 to 5.3) and bakers (OR=5.5; 95% CI: 1.0 to 29.8), also based on small number of subjects. An inverse association between lung cancer risk and occupation was seen in male heavy vehicle drivers (OR=0.4; 95% CI: 0.2 to 0.9).

Male construction workers experienced a slightly increasing risk of lung cancer with increasing duration of employment (OR=1.6; 95% CI: 1.1 to 2.4), with >28 years of employment (online supplemental table S2). A trend with duration of employment as a construction worker was observed (p value for trend >0.05). Duration of employment as a farmer was not associated with lung cancer risk in men (online supplemental table S3). Among female farmers, the magnitude of lung cancer risk was highest in the lowest category of duration of employment: (OR=4.7; 95% CI: 1.9 to 11.6) for ≤35 years vs (OR=1.5; 95% CI: 0.6 to 4.1) for >35 years of employment. There were no significant trends in ORs with the duration of employment as a farmer.

The joint effects of smoking status/opium consumption and ever/never having worked as a construction worker in men are shown in table 4. There was no evidence of interactions between smoking status and ever/never having worked as a construction worker, nor between opium consumption and construction work.

Table 1 Characteristics of the study population by case–control status and sex

Study participants' characteristics	Male n (%) Cases 501 (17.3)	Male n (%) Controls 2398 (82.7)	P value*	Female n (%) Cases 157 (12.7)	Female n (%) Controls 1079 (87.3)	P value*
Age categories, years	N (%)	N (%)	<0.001	N (%)	N	0.070
<40	12 (2.4)	204 (8.5)		8 (5.1)	114 (10.6)	
40–44	16 (3.2)	95 (3.9)		6 (3.8)	73 (6.8)	
45–49	38 (7.6)	222 (9.2)		14 (8.9)	108 (10.0)	
50–54	58 (11.6)	325 (13.5)		22 (14.0)	149 (13.8)	
55–59	106 (21.1)	423 (17.6)		24 (15.3)	173 (16.0)	
60–64	103 (20.6)	430 (17.9)		22 (14.0)	184 (17.0)	
65–69	77 (15.4)	331 (13.8)		32 (20.4)	147 (13.6)	
70–74	46 (9.2)	206 (8.6)		15 (9.5)	83 (7.7)	
75–79	27 (5.4)	99 (4.1)		7 (4.5)	26 (2.4)	
80–84	17 (3.4)	47 (1.2)		3 (1.2)	15 (1.4)	
85+	1 (0.2)	16 (0.7)		4 (2.5)	7 (0.6)	
Cigarette smoking status			<0.001			0.216
Never smokers	103 (20.6)	1442 (60.1)		146 (93.0)	1036 (96.0)	
Current smokers	212 (42.3)	440 (18.4)		5 (3.2)	18 (1.7)	
Former smokers	186 (37.1)	515 (21.5)		6 (3.8)	25 (2.3)	
Intensity of smoking (pack/year) in ever smokers			<0.001			0.026
<10	55 (11)	359 (15.0)		4 (2.5)	27 (2.5)	
10–20	48 (9.6)	167 (7.0)		4 (2.5)	5 (0.5)	
>20	295 (58.9)	430 (17.9)		3 (1.9)	11 (1.0)	
Opium consumption status (times/day)			<0.001			<0.001
Never	213 (42.5)	1970 (82.1)		133 (84.7)	1056 (97.8)	
<1/day	103 (20.6)	295 (12.3)		5 (3.2)	19 (1.8)	
1–2/day	120 (23.9)	99 (4.1)		11 (7.0)	2 (0.2)	
>2/day	65 (13.0)	34 (1.4)		8 (5.1)	2 (0.2)	
Waterpipe smoking			0.024			<0.001
Never	455 (90.8)	2245 (93.6)		127 (80.9)	993 (92.0)	
Ever	46 (9.2)	153 (6.4)		30 (19.1)	86 (8.0)	
Environmental tobacco smoke			0.047			<0.001
Never	317 (63.3)	1752 (73.1)		88 (56.1)	693 (64.2)	
Ever	184 (36.7)	646 (26.9)		69 (43.9)	386 (35.8)	
Respiratory disease history			<0.001			<0.001
Never	451 (90.0)	2259 (94.2)		131 (83.4)	1026 (95.1)	
Ever	50 (10.0)	139 (5.8)		26 (16.6)	53 (4.9)	
Histopathology classification						
Epithelial tumours						
Adenocarcinoma	168 (33.5)			81 (51.6)		
Squamous cell carcinoma	148 (29.5)			28 (17.8)		
Neuroendocrine tumours	99 (19.7)			15 (9.5)		
Other epithelial neoplasm	57 (11.4)			21 (13.4)		
Non-epithelial tumours	15 (3.0)			7 (4.5)		
Missing	14 (2.8)			5 (3.2)		
The longest occupation held (major groups of ISCO-68)			<0.001			0.6
0/1: Professional, technical and related workers	31 (6.2)	266 (11.1)		7 (4.5)	53 (4.9)	
2: Administrative and managerial workers	4 (0.8)	61 (2.5)		2 (1.3)	10 (0.9)	
3: Clerical and related workers	27 (5.4)	212 (8.8)		2 (1.3)	16 (1.4)	
4: Sales workers	38 (7.6)	181 (7.5)		0 (0.0)	11 (1.0)	
5: Service workers	22 (4.4)	125 (5.2)		0 (0.0)	32 (3.0)	
6: Agricultural, animal husbandry and forest	140 (27.9)	541 (22.6)		8 (5.1)	58 (5.4)	
7: Craft and related trades workers	29 (5.6)	147 (6.1)		6 (3.8)	39 (3.6)	
8: Plant and machine operators	48 (9.6)	172 (7.2)		0 (0.0)	1 (0.1)	
9: Elementary occupations	152 (30.3)	554 (23.1)		1 (0.6)	4 (0.4)	
X: Military force	9 (1.8)	130 (5.4)		–	–	
X1: Housewives	–	–		131 (83.4)	849 (78.7)	

continued

Table 1 continued

Study participants' characteristics	Male n (%)			Female n (%)		
	Cases 501 (17.3)	Controls 2398 (82.7)	P value*	Cases 157 (12.7)	Controls 1079 (87.3)	P value*
Missing, students, jobless	1 (0.2)	9 (04)		0 (0.0)	6 (0.5)	

*P value calculated using the χ^2 test.
–, no data; ISCO-68, International Standard Classification of Occupations.

Table 5 shows the risk of lung cancer in male construction workers and female farmers by histological subtype. Squamous cell carcinoma showed an elevated OR (1.9, 95% CI: 1.2 to 3.0), while adenocarcinoma lung cancer risk was not associated with construction working in men. The risk of neuroendocrine tumours subtype associated with construction workers in males were moderately elevated but not statistically significant (OR=1.5; 95% CI: 0.8 to 2.5). Female farmers experienced an increased risk of both adenocarcinoma and squamous cell carcinoma subtypes in all models. The risk estimates for squamous cell carcinoma were slightly higher than for the adenocarcinoma subtype.

DISCUSSION

To our knowledge, this is the largest case–control study to assess the risk of lung cancer associated with occupations in Iran, while adjusting for personal substance use.[9] We found in men an inverse association of lung cancer risk for two major groups of white-collar occupations (professional, technical and related workers; administrative and managerial workers),[24] and military service workers, and increased risk in workers in major group of 'elementary occupations' and 'plant and machine operators and assemblers'. All these positive and inverse associations in men were attenuated when adjusting for individual tobacco smoking and consumption of opium. In women, we observed an association with working in the major group of 'agricultural, animal husbandry and forest', the ORs remained slightly elevated after adjusting for tobacco smoking and opium consumption. Further analyses of specific occupations that were assumed to be high-risk occupations for lung cancer risk according to previous studies revealed increased lung cancer risk in male construction workers and petroleum industry workers. In addition, increased risks of lung cancer were observed among female farmers and female bakers in which the associations became stronger when adjusting for individual substances use.

Lifestyle profiles likely differ across major ISCO-68 groups, for example, it has been observed that smoking prevalence is higher in some 'elementary occupations'[25 26]; for this reason, adjustment is very important.

Elevated risk of lung cancer among construction workers, and especially bricklayers had been observed in previous epidemiological studies carried out in various countries including the USA, France and Indonesia.[16 27 28] The squamous cell carcinoma subtype accounted as the most prevalent subtype among ever construction workers as previously reported by other studies.[22 29] Moreover, the results of current study shows elevated risk of lung cancer has been associated with the length of employment as construction worker, which also is consistent with previous findings.[22] In most of those studies, crystalline silica, diesel fumes and asbestos have been mentioned as common carcinogen exposures in construction workers. We did not observe joint effects between construction work and individual substance use, although synergistic effects of individual substance use in addition to single occupational exposures, for example, asbestos have been shown in previous studies.[30–32]

Petroleum industry workers were found to have excess risk of lung cancer, although based on small numbers. This finding is broadly consistent with the result of a recent systematic review and meta-analysis, showing an increased risk of lung cancer for offshore workers. Potential exposures attributable to the risk of

Table 2 Risk of lung cancer related to ever having worked in ISCO-68 major occupational groups (compared with those that have not worked in respective group) stratified by sex

ISCO-68 major groups	Ever worked (cases/controls)		Model 0* OR (95% CI)		Model 1† OR (95% CI)		Model 2‡ OR (95% CI)	
	Male	Female	Male	Female	Male	Female	Male	Female
0/1: Professional, technical and related workers	37/319	9/74	0.5 (0.3 to 0.7)	0.8 (0.3 to 1.7)	0.6 (0.4 to 0.9)	0.8 (0.4 to 1.7)	0.8 (0.5 to 1.1)	0.9 (0.4 to 1.8)
2: Administrative and managerial workers	8/93	2/11	0.4 (0.2 to 0.8)	1.4 (0.3 to 6.4)	0.4 (0.2 to 0.7)	1.1 (0.2 to 5.8)	0.4 (0.2 to 1.0)	1.5 (0.3 to 7.5)
3: Clerical and related workers	31/252	2/23	0.5 (0.3 to 0.7)	0.6 (0.1 to 2.6)	0.6 (0.4 to 1.0)	0.5 (0.1 to 2.3)	0.7 (0.5 to 1.1)	0.6 (0.1 to 2.7)
4: Sales workers	62/282	3/16	1.1 (0.8 to 1.5)	1.5 (0.4 to 5.6)	1.0 (0.7 to 1.4)	1.5 (0.4 to 5.5)	1.0 (0.7 to 1.4)	1.1 (0.3 to 5.1)
5: Service workers	40/147	1/54	1.1 (0.8 to 1.6)	0.1 (0.0 to 1.0)	1.1 (0.7 to 1.7)	0.1 (0.0 to 0.9)	1.2 (0.8 to 1.9)	0.1 (0.0 to 1.2)
6: Agricultural, animal husbandry and forest	161/678	18/69	1.2 (0.9 to 1.5)	2.3 (1.2 to 4.5)	1.1 (0.9 to 1.4)	2.4 (1.2 to 4.6)	1.0 (0.8 to 1.3)	2.6 (1.3 to 5.3)
7: Craft and related trades workers	41/196	11/75	0.9 (0.6 to 1.4)	1.0 (0.5 to 2.0)	0.9 (0.6 to 1.3)	1.0 (0.5 to 2.0)	0.9 (0.6 to 1.4)	0.9 (0.4 to 2.0)
8: Plant and machine operators	61/229	0/3	1.4 (1.0 to 1.9)	No cases	1.1 (0.8 to 1.6)	No cases	0.9 (0.6 to 1.3)	No cases
9: Elementary occupations	187/723	2/8	1.4 (1.2 to 1.7)	2.2 (0.4 to 11.4)	1.2 (1.0 to 1.5)	1.6 (0.2 to 8.9)	1.2 (0.9 to 1.5)	1.7 (0.3 to 9.5)
X: Military force	14/147	–	0.4 (0.2 to 0.7)	–	0.5 (0.2 to 0.8)	–	0.5 (0.2 to 0.9)	–
XI: Housewives	–	132/874	–	0.9 (0.5 to 1.5)		0.9 (0.6 to 1.5)	–	0.9 (0.5 to 1.5)

Each occupational group is individually compared with the respective remaining group of samples.
*Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces).
†Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.
‡Model 2 (M2) is adjusted for M1 plus opium consumption.
–, no data; ISCO-68, International Standard Classification of Occupations.

Table 3 Risk of lung cancer associated with ever having worked in the selected specific occupations (ISCO-68) stratified by sex

	Ever worked N (cases/controls)		Model 0* OR (95% CI)		Model 1† OR (95% CI)		Model 2‡ OR (95% CI)	
ISCO-68 major groups	Male	Female	Male	Female	Male	Female	Male	Female
Textile industry workers	5/49	6/58	0.6 (0.1 to 2.0)	0.8 (0.3 to 2.3)	0.4 (0.1 to 1.2)	0.9 (0.4 to 2.4)	0.6 (0.3 to 1.6)	0.4 (0.1 to 1.1)
Painters	7/31	–	1.1 (0.5 to 2.7)	–	0.7 (0.3 to 2.0)	–	0.7 (0.3 to 2.0)	–
Construction workers	95/318	–	1.6 (1.2 to 2.1)	–	1.5 (1.1 to 1.9)	–	1.4 (1.0 to 1.8)	–
Drivers	53/250	–	1.0 (0.7 to 1.4)	–	0.8 (0.6 to 1.2)	–	0.9 (0.6 to 1.2)	–
Road drivers	46/190	–	0.9 (0.7 to 1.3)	–	0.8 (0.5 to 1.1)	–	0.8 (0.5 to 1.2)	–
Heavy vehicles drivers	9/69	–	0.6 (0.3 to 1.2)	–	0.4 (0.2 to 0.9)	–	0.4 (0.2 to 0.9)	–
Welders	16/53	–	1.5 (0.8 to 2.7)	–	1.2 (0.6 to 2.4)	–	1.0 (0.5 to 2.0)	–
Farmers	161/678	18/69	1.2 (0.9 to 1.5)	2.3 (1.2 to 4.5)	1.1 (0.9 to 1.4)	2.4 (1.2 to 4.6)	1.0 (0.8 to 1.3)	2.6 (1.3 to 5.3)
Only field farmers	130/576	14/63	1.1 (0.9 to 1.4)	2.0 (1.0 to 4.0)	1.1 (0.9 to 1.4)	2.0 (1.0 to 4.1)	1.0 (0.8 to 1.3)	2.4 (1.1 to 5.1)
Only animal farmers	16/60	3/5	1.4 (0.8 to 2.5)	3.1 (0.6 to 14.4)	1.2 (0.6 to 2.2)	3.0 (0.7 to 14.8)	1.0 (0.5 to 2.0)	3.9 (0.8 to 19.7)
Petroleum industry workers	5/13	–	1.7 (0.6 to 4.8)	–	2.5 (0.8 to 7.6)	–	3.2 (1.1 to 9.8)	–
Bakers	8/24	3/5	1.8 (0.8 to 4.0)	5.0 (1.1 to 22.2)	1.8 (0.8 to 4.3)	5.0 (1.1 to 23.2)	1.4 (0.5 to 3.7)	5.5 (1.0 to 29.8)
Rubber industry workers	3/9	–	1.7 (0.4 to 6.7)	–	2.5 (0.5 to 11.0)	–	2.7 (0.6 to 12.6)	–

*Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces).
†Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.
‡Model 2 (M2) is adjusted for M1 plus opium consumption.
–, no data; ISCO-68, International Standard Classification of Occupations; N, number.

lung cancer in this industry include combustion products and asbestos.[33] Working in the petroleum industry includes a very broad range of occupations, representing an example where more detailed information on occupations and work environments could help to identify exposures of concern.

We observed an increased risk of lung cancer among female farmers, but not in male farmers. In a previous study from Indonesia, an elevated OR of 3.6 (95% CI: 1.2 to 10.4) was reported among farmers (both sexes).[28] Another study carried out in Turkey observed an increased risk of lung cancer among workers in agriculture with OR of 1.9 (95% CI: 1.0 to 3.2).[34] A study among Italian female farmers, also reported an elevated OR of 1.7 (95% CI: 0.7 to 4.4) for lung cancer.[35] The female farmers in Iran mostly live in rural areas, who likely carry out other tasks in addition to farming, for example, baking and cooking, which raise the concerns about exposure to combustion of biomass fuels. We observed an increased risk of lung cancer among female bakers, which aligns with several studies including one from Finland that estimated exposure to flour dust using a job exposure matrix (FINJEM).[19 36 37] However, a recent pooling large study of 16 case–control studies from Europe and Canada did not show any associations.[20] One explanation could be that female bakers in rural area of Iran still mostly bake the bread in a traditional way using ovens without chimneys, for example, using wood, which expose them to combustion products. The Golestan cohort study from northeast Iran showed higher risk of gastrointestinal cancers in those who were exposed to biomass combustions from cooking and heating, without chimneys.[21]

Table 4 Effect modification between smoking or opium consumption and employment as a construction worker among men

Exposure status	N Case/Controls	OR (95% CI)
Never smoker and never construction worker	235/2304	Ref
Never smoker and construction worker	14/174	1.1 (0.6 to 2.1)
Ever smoker and never construction worker	328/855	3.4 (2.6 to 4.5)
Ever smoker and ever construction worker	81/141	4.8 (3.2 to 6.7)
P value multiplicative interaction		0.1
RERI*		1.2 (–0.4 to 2.8)
Never opium user and never construction worker	313/2786	Ref
Never opium user and construction worker	33/240	1.3 (0.8 to 2.0)
Ever opium user and never construction worker	250/373	4.7 (3.6 to 6.1)
Ever opium user and ever construction worker	62/78	6.4 (4.2 to 9.6)
P value multiplicative interaction		0.3
RERI†		1.4 (–1.1 to 3.9)

*Adjusted OR for age categories (5-year categories) and residence (provinces).
†Interaction on an additive scale.
N, number; RERI, relative excess risk due to interaction.

In our study, occupations that previously evaluated by the IARC monographs working groups and classified as 'carcinogenic to humans' (group 1) in relation to lung cancer; such as painter, welder, textile industry workers or having worked as rubber industry workers was not associated with excess lung cancer risk.[13 24 38–40] The reason of no association for these occupations could be the small sample size, and that the small numbers did not allow to evaluate the risk separately in various groups with different levels of exposure, for example, painters in construction industry, or automobile industry painters. Among the strengths of this study is that we were able to adjust for smoking habits, and for the first time (to our knowledge) we adjusted for opium consumption as carcinogenic to humans (group 1).[6] Even though the aim of the IROPICAN study was to evaluate the risk of cancers associated with the opium consumption, we had access to relatively detailed occupational information. This is important in view that previous estimations of occupational cancer risk predictions in Iran are extrapolated from data mostly from other countries.

One of the major limitations of our study is that we were only able to analyse the major ISCO-68 groups and the most common high-risk occupations for lung cancer. For many of the specific occupations, there were too few workers to obtain robust risk estimates. Because no adjustment was made for multiple comparisons, the results should be considered exploratory given the number of subgroup analyses to be compared. It would have been better to examine the effects of specific occupational exposures, since most exposures occur in several occupations

Table 5 Risk of lung cancer by histological subtype in male construction workers and female farmers

	N (cases)	Model 0* OR (95% CI)	Model 1† OR (95% CI)	Model 2‡ OR (95% CI)
Male construction workers				
Adenocarcinoma	26	1.1 (0.8 to 2.0)	1.1 (0.7 to 1.8)	1.0 (0.6 to 1.6)
Squamous cell carcinoma	24	2.2 (1.4 to 2.3)	2.0 (1.3 to 3.1)	1.9 (1.2 to 3.0)
Neuroendocrine tumours	20	1.6 (1.0 to 2.6)	1.4 (0.9 to 2.4)	1.5 (0.8 to 2.5)
Female agriculture workers				
Adenocarcinoma	9	3.4 (1.4 to 8.4)	3.4 (1.4 to 8.4)	3.8 (1.4 to 9.9)
Squamous cell carcinoma	4	3.9 (1.03 to 15.2)	4.2 (1.1 to 16.3)	4.3 (1.1 to 17.2)
Neuroendocrine tumours	0	No cases	No cases	No cases

*Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces).
†Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.
‡Model 2 (M2) is adjusted for M1 plus opium consumption.
N, number.

and therefore the numbers become larger. It also makes more sense given cancer prevention because most occupations cannot be prohibited but exposures can be eliminated or reduced. The reason we could not analyse occupational exposures directly was that there is no retrospective exposure assessment tool, such as job exposure matrices, available for the working environment in Iran.

In summary, we observed associations between working in the construction and petroleum industries and lung cancer risk in men as well as between working as farmers and as bakers and lung cancer risk in women, which remained after we controlled for tobacco smoking and opium consumption. These potential associations need to be replicated in further studies identifying the respective workplace exposure to provide evidence for plans regarding national regulations for worker protection.

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