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Investigating Occupational Exposures and Related Risks of Lung and Bladder Cancers in Iran: a Nationwide Case-Control Study

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Investigating Occupational Exposures and Related Risks of Lung and Bladder Cancers in Iran : A Nationwide Case- Control Study

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INVESTIGATING OCCUPATIONAL EXPOSURES AND RELATED RISKS OF LUNG AND BLADDER CANCERS IN IRAN: A NATIONAL CASE-CONTROL STUDY

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Doctor of Philosophy of Cancer Epidemiology

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English abstract

Occupational exposures play a major role in the development of cancer, which in most cases can be prevented by risk reduction/elimination in the workplace. To achieve this, we need to identify occupational environments with high cancer risk. Subsequently, the most important carcinogens causing increased cancer risk will be identified through systematic exposure assessment.

To date, most of the evidence identifying occupational carcinogens and describing their effects in humans has come from epidemiological studies conducted in high-income countries. Limited attempts have been made to describe exposure patterns and the resulting cancer risk in Iran, although Iran is an industrialised country and workers may be exposed to different chemical agents than in other countries.

This study aimed to characterise occupational patterns in Iran and to investigate the risk of lung and bladder cancer as a result of occupational exposure in this country. To our knowledge, this is the first systematic attempt to initiate and highlight this area of research in Iran. This work, aimed at characterizing occupational patterns in Iran and to investigate the risk of lung and bladder cancer as a result of workplace exposure in this country, is, to our knowledge, the first systematic attempt to initiate and highlight this area of research in Iran.

A literature review conducted as part of this work confirmed that the study of occupational exposures and cancers in Iran had only been started recently, and that there was no clear evidence on the pattern of occupational cancers nor assessment of occupational exposure to carcinogens in Iran. Mainly two types of studies have been conducted, namely epidemiological

studies and exposure monitoring studies. Exposure monitoring studies have been conducted mainly in industries, i.e., petroleum industry, metal industry, electronics industry, plastics industry, construction industry, and service industry.

The exposures have been measured using single sampling through personal and stationary air sampling. A majority of the epidemiologic studies were small case-control studies in which exposures were assigned to workers based on job/industry title.

Next, to assess the risk of lung and bladder cancer associated with occupation, we used available data from a nationwide case-control study titled IROPICAN. For this work, we used information from 717 bladder cancer cases, 658 lung cancer cases, and 3477 control subjects from the main study. Collected data included occupational history and information on tobacco smoking, opium use, and history of respiratory and urinary tract diseases. Unconditional logistic regression was applied to assess the risk of lung and bladder cancer associated with the major occupational group (ISCO68) and some occupations at high risk for lung and bladder cancer, adjusted for known confounders.

An inverse association of lung cancer has been observed among male workers in some white-collar occupations, while working as plant and machine operators, and elementary occupations increased the risk. All associations attenuated after adjustment for smoking and opium consumption. Increased risk of lung cancer has been found among male construction and petroleum industry workers, and female farmers, and bakers.

A reduced risk of bladder cancer has been observed for some white-collar occupations, while working as plant and machine operators, and elementary occupations increased the risk of bladder cancer. Also,

increased risk of bladder cancer was observed among metalworkers and a group of occupations with a high probability of exposure to aromatic amines.

In this study joint effects between construction work and smoking, and opium consumption for lung cancer risk, as well high-risk occupations for aromatic amines exposure and individual substance use for bladder cancer risk has not been found.

In summary, occupational cancer studies in Iran need to be expanded in terms of both epidemiological and exposure monitoring studies. Therefore, a coherent strategy to identify potential sources of exposure data in Iran industries and subsequently estimate occupational cancer burden in high-risk occupations such as petroleum industry, metal working industries, construction industry, and high-risk occupations for aromatic amines exposure is necessary. The result of this study also demonstrates the need for interdisciplinary collaboration across disciplines, e.g., hospitals, cancer registries, universities, and relevant ministries to support occupational research and exposure control in Iran.

Résumé en Français

À ce jour, la plupart des preuves des risques de cancer professionnels proviennent d'études épidémiologiques menées dans des pays développés. Bien que l'Iran soit un pays industrialisé et que les travailleurs puissent être exposés à divers agents cancérigènes, seules quelques études ont été réalisées pour décrire les profils d'exposition et le risque de cancer associé. Cette thèse avait donc pour objectif de caractériser les expositions professionnelles en Iran et d'étudier le risque de cancer du poumon et de la vessie selon différents types de professions dans cette même région.

D'après la littérature, nous avons constaté que les recherches épidémiologiques en milieu professionnel en Iran ont débuté au cours des dix dernières années. Les études sont limitées et ne permettent pas de fournir une vue d'ensemble complète des modèles d'exposition et des risques de cancer importants en Iran. La plupart des études épidémiologiques sont de petites tailles dans lesquelles les expositions étaient attribuées aux travailleurs en fonction de leurs intitulés d'emploi. Quelques études de surveillance de l'exposition ont été menées dans des industries telles que l'industrie pétrolière, métallurgique, plastique et la construction, où les expositions ont été mesurées à l'aide d'un échantillon unique par le biais d'un échantillonnage d'air individuel et stationnaire.

Par la suite, nous avons évalué le risque de cancer du poumon et de la vessie selon les professions occupées, en utilisant les données de la large étude cas-témoins nationale IROPICAN. Au total, 717 cas de cancer de la vessie, 658 cas de cancer du poumon et 3477 témoins ont été inclus de l'étude principale.

Les données collectées incluait des informations détaillées sur les antécédents professionnels, le statut tabagique, la consommation d'opium, ainsi que les antécédents de maladies respiratoires et des voies urinaires. Nous avons appliqué un modèle de régression logistique non conditionnelle pour évaluer le risque de cancer du poumon et de la vessie associé à des groupes de professions (CITP-68) et à certaines professions à haut risque pour le cancer du poumon et de la vessie, ajusté sur des facteurs de confusion connus.

Chez les hommes, une association inverse entre certaines professions de type «col blanc» et le cancer du poumon a été observé, tandis que le travail d'opérateur d'usine et de machine, et les professions élémentaires étaient positivement associés au risque de cancer du poumon. Après ajustement sur le statut tabagique et la consommation d'opium, toutes les associations observées se sont atténuées. Nous avons également constaté un risque accru de cancer du poumon chez les hommes travaillant dans la construction et l'industrie pétrolière, ainsi que chez femmes agricultrices et boulangères.

Une réduction du risque de cancer de la vessie a été observée pour certaines professions de type «col blanc», tandis que le travail d'opérateur d'usine et de machine, et les professions élémentaires étaient positivement associés au risque de cancer de la vessie. De même, un risque accru de cancer de la vessie a été observé chez les métallurgistes et parmi un groupe de professions présentant une forte probabilité d'exposition aux amines aromatiques.

En résumé, les études sur les cancers professionnels en Iran doivent être étendues à la fois en termes d'études épidémiologiques et de surveillance de l'exposition. Par conséquent, une stratégie cohérente est nécessaire pour identifier les sources potentielles de données d'exposition dans les industries iraniennes et pour estimer le fardeau des cancers professionnels dans les

professions à haut risque, tel que l'industrie pétrolière, la métallurgie et la construction, ainsi que les professions à haut risque d'exposition aux amines aromatiques. Le résultat de cette étude démontre également la nécessité d'une collaboration interdisciplinaire pour soutenir la recherche en milieu professionnel et le contrôle de l'exposition en Iran et au-delà.

Résumé Substantiel

Bien que la proportion de tous les cancers attribuables aux expositions professionnelles ne soit pas très élevée au niveau de la population générale, la proportion de cancers évitables dans la population exposée à des agents cancérigènes professionnels est beaucoup plus élevée, notamment pour les cancers du poumon et de la vessie, connus pour être associés à l'exposition à certains carcinogènes. Evaluer l'exposition aux divers agents cancérigènes professionnels est un outil précieux pour permettre la mise en place de mesures de prévention et d'indemnisation pour les travailleurs exposés.

L'Iran est un pays industrialisé du Moyen-Orient, mais nos connaissances sur l'étendue de l'exposition professionnelle aux agents cancérigènes dans ce pays sont encore très limitées. Dans ce projet de thèse, nous avons cherché à caractériser les modèles professionnels en Iran et à étudier le risque des cancers professionnels les plus courants, les cancers du poumon et de la vessie, résultant de l'exposition sur le lieu de travail dans ce pays.

Une revue de la littérature conduite dans le cadre de ce travail a confirmé que l'étude des expositions cancérigènes professionnelles en Iran était un domaine de recherche récent et qu'il n'existait pas, actuellement, de données claires sur le profil des cancers professionnels ni sur l'évaluation de l'exposition aux agents cancérigènes en Iran.

Les études identifiées dans cette revue peuvent être divisées en deux types, à savoir les études épidémiologiques et les études de surveillance de l'exposition. Les études de surveillance de l'exposition ont été principalement menées dans certaines des principales industries en Iran, par exemple, l'industrie pétrolière, l'industrie métallurgique, l'industrie électronique,

l'industrie plastique, l'industrie de la construction et l'industrie des services. L'exposition a été mesurée sur des échantillons individuels par le biais d'échantillonnage d'air personnel et stationnaire. Il y a également eu quelques tentatives d'estimation du risque de cancer, en particulier du risque de cancer de la vessie associé à l'exposition professionnelle.

La plupart des études épidémiologiques étaient des études cas-témoins de petit effectif, et les expositions étaient attribuées aux travailleurs sur la base de leurs emplois/industries. De plus, ces études ont été développées pour évaluer d'autres facteurs de risque de cancer que les expositions professionnelles et manquaient d'information détaillées sur l'histoire professionnelle.

Pour évaluer le risque professionnel de cancer du poumon et de la vessie, nous avons analysé les données d'une étude cas-témoins iranienne à l'échelle nationale intitulée IROPICAN. Elle a été lancée pour évaluer le risque de quatre cancers (poumon, vessie, tête et cou, et colorectal). Les données de 717 cas de cancer de la vessie, 658 cas de cancer du poumon et 3477 témoins ont été utilisées pour ce travail.

Les données recueillies comprenaient des informations détaillées sur l'histoire professionnelle, la consommation de substances des individus, notamment le tabagisme et la consommation d'opium, les maladies respiratoires et les maladies des voies urinaires. Nous avons réalisé une régression logistique non conditionnelle pour évaluer le risque de cancer du poumon et de la vessie associée aux principaux groupes professionnels (CITP-68) et à certaines professions à haut risque de cancer du poumon et de la vessie.

En comparaison aux « cols blancs » et aux militaires, certains groupes de professions élémentaires avaient un risque de cancer du poumon plus élevé. Toutes ces associations étaient atténuées après ajustement sur le

tabagisme et la consommation d'opium. En outre, nous avons observé un risque accru de cancer du poumon chez les hommes travaillant dans le secteur de la construction et dans l'industrie pétrolière, ainsi que chez les agricultrices et les boulangères.

Dans ces industries, les travailleurs peuvent être exposés à diverses substances chimiques, notamment la silice cristalline, les gaz d'échappement des moteurs diesel, l'amiante et les hydrocarbures aromatiques polycyclique (HAP), tous connus pour être des agents cancérigènes. Quant au risque de cancer de la vessie, il a diminué dans les professions comprenant des travailleurs administratifs et des cadres, tandis qu'un risque accru a été observé dans les professions de conducteurs d'installations et de machines et dans les professions élémentaires.

Un risque accru de cancer de la vessie a également été observé dans les professions liées au travail des métaux, un groupe de professions présentant une forte probabilité d'exposition à certaines amines aromatiques, à savoir le 4-APB, la benzidine et ses métabolites, le 2 NA et l'ortho-toluidine, qui ont été identifiés comme cancérogènes avérés (groupe 1 du CIRC) pour le cancer de la vessie chez l'homme. Il semble qu'en plus des amines aromatiques, certains HAPs puissent également augmenter le risque de cancer de la vessie dans les professions susmentionnées.

Nous n'avons pas observé d'effets conjoints entre le travail dans le secteur de la construction et la consommation de substances individuelles, à savoir le tabac et l'opium, pour le risque de cancer du poumon, bien que les effets synergiques du tabagisme en plus d'expositions professionnelles uniques, comme l'amiante, aient été démontrés dans des études antérieures. De même, aucun effet synergique n'a été observé entre la consommation individuelle de substances et l'exercice d'une profession à haut risque pour l'exposition aux amines aromatiques, pour le risque de cancer de la vessie.

Dans l'ensemble, les études sur les cancers professionnels en Iran doivent être étendues, tant en termes d'études épidémiologiques que d'études de surveillance de l'exposition. Par conséquent, une stratégie cohérente est nécessaire pour identifier les sources potentielles de données d'exposition dans l'industrie iranienne et pour estimer ensuite le fardeau des cancers professionnels dans les professions à haut risque, par exemple l'industrie pétrolière, l'industrie métallurgique, l'industrie de la construction et les professions exposées aux amines aromatiques.

Cette stratégie devra également viser à développer une matrice emplois-expositions pour l'Iran qui pourra être utilisée comme outil d'évaluation de base des expositions professionnelles pour de futures études épidémiologiques. Le résultat de notre étude démontre également la nécessité d'une collaboration interdisciplinaire pour soutenir la recherche professionnelle et le contrôle de l'exposition en Iran et au-delà.

Statement of original authorship

The work contained in this thesis has not been previously submitted to meet the requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, 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 International Agency for Research on Cancer / World Health Organization.

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program would have been begun. He has really pioneered this project by recognising the need of the country and the lack of knowledge in this field of research in Iran.

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Scientific production

In addition to my doctoral work, I also engaged in other activities to improve my knowledge and skills and build capacity. These included attending regular seminars and training courses for young scientists at IARC. One of the most important IARC courses is the summer school on Introduction to Cancer Epidemiology. Due to the pandemic, the course held online in June 2021. I also participated in an online course at the Nordic Institute for Advanced Training in Occupational Health (NIVA) called "Assessment of Cancer Risk."

Another precious experience during my PhD was attending the IARC Monographs meetings. The goal of the programme is to produce scientific reviews and assessments of evidence for the carcinogenicity of a wide range of substances with the participation of international, interdisciplinary working groups of experts. The monographs evaluate the strength of available evidence that a substance can cause cancer in humans based on three types of evidence: Cancer in humans, in experimental animals, and mechanistic evidence.

During my doctoral studies, I participated in two monographs, as a member of the secretariat involved in the preparation of the preliminary documents before and during the meetings. Session of monograph 126 on opium consumption assessment, September 10-20, 2020, held online, and session of monograph 132 on occupational exposure as a firefighter, June 7-14, 2022, held in person. Opium consumption strongly associated with cancers of the larynx, lung, and urinary bladder. Based on available epidemiologic data, the working group concluded that a causal association

exists between occupational exposure as a firefighter and mesothelioma and bladder cancer.

I have also had the opportunity to present the results of my thesis finding in congress and seminars, such as la 26e Journée Scientifique de l'EDISS November 2022, Second International Congress of Industrial and Environmental Toxicology in November 2020, the 7th All-Russian Congress of Occupational Physicians in Vladivostok in September 2021, the 28th International Symposium of Epidemiology in Moscow, and the 3rd All-Russian Congress of Occupational Physicians in Moscow. International Symposium on Epidemiology in Occupational Medicine (EPICOH) in October 2021, and at the 34th Annual Conference of the International Society for Environmental Epidemiology (ISEE 2022) in Athens, Greece, September 18-21, 2022.

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Preface

This thesis is the original final work of my Ph.D. study of EDISS doctoral school, university Lyon 1, under supervision of Dr. Joachim Schüz and co-supervision of Dr. Ann Olsson, and Professor Kazem Zendehdel conducted at the Environment and Lifestyle Epidemiology Branch (ENV) of the International Agency for Research on Cancer- World Health Organization (IARC-WHO). This thesis has been prepared in ENV of the Agency for Research on Cancer (IARC), 150 cours Albert Thomas, 69372 Lyon Cedex 08, France in collaboration with Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran.

Chapter 1 presents the background of my dissertation topic on the history of occupational cancers worldwide and in Iran. Following by the etiology of lung and bladder cancers. At the end of this chapter, the IROPICAN study on which this thesis is based is described in detail. Chapter 2 of this dissertation which has been published as a review paper in *Cancers* journal, provides a comprehensive overview of epidemiological studies on occupational cancers and exposure surveillance studies with projection of cancer risk in Iran and describes how relevant exposures were assessed and assigned to workers in these studies. In Chapter 3, the risk of lung cancer associated with occupations based on the results of IROPICAN study has been evaluated, the results of this chapter already published in *Journal of Occupational and Environmental Medicine*. Chapter 4 of this thesis is devoted to the bladder cancer results of the IROPICAN study. This dissertation ends with a conclusion, recommendations, and implications of the whole project.

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List of abbreviations

Acronym	Definition
4-APB	4-aminobiphenyl
BTEXs	Benzene, toluene, ethylbenzene, and xylene
CAREX	CARcinogen Exposure
CI s	Confidence Intervals
ENT	Ear/Nose/Throat
FINJEM	Finnish Job-Exposure Matrix
GCS	Golestan Cohort Study
HICs	High-Income Countries
IARC	International Agency for Research on Cancer
ICD-O	International Classification of Diseases for Oncology
IHC	ImmunoHistoChemistry
ILO	International Labour Organisation
ISCO-68	International Standard Classification of Occupations
INPCR	Iranian National Population-Based Cancer Registry
LMICs	Low- and Middle-Income Countries
2-NA	2-Naphthylamine
NIMAD	National Institute for Medical Research Development, Islamic Republic of Iran
NOCCA -JEM	Nordic Occupational Cancer Study- Job-Exposure Matrix
OR	Odds Ratios
RERI	Relative Excess Risk due to Interaction
SCC	Squamous Cell Carcinoma
SCLC	Small Cell Lung Carcinoma
SSH	Secure Shell
UICC	The Union for International Cancer Control
UTIs	Urinary Tract Infections
UTSs	Urinary Tract Stones
WHO	World Health Organization

Chapter 1: Background

1.1 CANCER STATISTICS

Cancer is the second leading cause of death worldwide, estimated at 9.8 million deaths in 2020. Lung, prostate, colorectal, stomach, and liver cancers are the most common cancers in men, while breast, colorectal, lung, cervical, and thyroid cancers are the most common in women, see figure 1.1- 1.2 [1].

Figure 1.1. Estimated number of new cancer cases in 2020, worldwide, males, all ages

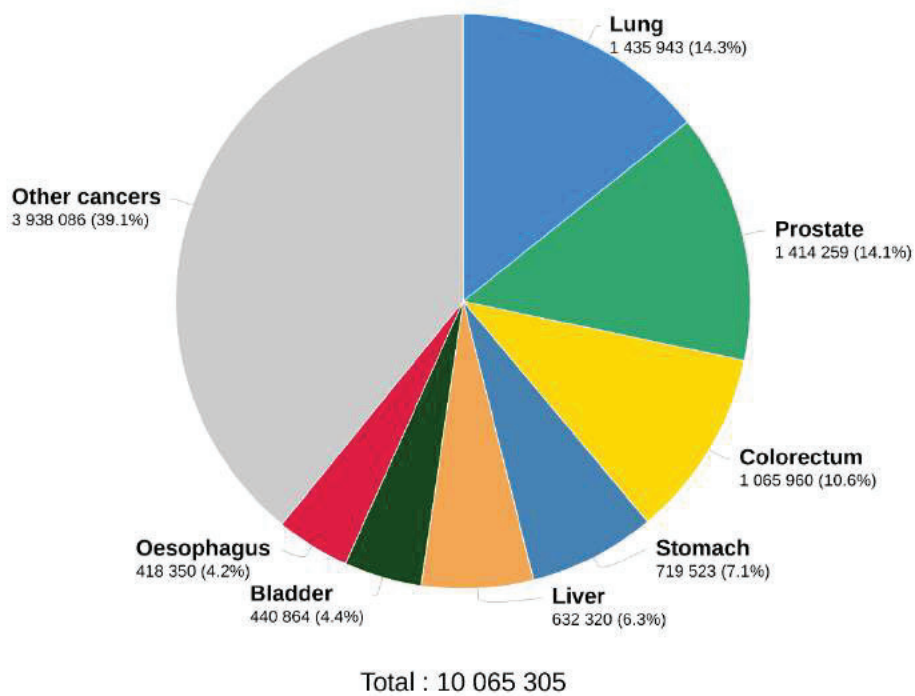
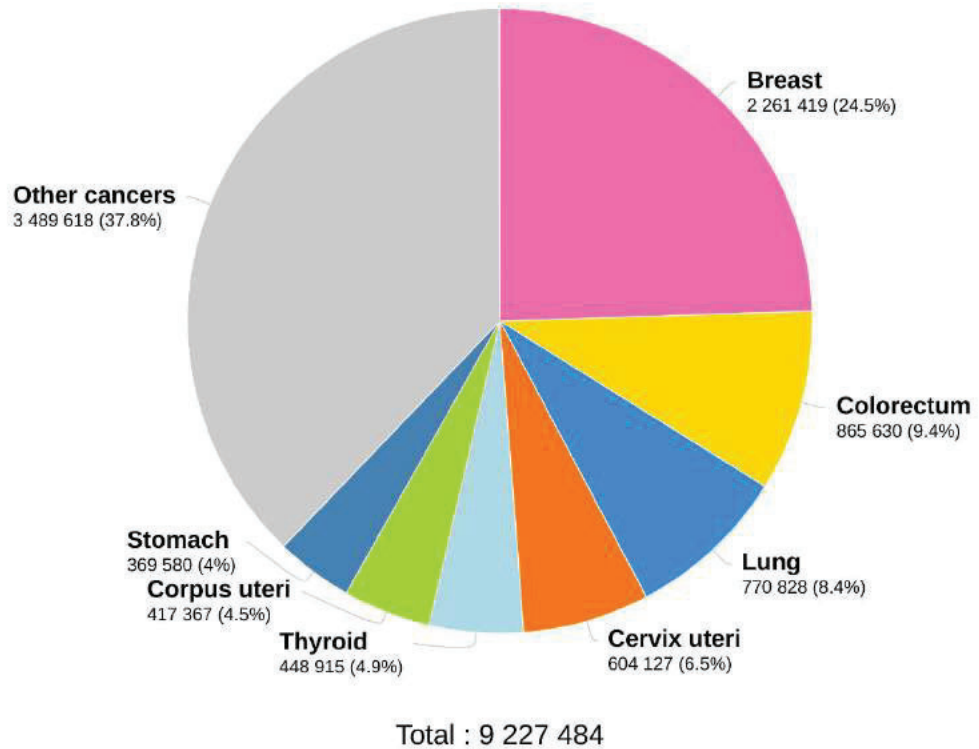


Figure 1.2. Estimated number of new cancer cases in 2020, worldwide, females, all ages



In Iran, the first official pathology-based cancer registry was introduced in 1968. In 2010, an Iranian national population-based Cancer Registry (INPCR) was established in collaboration with IARC. A 2020 INPCR report showed that the most common new cancer cases in Iran were stomach, prostate, lung, colorectal, and bladder cancer in men, while breast, stomach, colorectal, lung, and thyroid cancers were the most common in women [2, 3]. Liver cancer is among the five most common cancers in men in the world, surpassed by bladder cancer in Iran. Elsewhere, cancers in men are similar but in a different order. In women, cervical cancer is among the 5 most common cancers in the world, while in Iran it is surpassed by stomach cancer, and the order of 3 to 5 most common cancers is different, see figure 1.3- 1.4 [4]. These differences in cancer burden across regions suggest that the prevalence of risk factors may also differ between countries [5-7], some studies have shown that the prevalence of smoking have been on the increase in Iran, a rising prevalence of sedentary lifestyles and westernized diet in the

country, may contribute to an increasing burden due to changes in risk. Research into region-specific modifiable cancer risk factors should therefore be an important priority.

Figure 1.3. Estimated number of new cancer cases in 2020, Iran, males

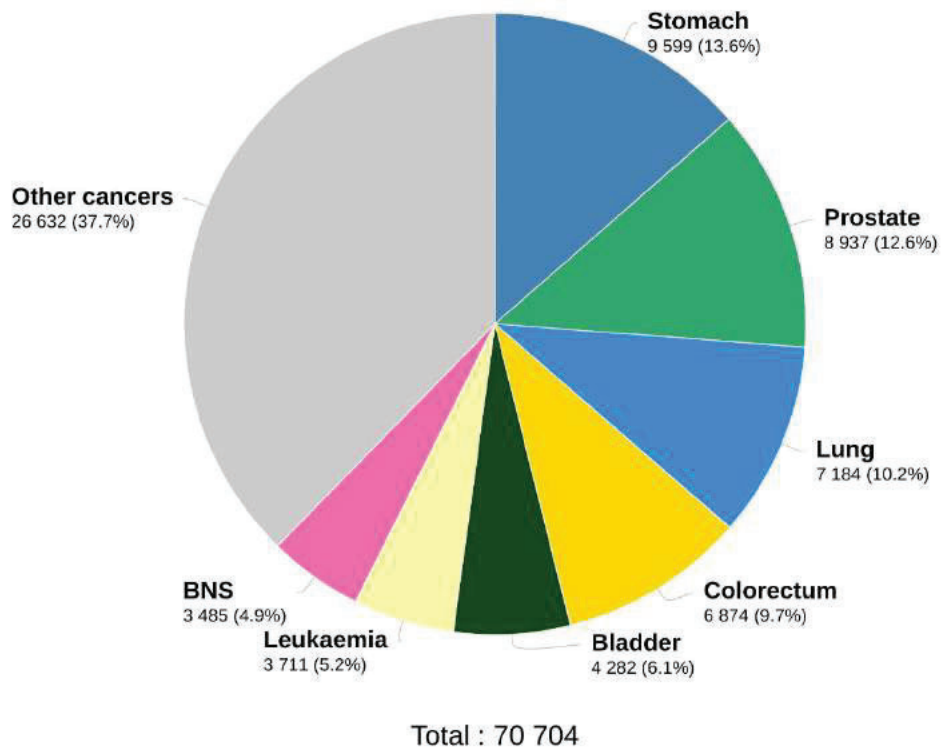
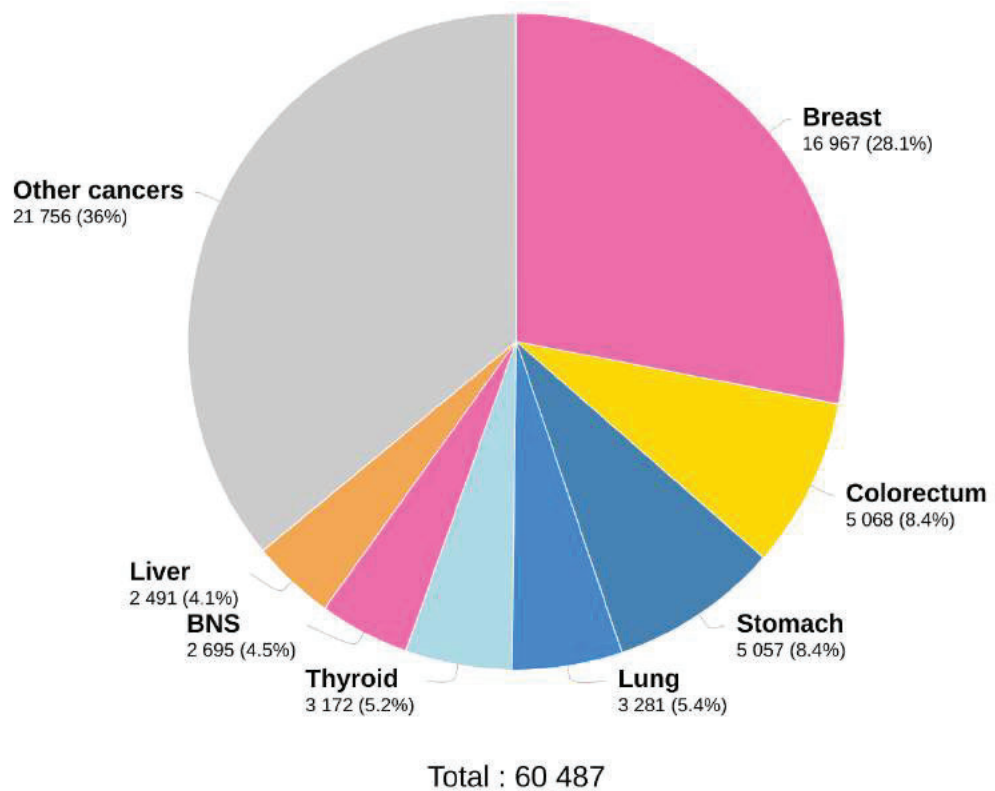


Figure 1.4. Estimated number of new cancer cases in 2020, Iran, females



1.2 OCCUPATIONAL CANCER HISTORY

The history of occupational cancer studies dates back to 1775 when Sir Percivall Pott reported the number of cases of scrotal cancer in English chimney sweeps [8]. By the early nineteenth century, the carcinogenicity of "pitch, tar, and tarry substances" was known to be an occupational skin cancer risk and was officially considered compensable in exposed workers in the United Kingdom. Following scientific evidence in the late nineteenth century that exposed workers in metal mines and coal tar production had unusually high incidences of lung and bladder cancer, etiologic studies began in the early twentieth century to determine the causes of cancer among workers. In the early days of modern cancer epidemiology, some important studies were conducted in industry, such as workers in the gas industry [9], asbestos industry workers [10], and chemical production industry workers [11]. Since then, epidemiological studies in workplaces have contributed significantly to the understanding of human carcinogenesis[12-19].

In 1972, the IARC Monographs the identification of carcinogenic hazards for humans, reviewed the published evidence on occupational exposures by interdisciplinary working groups of expert scientists. In 2009, some chemical agents and related occupations were finally classified by the IARC Working Group on Monographs [20].

Workers are at risk of exposure to high levels of many potentially hazardous substances in the workplace. However, many occupational hazards can also occur in the general population. This means that cancer risks from workplaces have a significance that extends beyond the workplace. On the other hand, almost half of all identified human carcinogens are occupational carcinogens. They affect many types of cancer [21]. It is noteworthy that occupational cancers are among the most preventable cancers due to the high likelihood of modifying exposure to carcinogens in industrial settings.

According to a 2015 global estimate, cancer accounts for a quarter of all work-related deaths [22]. The percentage of work-related cancer deaths was highest in high-income countries, where it reached 52% of work-related deaths [23-25]. A classic publication by Doll and Peto estimated that in 1980, 4% (uncertainty range 2-8%) of cancer deaths in the US population were attributable to occupational exposures [26]. Decades later, in 2005, Rushton et al. estimated that 5.3% of cancer deaths (8.2% in men, 2.3% in women) in the UK were attributable to occupational exposure [27], and in 2015, Marant Micallef et al. estimated that 2.3% of cancer deaths (3.9% in men and 0.4% in women) in France were attributable to occupational exposure [28]. Of all cancers, lung cancer, mesothelioma, and bladder cancer are generally the most common occupationally related cancers [28, 29], while the proportion attributable to occupational exposures is also high for nasopharyngeal and sinonasal cancers [28, 30]. Despite the importance of this issue, data on

occupational cancers in industrialised countries, including Iran, have not been available until recently, although occupational exposure is increasing in these countries.

1.2.1 Industries and occupational cancer in Iran

Almost 60% of the Iran's economy is centrally involved in gas and oil production. Iran hosts 10% of the oil reserves and about 15% of the gas reserves in the world, ranking the country as one of the world's oil provider. Given that the largest industries in Iran are petroleum, followed by the manufacture of motor vehicles and pharmaceuticals; mining and quarrying, especially copper and aluminium; and the manufacture of metals and rubber and plastic products [31]. Workers in these industries may be exposed to various known or suspected carcinogens such as BTEXs (benzene, toluene, ethylbenzene, and xylene), aromatic amines, crystalline silica, and heavy metals. Legislation and national efforts to reduce the burden of occupational cancers require evidence-based information on exposure to carcinogens and associated cancer risks among Iranian workers [32].

To date, evidence for this estimate is derived mostly from the epidemiological studies carried out in high-income countries and relevant evidence from Iran industries are limited to a few studies.

One of those studies, estimated that the attributable risk of lung cancer to occupational environment exposure to silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium, and asbestos was 12%. However, this estimation is based on industrial and occupational statistics reported to the International Labour Organisation (ILO), in which the estimated proportions of exposed workers in those industries came from the European CARcinogen Exposure (CAREX) databases, and relative risk

estimates from the international literature [33, 34], resulting in large uncertainties.

Even though industries in Iran has experienced rapid growth in recent decades to our knowledge, the presence of occupational carcinogens in workplaces has not been well characterized, and very little is known about the burden of occupational cancers in Iran [35]. However, epidemiological studies in various industries within the country could have a substantial impact to broaden available occupational cancer knowledge.

1.3 LUNG CANCER

Lung cancer is the leading cause of cancer mortality. Globally, lung cancer represents 14.3%, and 8.4% of all new cancer cases among men, and women and 21.5% and 13.7% of total cancer deaths among men and women [1]. Figures 1.5 and 1.6 shows the worldwide incidence map of lung cancer by sex.

Figure 1.5. Estimated age-standardized incidence rates worldwide in 2020, female lung cancer

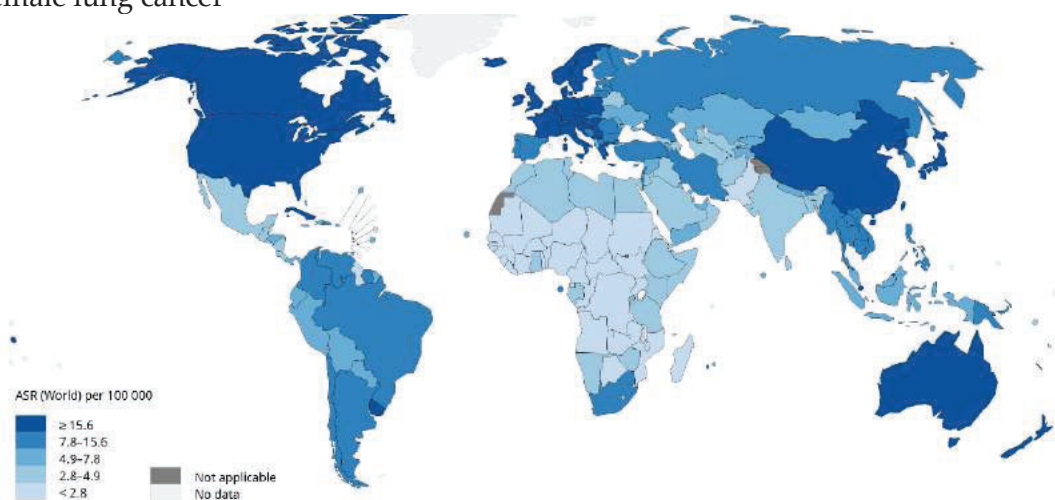
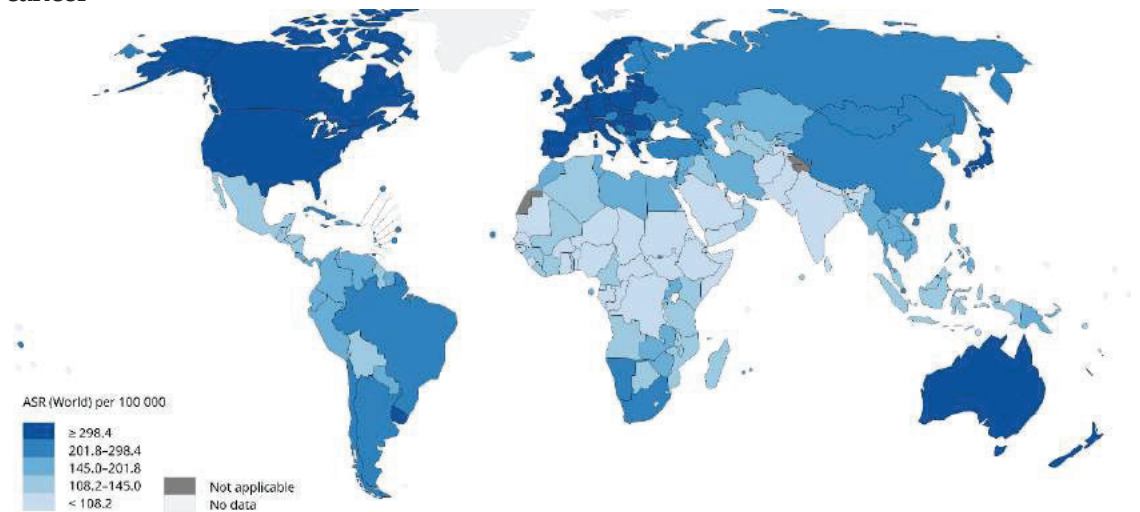


Figure 1.6. Estimated age-standardized incidence rates worldwide in 2020, male lung cancer



1.3.1 Lung cancer etiology

Decades of research have identified many causal risk factors for lung cancer, including tobacco smoking, opium consumption, radon exposure, other occupational exposures (e.g., asbestos), and outdoor air pollution [36].

Tobacco smoking

Cigarette smoking is the leading cause of lung cancer, with 1.19 million lung cancer deaths attributable to smoking worldwide in 2017. Estimated attributable fraction of tobacco smoking on lung cancer is more than 80% [37, 38]. Lung cancer does occur among never-smokers, at estimated rates between 5–10 cases per 100,000 population, but by contrast, the rates in smokers are as much as 20–30 times higher [39, 40]. To date the joint effects of some of occupational carcinogens and smoking in relation to the risk of lung cancer has been reported [41-43].

Opium consumption

Iran accounting for 42% of global opium consumption [44]. In 2020 IARC Monographs Working Group classified opium consumption as “group 1 carcinogenic to humans” according to sufficient evidence of carcinogenicity in humans. A positive association has been established for cancers of the larynx, lung cancer [45]. In the Golestan Cohort Study (GCS), the risk of lung cancer has been reported 2.2 among ever users of opium and a positive trend ($p < 0.0001$) for cumulative consumption were observed [46].

Opium, derived from the juice (latex) of the unripe seed pod of the poppy plant, is a highly addictive narcotic drug. A minimal amount of processing of the latex is required before it can be consumed. The traditional methods of processing the latex vary from place to place and may include drying in the air, drying with heat, or boiling [47, 48]. The main forms of opium are raw or crude opium, opium dross, refined opium, and other derivatives. In ancient times, opium was usually taken orally. However, after the introduction of the tobacco pipe in the 17th century, smoking opium became a popular method of opium consumption. In many countries, including Iran, smoking opium remains a common and preferred method of opium use [49, 50]. Iran accounting for more than 40% of global opium consumption [44]. In 2020 the IARC Working Group found “sufficient evidence” for the carcinogenicity of opium consumption in relation to bladder [45]. Smoking is the most common method of opium use in Iran (90.9 %). It is followed by oral consumption (8.8 %). Three-quarters of respondents to the survey described above reported smoking sukhteh and shireh as the predominant route of use. Ingestion was reported as the predominant route of sukhteh and shireh use by the remaining quarter [51].

Occupational Exposure

Although, smoking is the most important cause of lung cancer in general population, lung cancer is the most prevalent cancer associated with occupational exposure[52, 53]. Previous study found that occupational exposures were one of the important risk factors for lung cancer among never smokers[54, 55]. Chemicals known to increase the risk of lung cancer i.e., asbestos, chromium, nickel, silica, cadmium, arsenic, and beryllium, some of the most important occupation, industries or process that increases the risk of exposure to these chemicals including aluminium production, coal gasification/ destination, underground hematite mining with exposure to radon, metal manufacture, painter, rubber industry workers, welding [56].

Radon exposure

Radon exposure increases the risk for lung cancer. Radon is the leading cause of lung cancer in non-smokers and the second leading cause of lung cancer in smokers [57-59]. Strong evidence from multiple sources supports the causal association of exposure to radon in lung cancer in never smokers [58]. There is evidence that smoking synergistically modifies the carcinogenic effect of radon. Thus, indoor radon exposure might be an important cause of lung cancer [59]. In Iran, radon measurements were carried out intermittently in a few provinces such as Tehran, Tabriz, Shiraz, Ramsar. Despite some scattered regional surveys of indoor radon measurements, no radon mapping has been carried out in Iran using frequent monitoring [60].

Respiratory disease

The result of previous studies shows that respiratory disease i.e., chronic bronchitis and emphysema are positively associated with lung cancer. The positive association between pneumonia and lung cancer was also significant and even stronger when the diagnosis was made less than 2 years before the lung cancer diagnosis, compared with longer intervals [61, 62]. Also, previous studies found association between tuberculosis infection and adenocarcinoma lung cancer, but not squamous or small cell carcinoma. There was a stronger association with increasing the number of pulmonary diseases history (chronic bronchitis, emphysema, and pneumonia)[63, 64].

Other predisposing risk factors

Epidemiological studies show that waterpipe smoking trends as a local phenomenon among youth in the Middle East has become a global trend [65, 66]. The route of exposure is through the inhalation of smoke. A systematic review and meta-analysis in 2017, showed increased risk of lung cancer in water pipe smokers [67]. Second hand smoking is another risk factor for lung cancer as increased risk has been reported previously [68]. In many parts of the world, biomasses e.g., wood is burned for cooking and heating purposes, which produce a number of chemical components including the polycyclic aromatic hydrocarbons (PAHs). Household air pollution from burning biomass, is an important attributable risk factor for lung cancer in low- and middle-income countries (LMICs), due to being exposed to the PAHs chemical components [69-72]. In addition to the all behavioural and environmental risk factors for lung cancer, substantial evidence exists to support genetic susceptibility to lung cancer [73, 74].

1.3.2 Histological subtypes

Adenocarcinoma is the predominant lung cancer subtype among all lung cancer subtypes worldwide, followed by squamous cell carcinoma (SCC), small cell lung carcinoma (SCLC), and large cell carcinoma (LCC) [75, 76]. The other subtypes including lymphoproliferative tumours, and other miscellaneous tumours are relatively rare [77].

During the past decades, there has been a shift in the histological subtype due to changing the pattern of tobacco smoking worldwide. Smoking has a strongest association with SCC and SCLC. In the 1950s, SCC was the predominant among smokers, while adenocarcinoma was most frequent in never-smokers. In high-income countries during 1960s, the frequency of adenocarcinoma gradually had been increased, while SCC decreased.

1.4 BLADDER CANCER

Bladder cancer is the sixth cause of cancer incidence worldwide in men. Globally, bladder cancer contributes to 4.4% of total new cancer cases among men [1]. Figures 1.7 and 1.8 show the worldwide incidence map of bladder cancer by sex.

Figure 1.7: Estimated age-standardized incidence rates worldwide in 2020, male bladder cancer

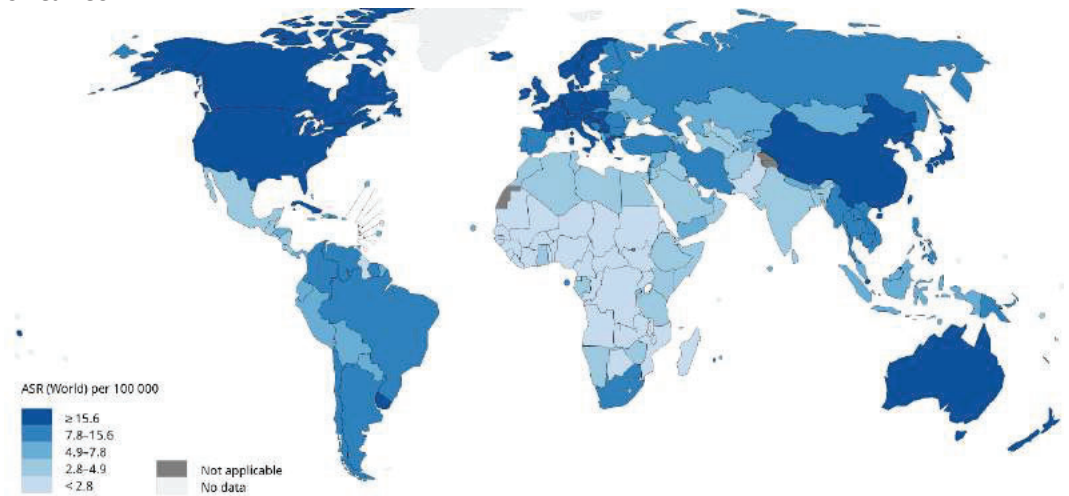
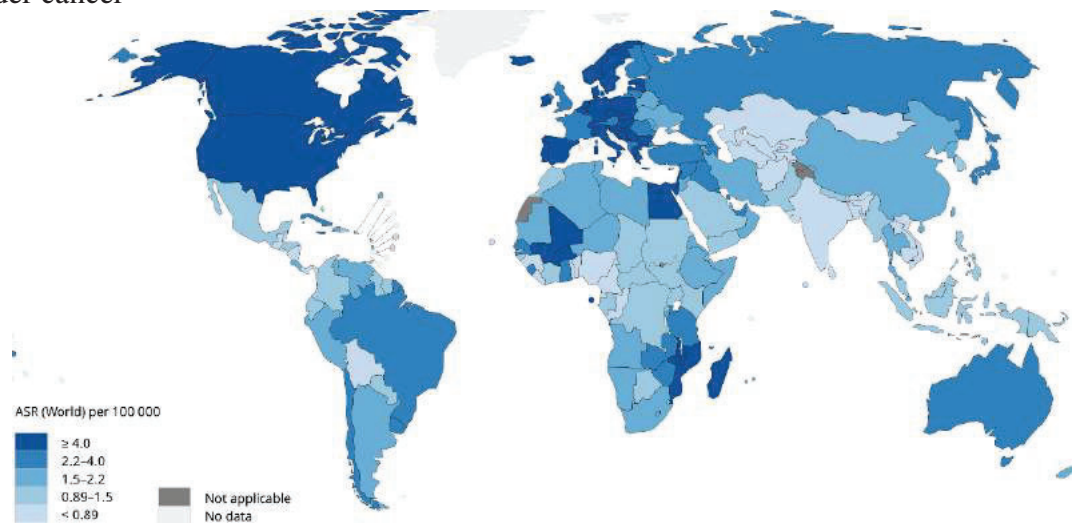


Figure 1.8: Estimated age-standardized incidence rates worldwide in 2020, female bladder cancer



1.4.1 Bladder cancer etiology

Previous studies have identified many risk factors for bladder cancer, including tobacco smoking, opium consumption, occupational exposures, urinary tract disease including urinary tract infections (UTIs), and urinary tract stones (UTSs), and some environmental exposures i.e., Arsenic in drinking water.

Smoking

Tobacco smoking is by far the greatest risk factor for bladder cancer, accounting for approximately 50-65% of new cases each year. Smoking has been shown to increase the risk of bladder cancer by three to four times [78]. Previous studies suggested that 2-naphthylamine (2-NA) and 4-aminobiphenyl (4-APB) may be the bladder carcinogens components presented in cigarette smoke [79-81].

Opium consumption

Opium, derived from the juice (latex) of the unripe seed pod of the poppy plant, is a highly addictive narcotic drug. A minimal amount of processing of the latex is required before it can be consumed. The traditional methods of processing the latex vary from place to place and may include drying in the air, drying with heat, or boiling [47, 48]. The main forms of opium are raw or crude opium, opium dross, refined opium, and other derivatives. In ancient times, opium was usually taken orally. However, after the introduction of the tobacco pipe in the 17th century, smoking opium became a popular method of opium consumption. In many countries, including Iran, smoking opium remains a common and preferred method of opium use [49, 50]. Iran accounting for more than 40% of global opium consumption [44]. In 2020 the IARC Working Group found “sufficient evidence” for the carcinogenicity of opium consumption in relation to bladder [45]. Smoking is the most common method of opium use in Iran (90.9 %). It is followed by oral use (8.8 %). Three-quarters of respondents to the survey described above reported smoking sukhteh and shireh as the predominant route of use. Ingestion was reported as the predominant route of sukhteh and shireh use by the remaining quarter [51].

Occupational Exposure

Exposure to the industrial chemicals is the second important risk factor for bladder cancer occurrence following tobacco smoking [82]. Previous studies have estimated that this may account for around 20% of bladder cancer cases, mainly in patient with the history of working as painter, dye, metalworkers, and petroleum products workers [56, 83]. Chemicals known to increase the risk of bladder cancer include aniline dyes, 2-NA, 4-APB, xenylamine, benzidine, o-toluidine[84, 85]. Occupations linked to an increased risk of bladder cancer are manufacturing jobs involving dyes, textiles, rubbers, paints, plastics, leather tanning[86, 87]. Some occupations have been associated to an increased risk of bladder cancer including taxi or bus drivers, as a result of regular exposure to diesel engine exhaust[88].

Urinary tract disease

A clear correlation has been observed between *Schistosoma haematobium* infection and bladder cancer [89, 90], but the role of other disease including UTI and UTS has been associated in some epidemiological studies is not clear [91-93].

Arsenic in drinking water

Some epidemiological studies show the association between exposure to arsenic in drinking water and bladder cancer risk [94-96].

Genetic risk factors

Previous studies have been reported association between genetic susceptibility and bladder cancer risk [97-100], also interaction between genes and occupational exposures has been observed [101].

1.4.2 Histological subtypes

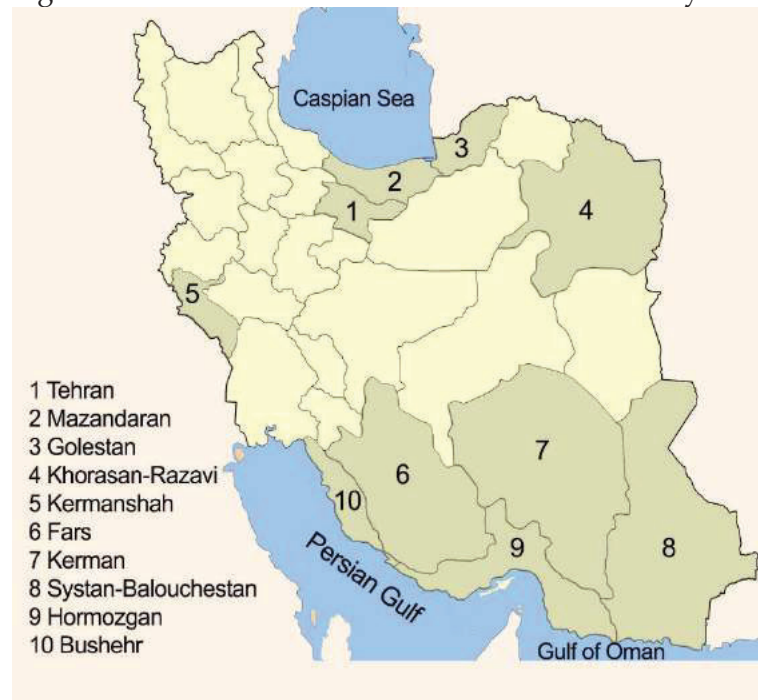
Urothelial cell bladder cancer is the predominated subtype of bladder cancer accounted for 90% of all cases that associated with exposure occupational chemicals and smoking [102]. 5% of cases counted for squamous cell carcinoma which mostly is due to schistosomiasis infection in endemic areas [89, 103]. The remain subtypes including adenocarcinoma and sarcoma [102].

1.5 IROPICAN STUDY

The IROPICAN study is a large nationwide case-control study that was initially conducted to investigate associations between opium consumption and the risk of various cancers of lung, bladder, head and neck, and colorectal. The study was conducted in 27 participating centres in ten provinces out of 22 across the country between 2016 to 2020. The provinces were chosen in a way to represent the different geographical and cultural areas of the country and included the capital of Iran Tehran, which accommodates almost 10% of the country's population.

The response rate was 99% among cases and 89% among the controls. The main reasons for non-participation were sickness and lethargy among cancer patients, and lack of time or unwillingness to donate a biological sample among controls.

Figure 1.9. Collaborative centres in IROPICAN study



1.5.1 Study populations

Cases and controls selected from referral hospitals and clinics in collaborative provinces. Cases and controls were current residents (at latest three years before recruitment) of Tehran, Kerman, Fars, Khorasan- Razani, Mazandaran, Kermanshah, Bushehr, Sistan Baluchistan, Hormozgan, and Golestan provinces (Figure 1.9), and above 18 years old.

We recruited eligible cases from referring cancer centres in each of the ten participating provinces. Normally, due to the diagnostic and treatment facilities for cancer patients, all patients attend the same referral hospital in each province, regardless of their socioeconomic background. To reduce selection bias, emergency departments and maternity wards were excluded from the control recruitment. The referral pattern of these wards is more likely to depend on residential area. Therefore, the study participants were recruited from units such as cardiology, neurology, ophthalmology, orthopaedic,

general surgery, obstetrics and gynecology, hematology, ear/nose/throat (ENT), rheumatology, neurosurgery, and endocrinology.

The interviews were only done with alive cases after diagnoses. Patients with cancer metastases, second primary cancers, and those without a confirmed pathology report were excluded.

They were incident cases (diagnosed less than a year before enrolling into the study), histologically confirmed according to the International Classification of Diseases for Oncology (ICD-O-3) including following topography (lung (C33-34), bladder (C67), head and neck (C03-06, C10-C14, and C32), and colorectal (C18-21)) [104].

For each case at least one control was recruited in the same hospital, frequency-matched by 5-years interval of the case's age (age \pm 5 years), sex, and place of residence. Controls were hospital visitors who were relatives or friends of hospitalized patients in non-oncology wards in the hospital.

Overall, 3299 cases (four cancer sites including lung, urinary bladder, colorectal, and head and neck cancer) and 3477 controls including (2,398 male, and 1,079 female controls) were enrolled in IROPICAN study.

Since lung and bladder cancer are the most common occupational cancer worldwide[105], we decided to analyse the data of lung and bladder cancer patients collected within the IROPICAN study. A total of 658 lung cancer and 717 bladder cancer patients and 3477 controls were ascertained as eligible individuals to participate in the study. Out of 744 lung cancer cases we included 658 cases. 86 cases who were diagnosed as primary cases at the interview date has been excluded, but during quality control of histopathological data via ImmunoHistoChemistry (IHC) revealed an alternative diagnosis e.g., mesothelioma. All 3477 controls were included for the analysis on occupational data.

1.5.2 Data collection and quality control of the data

After obtaining written informed consent from participants, the information was gathered through semi-structured questionnaire, through face-to-face interview by trained interviewers. The questionnaire includes information on demographic data, history of opium and tobacco, and alcohol consumption, socioeconomic status, and occupation history (appendix A). The data was entered into the web-based questionnaire for each participant by the end of the day in each collaborative centre.

Generally, the quality control of the data was done regularly by executive managers (manage the field work and data collection) in each collaborative centre. For each subtitle of data, the quality control was done by specific corresponding researcher assistant in Cancer Research Centre, Cancer Institute in Tehran. For instance, quality control of collected data e.g., occupational history, history of opium and tobacco use, were regularly checked and followed up by the responsible researchers.

The output of the databases from the web-based questionnaires for analysis is available in Excel worksheet format, 45 variables related to the occupational history are available in the output excel file (more details provided in section 1.3.3).

Data protection

The owner of the database is "Cancer Research Centre, Cancer Institute of IR. Iran". NIMAD (National Institute for Medical Research Development, Islamic Republic of Iran) grant organization accepted the sponsorship of the IROPICAN study. Access to the data had been possible after requesting the data by researcher (Bayan Hosseini) with prove of her supervisors (Ann

Olsson, Joachim Schüz) in IARC to the principal investigator of IROPICAN study (Prof. Kazem Zendehdel) and other co-investigators in all collaborative centre. The data was transferred via FTPs over SSL/TLS which allowed to move data over a Secure Shell (SSH) data stream, providing excellent security. Upon receiving the data, it was stored based on the IARC data safety rules (data transfer agreement). The dataset stored into the internal server of IARC and were accessible for researcher and her supervisors by password protected computers. Physical securities are provided by the IARC building guards.

1.5.3 Data characteristic

Data information related to job/ industry/ history of participants was gathered through a semi-structured questionnaire by face-to-face interview. Study participants were asked to report up to three job/industry or other type of work circumstance (to capture housewives, etc.) history in detail. The occupational history, including job title, industry or company title, job tasks, age at start and finish for each job, and the duration of work (hours worked per day, days per week, and months per year) were also recorded. The list of variables included in data dictionary file (Appendix B). In addition to occupational information, data on demographics, clinical history such as respiratory infections, UTIs or UTSs family and personal history of cancer, physical activity, individual consumption history of tobacco smoking, alcohol and opium consumption were also collected. The detailed information related to those individual consumption including lifetime (ever/never), regular user (at least once a week for six consecutive months), current user (at least once a week during the last months), and the pattern and amount of consumption/ smoking during the regulate using period.

1.5.4 Ethics consideration

The IROPICAN study was approved by the Institutional Review Boards of National Institute for Medical Research Development (IR.NIMAD.REC.1394.027).

1.6 OCCUPATION HISTORY DATA IN IROPICAN STUDY

Iranian scientists have a long-standing relationship of collaboration with IARC, in May 2018 Iran joined IARC as a participating State. In the meantime, Iranian scientists expressed their interest to extent this field of research in collaboration with IARC scientists. That leads to initiation the Union for International Cancer Control (UICC) technical fellowship hosted by IARC in 2018 titled “A Study to Evaluate Association of Occupational Exposure and Risk of Lung Cancer Multicentre: A Case- Control Study”. During a month of fellowship in IARC under supervision of Dr. Ann Olsson, I acquired the knowledge of translation of job/ industry titles into the standard international code systems. In September 2019, under supervision of Dr. Joachim Schüz finally I joined EDISS doctoral school of University Lyon 1 as a PhD student to pursue education in occupational cancer epidemiology focusing on lung and bladder cancer risk associated to occupations in Iran using IROPICAN data. Therefore, we decided to exploit the occupational data available in the large-scale ongoing cancer epidemiology study entitled IROPICAN.

1.6.1 Preparation and data procedure of IROPICAN occupational data

For applying statistical methods and providing an approach to comparison the outcome from the study to other studies all over the world,

we needed to translate all job titles into international standard codes i.e. ISCO-68 at the 5-digit level [106]. Initially, international standard classification of occupations (ISCO) was developed by ILO to provide a unique classification of occupations to facilitate comparisons of occupations between various countries all over the world.

Therefore, all job title (up to three job history per each participant) into (ISCO-68, ISCO-88), and industry information translated into the International Standard Industrial Classification of All Economic Activities (ISIC, revision 2 and 4), in case if during the analysis we need the industrial codes.

The job/industry titles were coded based on complete digit-level for each international classification. The corresponding digit-level for ISCO-68 is five digits and for ISCO-88, ISIC rev.2 and ISIC rev.2 are including four digits. For this thesis project only the occupational based codes rather than industries codes were used. Since industrial sectors including variety of occupations and subsequently enormous tasks, the analysis was limited to the occupations.

The coding process has been done between the time of UICC technical fellowship in IARC and initiation of the PhD program (between October 2018 and September 2019), including all study participants including 3299 cases (four study cancer sites) and 3477 controls. Figure 1.10 shows the screen capture of the coded IROPICAN occupational history.

Given that, the mean ages of IROPICAN participants including cases and controls are above 57.8 assumed, ISCO-68 classification is the best fit to classify all occupations held by this study population.

Figure 1.10: Screen capture of IROPICAN occupational history

PID	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl	LastJobIncl
55220006	AA03	AA03		بازنشسته تامین اجتماعی	AA003	AA03	3692	2394	راندند کامیون کارخانه سیما	98560	8324	8200	6510					39550	3432	
22241061	1110	0161		سرکارگر کشاورزی	60010	6111	9331	8610	منشی پزشکی	39430	4222	9310	8510					37090	4142	
22211336	6200	4711		مغازه دار (لوازم خانگی)	45130	5220	7191	7911	مدیریت تاکسی تلفی	21110	1319	7200	6100					85620	7244	
77220042	5819	2592		جوشکاری	87210	7212	3220	1392	خیاط	79100	7433	3813	2512					72430	8122	
44210280	9310	8521		آموزش و پرور	13210	2320	9310	8530	مسئول گزینش دانشگاه آزاد	58900	5169	9100	8412					20110	1130	
33240507	1110	0125		کشاورزی	61230	6112	AA03	AA03	بازنشسته شرکت فولاد	AA003	AA03	5710	2410					21990	1229	
33240208	1110	0110		کشاورزی	61220	6111	AA03	AA03	بازنشسته آموزش و پرورش	AA003	AA03	9310	8510					21950	1231	
22220881	5121	1079		کارخانه تصف	21980	1232	3121	1079	مدیر کارخانه کارخانه تصف	21980	1232	5832	2651					21980	1232	
22231452	1110	0124		باغداری	61230	6112	1110	0140	دامداری	61240	6121	9310	8510					13320	2331	
22241325	1110	0124		باغداری	61230	6112	9100	8422	کارمند فرمانداری	39310	4110	9310	8510					13320	2331	
44220595	9340	8890		خبریه	33990	4216	9310	8520	معاون دبیرساز اداره آموزش	21990	1229	9310	8510					13320	2331	
22210982	9310	8500		آموزش و پرورش	39310	4110	9310	8530	کارمند دانشگاه	39310	4110	9310	8510					13320	2331	
22240626	1110	0110		کشاورزی	61220	6111	3843	2910	مسئول انبار شرکت نفت	39141	4131	9310	8510					13320	2331	
22211124	1110	0150		کشاورزی و د	61110	6130	8322	6920	حسابدار	11010	2411	9310	8510					13320	2331	
22241055	9310	8500		معاون مدرسه	21990	1229	9310	8521	معلم ریاضی متوسطه	13220	2320	9310	8510					13320	2331	
22241411	1110	0110		کشاورزی	61220	6111	1120	0140	دامداری	61240	6121	9100	8412					11010	2411	
22211220	7113	4922		راندند سرویس	98530	8322	6200	4772	فروشنده عمده فروشی دار	06810	3228	6200	4772					06810	3228	
33240429	5320	5100		کار mdf	81120	7422	7113	4922	راندند آژانس تلفی	98590	8322	6200	4772					07990	5241	
22230524	7113	4922		راندند تاکسی	98530	8322	3831	790	جوشکار و تاسیسات	87220	7212	5134	1104					42220	5416	
33230230	9331	8610		کارشناس هوشبری	07120	5231	9331	8610	بهار	59940	5132	9331	8610					52120	4115	
33230399	9340	8890		مدیرعامل موسسه خبریه	21990	1229	AA03	AA03	بازنشسته شرکت مس	AA003	AA03	2302	0729					53120	4122	
55220015	5000	4100		شرکت تعاونی	99310	4110	5411	1701	شرکت تعاونی	73490	8142	5000	4100					99140	4131	

The histopathology subtypes of all lung cancer cases were classified according to the fifth edition of WHO Classification of Tumours series, thoracic tumour volume; into two major groups of epithelial (including adenocarcinoma, SCC), neuroendocrine tumours, and other epithelial tumours) and non-epithelial tumours [107].

1.6.2 Aim and objectives the thesis

The aim of this study was to characterize occupational patterns in Iran and investigate the risk of lung cancer and bladder cancer arising from workplace exposures in this region. The thesis objectives were:

1. To describe the major occupation groups in Iran by sex and age group, geographical regions, and personal substance use (e.g., tobacco, opium). Refer chapter 2.
2. To assess the risk of lung cancer and bladder cancer in selected occupations in Iran. Refer to chapter 3 and 4.
3. To interpret findings from objectives 1 and 2 in the context of what is known about exposures encountered in those occupations and industries on a global scale and within Iran. Refer to chapter 5.
4. To develop recommendations to guide further investigations of occupational cancers in Iran. Refer to chapter 5.

1.6.3 Statistical analysis of occupational data

Descriptive analysis performed to assess distribution 5-years interval age group, residential area (10 participating provinces), and individual substance use including tobacco smoking and opium consumption by sex in controls.

A binary variable (ever- never) of ISCO-68 major groups, and a list of selected ever lifetime high-risk occupations for lung and bladder cancer (ever/never) has been created for the analysis to investigate the association between occupation held– and lung and bladder cancer risk, odds ratios (ORs) and 95% confidence intervals (CIs) were computed using unconditional logistic regression models.

The selected high-risk occupations for lung cancer including construction worker, textile industry workers, painters, welders, petroleum industry workers, rubber industry workers, farmers, drivers, and bakers. The 5-digit ISCO-68 codes corresponding to each selected occupation is available in Appendix C, table S1, and textile industry workers, painters, welders, petroleum industry workers, rubber industry workers, hairdresser/ barbers, leather goods makers, electronic workers, glass industry workers, plumbers, painters, print workers for bladder cancer. Since the risk of bladder cancer previously has been reported among Iranian construction workers, and drivers (road drivers, heavy vehicle drivers), these two occupations were evaluated in the current study.

In addition, due to a large sample size of farmers in our study which provide an adequate power; farmers were included (field farmers, animal farmers). A list of high-risk occupations for bladder cancer has been provided in Appendix C, table S2. Occupations that potentially have a high-risk of exposure to aromatic amines according the IARC Monographs (i.e.

exposure to 4-APB, Benzidine and metabolites, 2-NA, and ortho-toluidine that has been identified as a group 1 of carcinogens for human bladder cancer) were combined [108]. The list of those occupations have been provided in Appendix C, table S3.

Unconditional logistic regression was fitted on individual data of ever working in major ISCO-68 groups and selected high-risk occupations for lung and bladder cancer; to estimate odds ratios (OR). The models were stratified by sex and adjusted for 5-years interval age groups, residential areas, and potential confounding variables including cigarettes smoking, opium consumption, and the history of UTI, UTS (for bladder cancer).

Since only 13% of bladder cancer cases are women whereof almost 85% are housewives, they were excluded from the analysis of bladder cancer data.

The interaction on an additive scale by calculating the relative excess risk due to interaction (RERI), and on a multiplicative scale using an interaction term between experiencing construction work and opium consumption, as well smoking and construction work in lung cancer risk were examined [109]. The same approach has been applied for exposed workers to aromatic amines and their smoking [110], as well their opium consumption status, to test for potential interaction between being exposed to aromatic amines and opium consumption for the risk of bladder cancer risk in those group of occupations.

The risk of lung cancer associated with the duration of employment as a construction worker and farmer and by histopathology subtypes has been examined.

Chapter 2: The pattern of occupations and occupational epidemiological cancer studies in Iran

This chapter begins with the rationale of literature review on the background of occupational cancer and related exposure in Iran in (section 2.1), (section 2.2) describe the distribution of occupational groups in Iran, in (section 2.3) elaborate on the main finding of literature review, (section 2.4) and highlights the conclusions from the literature and develops the conceptual framework for the study (Section 2.5) including the publication of objective number 1.

2.1 RATIONALE

Knowing about the prevalence of the exposure to the potential carcinogens among workers, and the associated relative risk of developing the cancer for exposed workers is necessary as a fundamental parameters in occupational cancer epidemiological studies [111]. Nevertheless, it is necessary to provide a comprehensive picture of availability and reliability of those components in specific region with the same exposure backgrounds.

To our knowledge the pattern of occupational carcinogens exposure in high-risk industries in Iran is not well characterized; and very little is known about the burden of occupational cancer arise from workplaces in Iran and even in Middle East countries. Therefore, a literature search was conducted to capture relevant publications to provide an overview of conducted epidemiological studies of occupational cancers in Iran to evaluate the state of

knowledge on this topic, identify gaps, and describe how relevant exposures were assessed (direct/ indirect exposure measurement) and assigned to workers in those studies.

In addition, descriptive analysis was performed on IROPICAN controls data to describe the pattern of tobacco smoking and opium consumption within various occupation groups. Identifying the prevalence of individual substance use in various occupation groups may be useful in revising current strategies, guiding policies, and or developing new approaches to smoking cessation programs. Furthermore, it may help in evaluating the effectiveness of current smoking cessation, prevention, and intervention efforts.

2.2 DISTRIBUTION OF MAJOUR OCCUPATIONS IN IRAN

In this study, the distribution of age groups, residential area, and individual substance use including cigarette smoking and opium consumption by major occupation groups of ISCO-68, using IROPICAN controls data for working adults aged ≥ 18 years has been shown.

The distribution of major occupation groups has been shown by age-group and sex in table 1 & 2, geographical regions/ provinces table 3 & 4, smoking statues table 5, and opium consumption table 6, at last table 7 compared the distribution of major group of occupations using ILO major group (ISCO-08) of occupations with IROPICAN study participants (ISCO-68).

As it's shown in table 1 and 2, the prevalence of some blue-collar major groups of occupations has a descending trend with age in men. Those groups including sale workers, plant and machine operators, and elementary occupations. The ascending trend has been observed for agricultural workers. Since the majority of women are housewives, due to small sample size in other groups of occupations, regular trend for other groups has not been observed.

Table 1: Distribution of major occupation groups by age-group in controls in men (N= 2,398)

ISCO-68 major groups	Age groups N (%)												
	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	
0/1: Professional, Technical and Related Workers	9 (12.3)	6 (6.9)	9 (6.5)	23 (10.4)	34 (10.5)	35 (8.3)	41 (9.5)	44 (13.3)	22 (10.7)	14 (14.1)	4 (8.5)	0	
2: Administrative and Managerial Workers	3 (4.1)	1 (1.1)	3 (2.2)	12 (5.4)	8 (2.5)	18 (4.3)	13 (3.0)	9 (2.7)	2 (1.0)	6 (1.1)	0	0	
3: Clerical and Related Workers	4 (5.5)	12 (13.8)	11 (8.0)	17 (7.7)	26 (8.0)	34 (8.1)	34 (7.9)	32 (9.7)	18 (8.7)	9 (9.1)	3 (6.4)	0	
4: Sales Workers	10 (13.7)	14 (16.1)	14 (10.1)	23 (10.4)	23 (7.1)	43 (10.2)	36 (8.4)	32 (9.7)	14 (6.8)	6 (6.1)	1 (2.1)	4 (25.0)	
5: Service Workers	4 (5.5)	9 (10.3)	6 (4.3)	14 (6.3)	18 (5.6)	21 (5.0)	26 (6.0)	16 (4.8)	10 (4.8)	8 (8.1)	3 (6.4)	1 (6.3)	
6: Agricultural, Animal Husbandry and Forest	7 (9.6)	9 (10.3)	19 (13.8)	39 (17.6)	69 (21.3)	85 (20.1)	96 (22.3)	74 (22.4)	70 (34.0)	29 (29.3)	22 (46.8)	8 (50.0)	
7: Craft and related trades workers	5 (6.8)	4 (4.6)	9 (6.5)	9 (4.1)	12 (3.7)	26 (6.2)	25 (5.8)	15 (4.5)	9 (4.4)	6 (6.1)	1 (2.3)	3 (6.4)	
8: Plant and machine operators	5 (6.8)	8 (9.2)	20 (14.5)	17 (7.7)	21 (6.5)	18 (4.3)	23 (5.3)	16 (4.8)	10 (4.8)	2 (2.0)	2 (4.2)	0	
9: Elementary occupations	20 (27.4)	22 (25.3)	42 (30.4)	56 (25.3)	95 (29.3)	111 (26.3)	91 (21.2)	71 (21.4)	36 (17.5)	16 (16.2)	9 (19.1)	2 (12.5)	
X: Military Force	1 (1.4)	1 (1.1)	5 (3.6)	7 (3.2)	14 (4.3)	17 (4.0)	29 (6.7)	7 (2.1)	9 (4.4)	1 (1.0)	1 (2.1)	0	

Table 2: Distribution of major occupation groups by age-group in controls in women (N= 1,079)

ISCO-68 major groups	Age groups N (%)												
	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	
Women 1,079 (31.0)													
0/1: Professional, Technical and Related Workers	5 (11.1)	4 (7.7)	4 (4.4)	7 (6.4)	6 (4.0)	13 (7.5)	7 (3.8)	14 (9.5)	6 (2.9)	2 (2.0)	1 (2.1)	1 (6.2)	
2: Administrative and Managerial Workers	0	0	0	1 (0.9)	0	4 (2.3)	1 (0.5)	0	1 (1.2)	0	0		
3: Clerical and Related Workers	1 (2.2)	3 (5.8)	0	2 (1.8)	2 (1.3)	3 (1.7)	2 (1.1)	1 (0.7)	1 (1.2)	0	0		
4: Sales Workers	1 (2.2)	0	3 (3.3)	2 (1.8)	2 (1.3)	3 (1.7)	2 (1.1)	0	0	0	0		
5: Service Workers	2 (4.4)	3 (5.8)	3 (3.3)	5 (4.6)	8 (5.3)	1 (0.6)	6 (3.3)	4 (2.7)	1 (1.2)	0	0		
6: Agricultural, Animal Husbandry and Forest	1 (2.2)	1 (1.9)	3 (3.3)	3 (2.7)	10 (6.7)	7 (4.0)	10 (5.4)	8 (5.4)	4 (4.8)	0	1 (6.7)		
7: Craft and related trades workers	2 (4.4)	2 (3.8)	4 (4.4)	4 (3.7)	3 (2.0)	5 (2.9)	6 (3.3)	6 (4.1)	3 (3.6)	1 (3.8)	0		
8: Plant and machine operators	0	0	0	0	0	1 (0.6)	0	1 (0.7)					
9: Elementary occupations	0	3 (5.8)	2 (2.2)	1 (0.9)	1 (0.7)	1 (0.6)	1 (0.6)	0					
X: Housewives	32 (71.1)	34 (65.4)	72 (76.1)	84 (77.1)	116 (77.3)	134 (77.0)	148 (80.4)	111 (75.5)	66 (79.5)	25 (96.5)	14 (93.3)	7 (100.0)	

Table 3 and 4 shows the distribution of occupations in each participating geographical regions in controls.

Table 3: Distribution of major occupation groups by geographical regions in male controls (N= 2,398)

ISCO-68 major groups	Provinces N (%)									
	Tehran	Fars	Kerman	Golestan	Mazandar an	Kermansha h	Khorasan	Bushehr	Hormoz gan	Systan- Balouches tan
0/1: Professional, Technical and Related Workers	54 (10.7)	90(12.1)	35 (8.9)	25 (11.9)	6 (6.7)	18 (9.9)	4 (5.3)	4 (6.4)	4 (7.4)	1 (1.2)
2: Administrative and Managerial Workers	15 (3.0)	27 (3.6)	23 (5.8)	6 (2.9)	0	1 (0.5)	2 (2.6)	0	0	1 (1.2)
3: Clerical and Related Workers	53 (10.5)	68 (9.1)	22 (5.6)	13 (6.2)	13 (14.6)	11 (6.0)	2 (2.6)	9 (14.5)	4 (7.4)	5(6.2)
4: Sales Workers	62 (12.3)	60 (8.1)	24 (6.1)	20 (9.6)	2 (2.5)	21 (11.5)	8 (10.5)	16 (25.8)	3 (5.5)	4 (5.0)
5: Service Workers	33 (6.5)	38 (5.1)	21 (5.3)	10 (4.8)	3 (3.4)	6 (3.3)	7 (9.2)	6 (9.7)	7 (13.0)	5 (6.2)
6: Agricultural, Animal Husbandry and Forest	51 (10.1)	167 (22.4)	102 (25.9)	70 (33.5)	28 (31.5)	45 (24.7)	15 (19.7)	12 (19.3)	9 (16.7)	28 (35.0)
7: Craft and related trades workers	39 (7.7)	26 (3.5)	17 (4.3)	8 (3.8)	11 (12.4)	9 (4.5)	1 (1.3)	4 (6.4)	2 (3.7)	4 (5.0)
8: Plant and machine operators	54 (10.7)	37 (5.0)	15 (3.8)	10 (4.8)	6 (6.7)	6 (3.3)	10 (13.2)	0	2 (3.7)	2 (2.5)
9: Elementary occupations	121 (23.9)	187 (25.1)	96 (24.4)	39 (18.7)	12 (13.5)	49 (26.9)	22 (28.9)	10 (16.1)	15 (27.8)	20 (25.0)
X: Military Force	10 (2.0)	36 (4.8)	10 (2.5)	5 (2.4)	2 (2.2)	14 (26.9)	3 (3.9)	1 (1.6)	4 (7.4)	7 (8.7)

Table 4: Distribution of major occupation groups by geographical regions in female controls (N= 1,079)

ISCO-68 major groups	Provinces N (%)									
	Tehran	Fars	Kerman	Golestan	Mazandar an	Kermansha h	Khorasan	Bushehr	Hormoz gan	Systan- Balouches tan
0/1: Professional, Technical and Related Workers	25 (8.0)	16 (8.0)	13 (9.8)	5 (3.0)	2 (4.3)	1 (1.4)	3 (3.2)	0	1 (4.2)	0
2: Administrative and Managerial Workers	1 (0.3)	1 (0.5)	1 (0.7)	0	0	1 (1.4)	1 (1.1)	0	2 (8.3)	0
3: Clerical and Related Workers	5 (1.6)	4 (2.0)	2 (1.5)	1 (0.6)	0	0	1 (1.1)	0	2 (8.3)	0
4: Sales Workers	2 (0.6)	2 (1.0)	0	7 (4.2)	1 (2.1)	1 (1.4)	0	0	0	0
5: Service Workers	9 (2.9)	3 (1.5)	7 (5.5)	6 (3.6)	1 (2.1)	2 (2.9)	5 (5.3)	0	0	0
6: Agricultural, Animal Husbandry and Forest	1 (0.3)	1 (0.5)	1 (0.7)	41 (24.8)	0	3 (4.3)	1 (1.1)	0	0	0
7: Craft and related trades workers	4 (1.3)	5 (2.5)	7 (5.3)	12 (7.3)	0	5 (7.2)	2 (2.1)	1 (4.5)	0	0
8: Plant and machine operators	2(0.6)	0	0	0	0	0	0	0	0	0
9: Elementary occupations	1(0.3)	0	0	0	0	0	0	0	0	0
X:: Housewives	259(83.3)	163 (81.9)	98 (74.2)	91 (55.1)	43 (91.5)	56 (81.1)	74 (78.7)	20 (90.9)	19 (79.2)	20(100.0)

In average, the prevalence of ever smoking among male controls is 21.5% former smokers, and 18.4% current smokers, while the prevalence in women is notably lower than men, including 2.3% former smokers, and 1.7% current smokers.

By occupation major groups of male controls, the highest smoking prevalence is among blue collar workers, including plant and machine operators 50.0%, followed by workers in craft and related trades 49.6%, and elementary occupations 45.4%. The lowest smoking prevalence was among clerical and related workers 28%, followed by workers in professional, technical and related workers 30.6%, Table 5.

Table 5: Distribution of major occupation groups by smoking in male controls

ISCO-68 major groups	Never n (% , row)	Current n (% , row)	Former n (% , row)
0/1: Professional, Technical and Related Workers	167 (69.3)	37 (15.3)	37 (15.3)
2: Administrative and Managerial Workers	47 (62.7)	7 (9.3)	21 (28.0)
3: Clerical and Related Workers	144 (72.0)	29 (14.5)	27 (13.5)
4: Sales Workers	132 (60.0)	27 (12.3)	61 (27.7)
5: Service Workers	89 (65.4)	21 (15.4)	26 (19.1)
6: Agricultural, Animal Husbandry and Forest	322 (61.1)	94 (17.8)	111 (21.1)
7: Craft and related trades workers	61 (50.4)	22 (18.2)	38 (31.4)
8: Plant and machine operators	71 (50.0)	28 (19.7)	43 (30.3)
9: Elementary occupations	312 (54.6)	96 (16.8)	163 (28.5)
X: Military Force	59 (64.1)	12 (13.0)	21 (22.8)

The average of ever opium consumption among male controls is 17.8%, and 2.1% among women. The highest opium consumption is among blue collar workers, including plant and machine operators 24.4%, followed by elementary occupations 22.4%, and agricultural workers 22.2%. The lowest opium consumption was among clerical and related workers 5.5%, followed by workers in professional, technical and related workers 8.7%, Table 6.

Table 6: Distribution of major occupation groups by opium consumption in male controls

ISCO-68 major groups	Never	<1/day	1-2/day	>2/day
0/1: Professional, Technical and Related Workers	220 (91.3)	17 (7.0)	4 (1.7)	0
2: Administrative and Managerial Workers	65 (86.7)	5 (6.7)	5 (6.7)	0
3: Clerical and Related Workers	189 (94.5)	6 (3.0)	3 (1.5)	2 (1.0)
4: Sales Workers	178 (80.9)	33 (15.0)	7 (3.2)	2 (0.9)
5: Service Workers	117 (86.0)	16 (11.8)	1 (0.7)	2 (1.5)
6: Agricultural, Animal Husbandry and Forest	410 (77.8)	76 (14.4)	34 (6.5)	7 (1.3)
7: Craft and related trades workers	101 (83.5)	12 (9.9)	7 (5.8)	1 (0.8)
8: Plant and machine operators	106 (74.6)	21 (14.8)	12 (8.5)	3 (2.1)
9: Elementary occupations	443 (77.6)	91 (15.9)	24 (4.2)	13 (2.3)
X: Military Force	82 (89.1)	10 (14.5)	1 (1.5)	2 (2.9)

In table 7, the ILO major occupation groups using ISCO- 08 compared to the IROPICAN study control population by major groups of ISCO-68 occupational groups. The distribution of occupation groups of IROPICAN controls participants are slightly different from ILO data. In which the ILO data deposit by the Iranian Minster of Cooperatives, Labour and Social Welfare which cover the population aged 15-65, while IROPICAN included the population above 18. In addition, there is a different in classification of ISCO-68 and ISCO-08, so comparison might be slightly difficult. That means the covered population of ILO is younger compared to the IROPICAN study population.

Table 7: Comparison of ILO major group (ISCO-08) of occupations with IROPICAN study participants (ISCO-68)

year	2013	2014	2015	2016	2017	2018	2019	2020	IROPICAN controls
Total									
1. Managers	2.7	2.9	3.1	2.9	3.0	3.2	3.2	3.2	2.8
2. Professionals	9.1	9.3	9.8	9.9	10.3	11.2	11.2	11.35	9.1
3. Technicians and associate professionals	5.2	5.2	5.1	5.256	5.8	5.7	5.8	5.8	2.6
4. Clerical support workers	4.8	4.8	4.8	4.8	3.8	3.8	3.8	3.7	8.6
5. Service and sales workers	13.2	13.0	13.2	13.9	16.2	15.7	15.9	16.1	6.0/7.7
7. Craft and related trades workers	19.5	19.6	19.4	19.8	20.0	19.3	19.2	19.1	7.4
8. Plant and machine operators, and assemblers	12.7	12.6	13.0	12.5	12.6	13.0	13.1	13.1	7.4
96. Elementary occupations and agricultural	32.6	32.3	31.5	30.7	28.1	28.0	27.8	27.5	23.7/24.9
Male									
1. Managers	2.7	2.8	3.1	3.0	3.0	3.2	3.2	3.2	2.7
2. Professionals	6.2	6.3	6.7	6.7	6.9	7.8	7.8	7.9	8.1
3. Technicians and associate professionals	5.1	5.0	4.8	4.9	5.4	5.5	5.4	5.5	2.4
4. Clerical support workers	4.2	4.2	4.2	4.1	3.4	3.5	3.4	3.4	8.7
5. Service and sales workers	13.8	13.6	13.792	14.5	17.1	16.5	16.6	16.8	5.4/8.0
7. Craft and related trades workers	19.6	19.7	19.4	19.6	19.8	18.7	18.7	18.5	6.4
8. Plant and machine operators, and assemblers	14.7	14.6	15.3	14.8	15.1	15.4	15.5	15.5	8.1
96. Elementary occupations and agricultural	33.6	33.5	32.6	31.9	29.1	29.3	29.1	28.9	25.5/24.8
Female									
1. Managers	3.0	3.6	3.1	2.9	3.1	3.6	3.5	3.4	3.9
2. Professionals	25.9	26.9	26.9	25.4	25.3	26.4	26.7	26.9	20.0
3. Technicians and associate professionals	6.5	6.6	6.4	6.5	7.6	7.2	7.3	7.2	4.7
4. Clerical support workers	8.1	8.3	8.1	8.0	5.8	5.2	5.2	5.1	7.0
5. Service and sales workers	9.8	9.6	9.9	10.8	12.4	12.2	12.3	12.2	12.5/4.3
7. Craft and related trades workers	18.8	18.8	19.0	20.4	20.7	21.5	20.9	21.7	17.6
8. Plant and machine operators, and assemblers	1.1	1.1	1.0	1.2	1.4	1.9	1.9	1.9	0.4
96. Elementary occupations and agricultural	26.5	24.9	25.4	24.6	23.5	21.9	21.9	21.3	3.5/25.9

2.3 MAIN FINDINGS

In this thesis research, the systematic literature search has been done to understand about the status of epidemiological studies of occupational cancers and exposure monitoring studies in Iran and describe how relevant exposures were assessed and assigned to workers in these studies. The initial systematic searches identified 1255 publications. After removing the duplicates and screening, 49 publications including 1 cohort study, 11 case-control studies, 34 exposure monitoring studies with cancer risk projection as an outcome, and 3 cancer burden studies in which using available national and international data the cancer risk was projected, were retained to review. The frequency of exposure assessment methods by study design are shown in Tables 6.

Table 8: Relative frequencies of exposure assessment methods and study outcomes by study design

Study Characteristics	Cohort <i>n</i> = 1 (%)	Case- Control <i>n</i> = 11 (%)	Exposure Monitoring <i>n</i> = 34 (%)	Cancer Burden Studies <i>n</i> = 3 (%)
Direct exposure assessments	-	0 (0.0)	32 (94.1)	-
Personal Air Sampling	-	-	16 (47.0)	-
Stationary Air Monitoring	-	-	13(38.2)	-
Stationary/Personal Air Sampling	-	-	3(8.8)	-
Indirect Exposure Assessment Methods:	1 (100)	11 (100.0)	2 (5.8)	3 (100)
Self-report of job or exposure history	-	11 (100.0)	-	-
Available databases	-	-	1 (2.9)	3 (100)
Expert Assessment	-	-	1 (2.9)	-
Not applicable	1 (100)	-	-	-
Cancer Outcomes				
Cancer, general ¹	1 (100)	-	24 (70.5)	1 (33.3)
Lung cancer	-	1 (9.0)	8 (24.3)	-
Bladder and urinary tract cancer	-	5 (45.4)	-	1 (33.3)
Hematological cancer	-	2 (18.1)	2 (8.1)	1 (33.3)
Head and neck cancer	-	1 (9.0)	-	-
Breast cancer	-	1 (9.0)	-	-
Gastrointestinal cancer	-	1 (9.0)	-	-

¹ General term representing lifetime cancer risk, long-term exposure cancer risk, risk of any cancer, etc.

The only eligible cohort study included a random selection of 15,162 military veterans from the Iran–Iraq war, who were followed up to 25 years, to investigate the association of single exposure to the sulfur mustard in relation to cancer incidence.

Out of the 11 eligible case-control studies, 5 publications evaluated bladder cancer risk. The studies had in common that they were all relatively small, cases (range 31-300) and controls (range 32-500). The exposure assessment was entirely based on self-report of jobs/exposures, and no subsequent attempt was made to assign exposures to these jobs via for example expert assessment or existing job-exposure-matrices (JEMs). Two publications considered specific exposure (pesticides), while the majority covered all jobs and industries.

Exposure monitoring studies including cancer risk predictions mostly applied personal or/ and stationary air monitoring to estimate the level of exposure in individual workers. Most of exposure monitoring studies (30 out of 34) measured exposures only once over an entire working shift. The most frequently monitored agents in the monitoring studies including BTEXs, following by crystalline silica in a variety of industries, e.g., in petroleum industry, manufacture of basic iron and steel, construction workers, foundries, glass manufacturing. Based on the monitoring results the risk of cancer was estimated.

2.4 CONCLUSION

The distribution of major occupation groups in our study controls shows that the most prevalent major occupations is elementary occupations and agriculture following by clerical occupations in men. In women, 80% of controls were housewives the most frequent major group of occupations is

agricultural works following by white-collar professional occupations, and services related works.

In terms of individual substance use prevalence, the highest prevalence of smoking has been observed among blue collar workers, including plant and machine operators, workers in craft and related trades, and elementary occupations in contrast the lowest prevalence among clerical and related workers, and other professional occupations. The highest opium consumption blue-collar workers are among plant and machine operators, elementary occupations, and agricultural workers. Whilst the lowest consumption was among clerical and related workers, and professional, technical and related workers.

The low prevalence of smoking among the white-collar occupations may be explained, in part, by the fact, that a high percentage of workers in these occupations are covered and required to abide by smoke-free workplace policies, including smoke-free workplaces. Iran's accession to the Framework Convention on Tobacco Control (FCTC) was implemented in 2006. Although implementing the tobacco-use cessation encourages the country to implement operational plans, including prevention measures, However, there are several challenges in developing effective policies for tobacco control in the Iranian setting.

Further, according to the result of our literature review occupational cancer epidemiology is a relatively new topic in Iran. This fact may reflect those scientists and occupational physicians have focused on acute diseases, and lack of collaboration across disciplines in this area of research. Despite the existence of very important industries such as petroleum industry in Iran, limited consideration focused on these industries which could be due to confidentially and safety matters that would require permissions.

In epidemiological studies, occupational information was collected on self-report of jobs/ exposures with a relatively small sample size focused on major occupation group rather than of specific jobs.

The results of the review also revealed that exposure monitoring studies mostly focused on projection of cancer risk by single measurements through personal and stationary air sampling, although exposure levels often differ within and between worker, manufacturing units, days, months, and seasons.

Identifying the burden of occupational cancers is an important step towards acting for reducing occupational cancer risks. Therefore, well-designed and large-scale studies that include accurate exposure assessment methods are needed, e.g., development of valid job-exposure matrices specifically for Iran. These studies in major industries should be initiated to inform cancer control in Iran and efforts on a global scale, as data from emerging economies is lacking worldwide. Also, exposure monitoring needs to be more systematic, to develop risk reduction measures. All this research is essential for the ultimate goal of prevention of occupational cancer in Iran.

2.5 PUBLICATION I




Title: Occupational Exposure to Carcinogens and Occupational Epidemiological Cancer Studies in Iran: A Review

Status: published in Cancers journal, July 2021 [35].

This paper provided an overview of epidemiological studies of occupational cancers and exposure monitoring studies in Iran and describe how relevant exposures were assessed and assigned to workers in these studies.

Review

Occupational Exposure to Carcinogens and Occupational Epidemiological Cancer Studies in Iran: A Review

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Simple Summary: Occupational cancers can be prevented by eliminating hazardous substances or by reducing workers' exposures. Characterizing the extent of exposure to carcinogens in workplaces and industries is a crucial first step to exposure control. Iran is one of the most industrialized countries in the Middle East, yet lacks an overview of the extent of exposure to carcinogens and comprehensive risk management. This review provides an overview of studies conducted to date and demonstrates the need for interdisciplinary collaboration to inform occupational research and exposure control in Iran and beyond.

Abstract: Introduction: The extent of exposure to occupational carcinogens is not well characterized in Iran, and little is known about the burden of occupational cancer. Objectives: This study aimed to describe exposure to occupational carcinogens and occupational epidemiology studies in Iran. Methods: Relevant studies up to January 2021 in Iran were identified through three databases (PubMed, Web of Science, and Google Scholar). Results: Forty-nine publications from 2009 to 2020 (one cohort, 11 case-control, 34 exposure monitoring studies, and three cancer burden studies) were included. The exposure monitoring studies were conducted mainly in the petroleum industry, metal industry, manufacturing of electronics, manufacturing of plastics, construction industry, and service industry. A few of the case-control studies also reported increased risk of cancers in relation to work in those industries. Conclusions: Occupational cancer epidemiology in Iran is at an early stage. Both epidemiological and exposure monitoring studies are generally limited in size to provide robust evidence of occupational cancer risks. A coherent strategy to estimate the occupational cancer burden in Iran should start with conducting epidemiological studies along with systematic monitoring of occupational carcinogens for use in hazard control and research.

Keywords: occupation; occupational exposures; exposure measurement; cancer; Iran



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1. Introduction

Industries in Iran have undergone rapid growth in recent decades. The largest industrial sectors are petroleum industries, followed by the manufacturing of motor vehicles and the pharmaceutical industry, mining and quarrying especially copper and aluminum, and manufacturing of metals and rubber and plastics products [1]. Workers in these industries may be exposed to various known or suspected carcinogens such as BTEXs

(benzene, toluene, ethylbenzene, and xylene), crystalline silica, and heavy metals. National efforts to reduce the burden of occupational cancers require evidence-based information on exposures to carcinogenic agents and their related cancer risks in Iranian workers [2].

Exposure assessment is a critical component of all epidemiological studies and can be particularly complex in studies of occupational cancers. The choice of method depends to a large extent on the study's design, resources, and what data are available. Exposure assessment applied in epidemiological studies frequently comprises indirect methods, including self-reports of jobs and/or various job-related exposures, and subsequent assignment of exposures by case-by-case expert assessment or job exposure matrices. In industrial cohort studies, employment records of workers and long-term routine surveillance of exposures in the workplace may be applied to conduct objective, detailed, and quantitative exposure assessment. Quantitative exposure assessment methods include personal air sampling, stationary air sampling, and biomonitoring to represent individual exposures during a specific time period. These direct exposure assessment methods are likely to be the most precise methods but reflect current or very recent exposures, unless repeated regularly over a long time period [3,4].

To our knowledge the presence of occupational carcinogens in workplaces in Iran have not been well characterized, and very little is known about the burden of occupational cancer in Iran and other Middle East countries. This is important because not just materials and technologies but also workplace environments and practices, legislated exposure controls used in industries might be different and unique for this region, making them difficult or impossible to infer from studies conducted elsewhere. For instance, the Iranian government adopted laws prohibiting the use of asbestos in final products in 2000 and the import of white asbestos in 2012, but it is still used in some industries such as automobile manufacturing instead of changing to non-asbestos materials [5]. Other factors determining differences in occupational exposures include the content of respirable crystalline silica in ground construction materials and the standard and types of busses and trucks affecting the motor emissions, etc. [6].

The objective of this review was to identify and characterize epidemiological studies of occupational cancers and exposure monitoring studies with projection of cancer risk in Iran and describe how relevant exposures were assessed and assigned to workers in these studies.

2. Materials and Methods

2.1. Literature Search and Inclusion/Exclusion Criteria

A literature search was conducted to identify publications related to occupational cancer in Iran through three bibliographic databases (PubMed, Web of Science, and Google Scholar) from 1973 to January 2021. Select keywords were searched through title, abstracts, and body text to identify relevant publications.

The search queries (Tables S1 and S2) included keywords according to the PECO statement (Population: workers, and Iran, Exposure: occupational carcinogenic exposures, Comparison: unexposed/exposed workers, Outcomes: cancer) [7]. The search strategy combined the above terms by Boolean search operations (AND, OR, NOT) and Mesh terms.

We included full publications of epidemiological studies (cohort and case-control studies on occupational cancer) and exposure monitoring studies in which the authors projected the subsequent risk of cancer. Occupational agents were restricted to chemical agents that had been evaluated by the International Agency for Research on Cancer's (IARC) Monograph Programme on the Identification of Carcinogenic Hazards to Humans irrespective of its IARC classification, i.e., Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans), and Group 3 (not classifiable as to its carcinogenicity to humans). All articles had to be published in English or Farsi.

2.2. Data Extraction

Identified articles were imported into EndNote reference manager, and duplicates were removed. Two reviewers (B.H. & F.M.O.) independently screened the articles according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [8]. Titles and abstracts of all identified references in the primary search were screened to determine potential eligibility. In any case of disagreement between reviewers, the full-text publication was reviewed and discussed to resolve discrepancy; a third reviewer (A.O.) was consulted to reach consensus if needed. Following the primary screening, full texts of the relevant references were obtained. Five full-text articles had to be requested from authors via E-mail or ResearchGate, and all were successful.

The following data were extracted from each retained publication: name of author, publication year, geographical region of Iran (North/South/West/East/Centre/Tehran), study design (Cohort/Case-control/Exposure monitoring with cancer risk projection as an outcome/burden of cancer studies with nonspecific study design, e.g., cancer projection using available data on exposure and outcomes), occupation (Title), industry (Title), exposure agents (Names), population size/sample size (Number of workers/samples), exposure assessment methods (Personal air monitoring/Biological monitoring/Stationary air monitoring/Self-report of job or exposure history/Registries/Expert Assessment), and study outcomes (Overall and specific cancer sites).

3. Results

The publication selection process is summarized in the modified PRISMA flow diagram in Figure 1. The initial systematic searches identified 1255 publications (718 from PubMed, 391 from Web of Science, 146 from Google scholar). After removing the duplicates ($n = 279$), 976 publications remained. Of these, 835 were excluded by screening the titles and abstracts (in vitro and in vivo, nutritional studies, editorial, case reports, reviews and systematic reviews, physical and psychosocial exposure in the workplaces).

The remaining 141 full-text publications were reviewed, and 92 were additionally excluded, i.e., studies evaluating occupational exposures in relation to health outcomes other than cancer.

In total, 49 relevant publications (one cohort study, 11 case-control studies, 34 exposure monitoring studies with cancer risk projection as an outcome, and three cancer burden studies using national and international data) were retained for data extraction. The frequency of exposure assessment methods by study design are shown in Table 1.

Table 1. Relative frequencies of exposure assessment methods and study outcomes by study design.

Study Characteristics	Cohort $n = 1$ (%)	Case-Control $n = 11$ (%)	Exposure Monitoring $n = 34$ (%)	Cancer Burden Studies $n = 3$ (%)
Direct exposure assessments	-	0 (0.0)	32 (94.1)	-
Personal Air Sampling	-	-	16 (47.0)	-
Stationary Air Monitoring	-	-	13(38.2)	-
Stationary/Personal Air Sampling	-	-	3(8.8)	-
Indirect Exposure Assessment Methods:	1 (100)	11 (100.0)	2 (5.8)	3 (100)
Self-report of job or exposure history	-	11 (100.0)	-	-
Available databases	-	-	1 (2.9)	3 (100)
Expert Assessment	-	-	1 (2.9)	-
Not applicable	1 (100)	-	-	-

Table 1. Cont.

Study Characteristics	Cohort <i>n</i> = 1 (%)	Case-Control <i>n</i> = 11 (%)	Exposure Monitoring <i>n</i> = 34 (%)	Cancer Burden Studies <i>n</i> = 3 (%)
Cancer Outcomes				
Cancer, general ¹	1 (100)	-	24 (70.5)	1 (33.3)
Lung cancer	-	1 (9.0)	8 (24.3)	-
Bladder and urinary tract cancer	-	5 (45.4)	-	1 (33.3)
Hematological cancer	-	2 (18.1)	2 (8.1)	1 (33.3)
Head and neck cancer	-	1 (9.0)	-	-
Breast cancer	-	1 (9.0)	-	-
Gastrointestinal cancer	-	1 (9.0)	-	-

¹ General term representing lifetime cancer risk, long-term exposure cancer risk, risk of any cancer, etc.

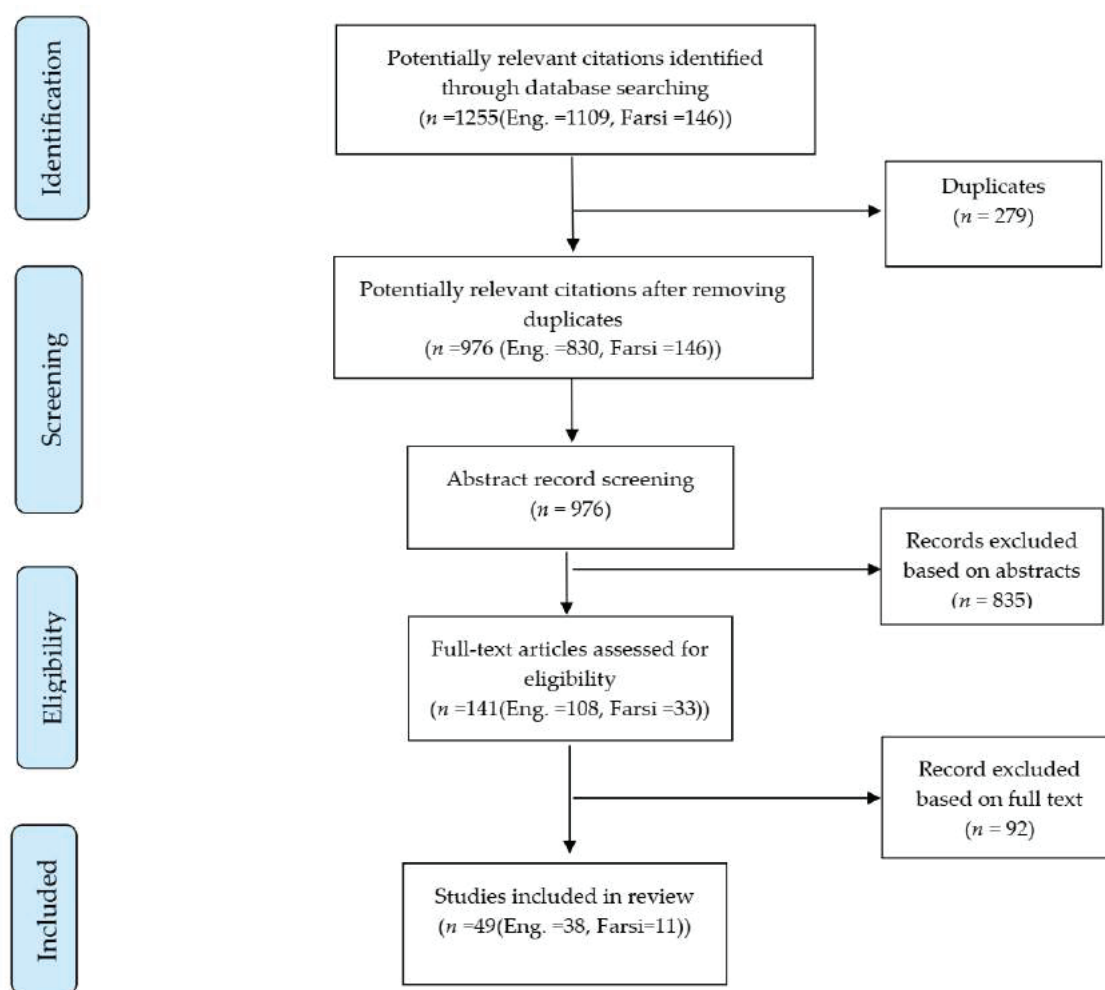


Figure 1. PRISMA flow diagram.

3.1. Epidemiological Studies

The retained epidemiological studies (one cohort study and 11 case-control studies) are summarized in Table 2.

Table 2. Characteristics of epidemiological studies.

Reference/Location/ Study Year	Cancer Sites	Population Size/Description	Source of Exposure Assessment	Exposure Duration Measure	Covariates Controlled for in Modelling	Outcome (Risk of Cancer)
Prospective cohort						
Zafarghandi/Iran/ 1984–2010 [9]	Cancer	7570; Male veterans, Exposed to sulfur mustard during the Iran–Iraq war (1984–1987); 7592; Male veterans, unexposed to sulfur mustard (instead, e.g., physical injuries).	Documented medical records on at least one acute exposure while the participant presented in the battlefield between 1984 and 1987	Single exposure to sulfur mustard during the war	Stratified by age, smoking status, educational level, marital status	Yes
Case-control						
Khoubi/Isfahan, Iran/2004–2009 [10]	Bladder	Cases: 300; bladder cancer patient recruited from registry Controls: 500; population-based controls	Questionnaire; Phone/face-to-face interview; Collected data on industry title, duration, hours of work per day, self-report of exposures	Lifetime occupation history: Jobs held > 6 months	Age, sex, smoking status (never/current/former smoker, duration of smoking (year), average number of cigarettes per day)	Yes
Aminian/Tehran, Iran/2007–2009 [11]	Bladder	Cases: 160; Male-Histologically confirmed Controls: 160 Male without occupational exposure to the chemicals (source of controls recruitment is unclear)	Study specific questionnaire; Face-to-face interview; Collected data on job title, duration, exposure to the specific chemicals in each job, history of cancer occurrence in coworkers	Current and former jobs	Sex	Yes
Farzaneh/Yazd, Iran/2009–2013 [12]	Bladder	Cases: 200; Histologically confirmed Controls: 200 healthy neighbors	Questionnaire; Face-to-face interview; Collected data on job titles	Lifetime occupation history: jobs held > 1 year	Age, sex, family history of bladder cancer, chronic urinary tract infections (times per year), kidney and bladder stones, hair dyeing, and educational level	Yes
Ghadimi/Kurdestan, Iran/2012–2015 [13]	Bladder	Cases: 152; Histologically confirmed recruited from cancer registries Controls: 152, Hospital based	Semi-structured questionnaire; Interview; Collected data on job titles, and tasks	Last 20 years jobs	Age, sex, and place of residence, univariable analysis	Yes

Table 2. Cont.

Reference/Location/ Study Year	Cancer Sites	Population Size/Description	Source of Exposure Assessment	Exposure Duration Measure	Covariates Controlled for in Modelling	Outcome (Risk of Cancer)
Tajvidi/Isfahan, Iran/2001–2010 [14]	Kidney	Cases: 200; kidney cancer cases recruited from cancer registry Controls: 400; healthy population based	Semi-structured questionnaire; Collected data on job title, and self-report of exposures	Not clear	Age, sex	Yes
Aminian/Tehran, Iran/2011–2015 [15]	Non- Hodgkin/ Hodgkin’s lymphoma	Cases: 150; male; Histologically confirmed Controls: 150; relative controls (case’s brother or close relative)	Semi-structured questionnaire; Interview; Collected data on job title, duration, exposure to the specific chemicals in each job, history of cancer occurrence in coworkers	Current and former jobs: Jobs held > 1 year	Age, sex	Yes
Zakerinia/Fars, Iran/2007–2008 [16]	Malignant lymphoma	Cases: 200; Histologically confirmed Controls: 200; Hospital based	Semi-structured questionnaire; Face-to-face interview; Collected data on job history, specific exposures for each job, a question on extra jobs in farming including pesticides exposure (herbicides, fungicides, insecticides), reason for exposure, duration	Lifetime occupation history: Jobs held > 1 year	Age, sex, center	Non-Hodgkin lymphoma: Yes Hodgkin lymphoma: No
Amizadeh/Not clear [17]	Head and neck	Cases: 31; Histologically confirmed Controls: 32; Hospital based	Structured questionnaire; Face-to-face interview; Collected data on type of crops, tasks, duration, farming surface size, name of pesticide, frequency of apply per year, and methods, personal protective equipment; biomonitoring (residual pesticide was extracted from adipose tissue)	At least 1 year of agriculture	Age, sex, smoking status	Yes

Table 2. Cont.

Reference/Location/ Study Year	Cancer Sites	Population Size/Description	Source of Exposure Assessment	Exposure Duration Measure	Covariates Controlled for in Modelling	Outcome (Risk of Cancer)
Hosseini/Tehran, Iran/2002–2005 [18]	Lung	Cases: 242; primary cases; Histologically confirmed Controls: 484; Hospital based (242; Healthy visitors and 242; patients except oncology ward patients)	Structured questionnaire; Face-to-face interview; Collected data on workplace conditions, exposure to suspected occupational lung carcinogens	Not clear	Age, sex, and-place of resident	Yes
Aghilnejad/Tehran, Iran/2014–2015 [19]	Gastrointestinal	Cases: 243; Male; Histologically confirmed Controls: 243; Male; Hospital based (cancer patient other than gastrointestinal cancer)	Questionnaire; Interview; In the method the author stated, “occupational history” but no details provided on the collected data	Childhood until 5 years before cancer diagnosis	Age	Yes
Rafeemaneh/Khorasan- Razavi, Iran/2010–2014 [20]	Breast	Cases: 104; Histologically confirmed (employed women) Controls: 112; Women; Healthy controls (who referred to the health care centers to receive routine examination); Employed women	Questionnaire; Face-to-face Interview; Collected data on recent job title; In the methods “occupational exposures” are stated, with no details provided	Not clear	Not clear	Yes

The only eligible cohort study included a random selection of 15,162 military veterans from the Iran–Iraq war between 1984 and 1987, who were followed prospectively for up to 25 years, with a particular interest of investigating the association of single exposure to sulfur mustard in relation to cancer incidence. Almost half of the cohort ($n = 7570$) had been exposed to sulfur mustard (at least one exposure documented in medical records while they were present in the battlefield) during the war and the other half had not been exposed (e.g., injured veterans). Survivors were followed up yearly by medical doctors, via telephone interview to confirm cancer occurrence or death. The outcomes of interest included the incidence of all types of cancer. Verification of cancer was performed by pathological confirmation [9].

Out of the 11 retained case-control studies, five examined bladder and urinary tract cancers. The exposure assessment in all case control studies was based on self-reported job histories and self-reported specific chemical exposures. The largest case–control study was conducted by Khoubi et al. (2013) [10] in the Isfahan Province. Using lifetime occupational history, job titles were coded according to the International Standard Classification of Occupation from 2008 (ISCO-08), and risks were estimated for 22 pre-defined occupational groups. This study observed a significantly increased risk of bladder cancer in certain occupations, including truck and bus drivers, agricultural workers, metal industry workers, construction workers, and domestic housekeepers.

Aminian et al. (2014) [11] conducted a hospital-based case-control study in men to evaluate the risk of bladder cancer in relation to occupational exposure. The authors stated, “controls were male cases without cancers and occupational exposures”. The results were presented for a priori assigned high and low cancer-risk jobs. The statistical analysis section comprised very limited information, and the study reported elevated crude odds ratios for jobs allocated to high-risk occupations including bus and truck drivers, road and asphalt workers, mechanics, refinery and petrochemical workers, plastic manufacturing, metal manufacturing, welding, and pipeline workers.

Farzaneh et al. (2017) [12] conducted a case-control study on bladder cancer in the Yazd Province. Job titles were classified into a priori “high-risk” and “low-risk” jobs based on their potential (according to the literature and expert’s opinion) for exposure to bladder carcinogens such as aromatic amines, amino-biphenyl, polycyclic aromatic hydrocarbons [PAH], and azo dyes. An elevated risk of bladder cancer was observed among a priori high-risk jobs including metal manufacturing, textile, driving, agriculture and livestock, and construction.

Ghadimi et al. (2015) [13] reported on a hospital-based case-control study on urinary bladder cancer in relation to occupation, smoking, and opium consumption, conducted in the Kurdistan Province. By the occupation classification ISCO-08, univariable analysis showed an elevated risk of bladder cancer in workers in metal manufacturing.

Tajvidi et al. (2013) [14] conducted a case-control study of kidney cancer in the Isfahan Province. Study participants were asked about occupations held as well as selected exposures in a questionnaire. Results were reported based on Chi-square and T-test analysis, which compared the occupations and exposure difference between cases and controls. In case subjects the frequency of agriculture and laborers in various industries was higher than that in other occupations. Exposures to pesticides, paint, petrol, chemicals, and mineral agents were significantly more frequent in cases than in control subjects.

A small case-control study of head and neck cancer showed an association with pesticide exposure. Exposure to pesticides was confirmed by residual pesticide from the adipose tissue of the neck of cases and controls. Information on pesticide exposure was classified into non exposed, low, and high exposed based on occupational, residential, and agricultural activities history [17].

A study of malignant lymphoma conducted in the Fars Province observed an elevated risk of Non-Hodgkin lymphoma related to pesticide exposure. Information on all jobs held and exposures for each job, as well as detailed information of agricultural exposures was collected. For the analyses, job titles were classified by major groups of ISCO-68. The results showed elevated risk of lymphoma in farmers compared to all other jobs. The elevated risk was present for any type of pesticide exposure whether occupational or residential [16].

Another hospital-based case-control study of non-Hodgkin and Hodgkin's lymphoma was conducted in the Tehran Province. In this study, job titles were classified into high- and low-risk jobs based on the literature. Elevated risks of non-Hodgkin lymphoma were observed in unadjusted analyses for occupations such as welders and metal workers, with increased risk of Hodgkin lymphoma in drivers [15].

Hosseini et al. (2009) [18] conducted a hospital-based case-control study to investigate the lung cancer risk related to known and suspected environmental and occupational lung carcinogens. In this study, increased risk of lung cancer was observed for occupational exposure to inorganic dusts, chemical compounds, and heavy metals. The same results were observed in smokers and nonsmokers.

A hospital-based case-control study on gastrointestinal cancer among male patients was conducted in the Tehran Province. One-digit major groups of the ISCO-08 classification were analyzed. The results reported an elevated risk of gastrointestinal cancers in plant and machine operators, assemblers, agricultural workers, and laborers [19].

A case-control study of breast cancer conducted in the Mashhad Province recruited participants among employed women classified into four major groups: teachers, administrative/clerical workers, healthcare workers, and miscellaneous jobs (carpenters, hairdressers, tailors, cooks), and the results showed only an increased risk of breast cancer in teachers compare to the other occupations [20].

All case-control studies were relatively small, with a mean number of 180 cases (range 31–300) and 221 controls (range 32–500). The cases were mostly recruited from hospitals ($n = 8$) and in three publications from cancer registries. The controls were recruited from hospitals ($n = 6$), general population ($n = 2$), neighbors ($n = 1$), relatives of cases ($n = 1$), and unclear ($n = 1$). Most studies included only histologically confirmed cases ($n = 8$). The exposure assessment in all case-control studies was mostly based on self-reported jobs and/or exposures. Except two studies which allocated jobs to the low- vs high-risk jobs based on the literature review or expert judgement, no subsequent attempt was made to assign exposures to these jobs (e.g., expert assessment or existing job-exposure-matrices). Two publications considered specific exposure to pesticides, while the others addressed jobs and industries as proxies for occupational exposures.

3.2. Exposure Monitoring Studies Including Cancer Risk Predictions

Table 3 describes characteristics of the 34 exposure monitoring studies that subsequently estimated cancer risk. Sixteen studies used personal air monitoring, 13 used stationary air monitoring, and three studies applied a combination of personal and stationary air monitoring to estimate the level of exposure of individual workers and workplaces. One additional study estimated the lung cancer risk based on available exposure measurement data from previous studies (used available input parameters, e.g., intensity of nickel and chromium exposure in welders from published studies) [21]. Another study calculated exposure using an exposure index (EI) based on the physical characteristics of the agent, e.g., the olfactory threshold value, inhalable fraction and vapor, the preventive measures including personal and environmental protection, level of benzene exposure, and work duration per week, and estimated the risk of leukemia [22].

The majority of exposure monitoring studies (14/16 of personal air sampling and 12/13 of stationary air sampling) measured the exposure of workers only once over an entire work shift, while two studies collected repeated measurements of the same worker on two or three occasions during an entire work shift [23,24]. One study measured exposure via personal air sampling over the full duration of a work shift for three consecutive

months [25]; another assessed exposure by taking four short-term personal air measurements (90 min) in different hours of a work shift for five consecutive weeks [26].

In larger industries, exposures were assigned to workers based on their tasks in relevant production units [24,27–29]. In small workplaces, e.g., beauty salons [30,31], waterpipe cafés [32,33], and gas stations [34], stationary air monitoring was applied to estimate exposure during a work shift.

The most frequently monitored agents in the monitoring studies were volatile organic compounds (VOCs) including benzene, toluene, ethylbenzene, and xylenes (BTEXs). Personal and stationary air sampling of these agents was conducted in a variety of industries, e.g., petroleum industry [23,27,35], manufacture of basic iron and steel [36], automobile manufacturing [37], painting units of automobile manufacturing [38], poultry slaughterhouse [26], and gasoline and Compressed Natural Gas (CNG) refueling stations [39].

In exposure monitoring studies, monitoring results were used to project the risk of cancer using different terms, e.g., Excess Lifetime Cancer Risk (ELCR), Incremental Lifetime Cancer Risk (ILCR), Inhalation Lifetime Cancer Risk (LTCR), and Lifetime Cancer Risk (LCR).

In water pipe cafés [32], and beauty salons [30,31], the investigators used stationary air monitoring exclusively to measure the exposure to BTEXs and PAHs. Exposures were monitored with consideration of sampling sites, e.g., type of ventilation system and the location at which those salons or cafés were located, e.g., ground floor or basement.

Crystalline silica was the second most frequently monitored agent. Workers' exposure was measured by personal and stationary air sampling in a variety of industries such as casting of iron and steel manufacture [40], manufacture of ceramic pin insulators [41], construction workers at building demolition sites [42,43], and in sectors including stone cutting and milling, foundries, glass manufacturing, asphalt manufacturing, construction, sand and gravel mining, sand blasting, and ceramics, bricks and cement manufacturing [44]. Based on the monitoring results, the risk of lung cancer was estimated.

In a few studies, exposure to formaldehyde was monitored in pathology laboratory staff through personal and stationary air sampling [45–47], and in one study exposure to formaldehyde was assessed by personal air sampling of plastic product workers to estimate their cancer risk [48].

Exposure to vinyl chloride was measured among plastic manufacturing workers through personal air samplers to estimate the ELCR [49].

Table 3. Characteristics of studies with exposure monitoring design.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Heibati/North of Iran/2016 [27]	Petroleum	50 workers selected randomly (tanker loading workers, tank-gauging workers, drivers, firefighters, and office workers)	BTEXs ¹ (benzene, toluene, ethylbenzene, and xylene)	Personal air sampling; over one 8-h work shift	Elevated ELCR ² in tanker loading and tank-gauging workers attributable to tasks, e.g., dispensing, loading, and unloading of petrol
Shanh/Iran/2013– 2014 [23]	Petroleum	338 samples from 169 workers in 21 petrochemical complexes including mechanics, security, samplers, site men, technicians, laboratory staff, and office workers	VOCs ³ (benzene, epichlorohydrine, trichloroethylene, styrene, ethyl benzene, and 1,3-butadiene)	Personal air sampling; two samples taken over a work shift for each subject; each sample duration 3.5–4 h	Elevated LCR ⁴ for all workers attributed to VOC carcinogenic components; the highest LCR was attributable to benzene exposure
Sadeghi-Yarandi/Isfahan, Iran/2018 [24]	Petroleum	150 samples from 50 workers including fire-fighters, polybutadiene latex (PBL), dryer, and coagulation workers, mechanics, electricians, packing, and laboratory workers	1,3-butadiene	Personal air sampling; 90 min for each sample (beginning, middle, and end of work shift)	Elevated LCR for all workers, highest LCR attributable to 1,3-butadiene observed in safety and fire-fighters of petroleum complexes
Barkhordari/Iran/2013 [21]	Petroleum	30 welders were assigned to different groups by exposure to Ni and Cr (VI) and also health situation (healthy and asthmatic welders)	Nickel and hexavalent chromium from welding fumes	Personal air measurement data; parameters (e.g., intensity and duration of exposure) were used from previous studies; information on daily work hours, daily tasks collected by questionnaires	Elevated ILCR ⁵ in exposed group in both asthmatic and healthy welders
Golbabaie/Iran/study year is unknown [22]	Petrochemical	Not applicable	Benzene	Exposure data used from previous prospective study in rubber industry workers; exposure index (EI) determined by experts using physical characteristics of exposure agent (e.g., the olfactory threshold value, inhalable fraction and vapor), and preventive measures including personal and environmental protection.	Elevated risk of leukemia attributable to benzene exposure in all workers

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Harati/Iran/2016 [35]	Petrochemical	123 samples from 60 workers	VOCs (benzene, toluene, xylene, pentane, hexane, heptane, octane, and nonane), and hydrogen sulfide (H ₂ S)	Personal air sampling; two samples from each worker (one to measure VOCs, another to measure H ₂ S), and 3 control samples; details on sampling duration were not provided	Elevated ELCR in workers attributable to benzene exposure in all workers
Hazrati/Ardabil, Iran/study year is unknown [39]	Gasoline and CNG refueling stations	Samples from 24 refueling stations including 15 petrol and 9 CNG stations; the population sample size was not clarified	BTEXs	Personal air sampling over a full work shift	Elevated long-term exposure cancer risk related to BTEX compound exposure
Javadi/Isfahan, Iran/2016 [34]	Gasoline and CNG refueling stations	24 samples from 12 refueling stations (12 workers, 12 stationary air sampling)	BTEXs	Personal air sampling and stationary air sampling over a full work shift	Elevated risk of cancer attributable to benzene exposure
Omidi/Tehran, Iran/2018 [26]	Poultry slaughterhouse	200 samples and 40 blank samples from all workers	VOCs (benzene, toluene, ethylbenzene), and CS ₂ (Carbon disulphide)	Personal air sampling; 4 samples in a different hours of a full work shift; sampling repeated in 5 consecutive weeks for each worker; each sampling duration was between 50 and 90 min	Elevated LCR attributable to benzene exposure
Mohammadyan/Neyshabur, Iran/2017–2018 [50]	Electronic manufacturing, plastic compress unit	141 samples from 59 workers including primary granule warehouse, plastic injection workers, shift managers, miscellaneous (forklift drivers, quality control engineers, and crew)	Styrene	Personal air sampling, details on sampling duration were not provided	Elevated LCR attributable to styrene exposure in plastic injection operators and shift supervisors
Mohammadyan/Neyshabur, Iran/2017–2018 [28]	Electronics manufacturing	40 samples from 40 female soldering workers (cutting electrical wires and coating, initial soldering, voltage testing and secondary soldering workers, and shift supervisors)	Lead	Personal air sampling over a full work shift	ELCR not increased in high-risk exposed group

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Tayfeh Rahimian/Tehran, Iran/study year is unknown [49]	Manufacturing of plastics products	100 workers from mixing, winder, coating, finishing, rewinder, warehouse used to manufacture two plastic products	Chloride vinyl	Personal air sampling over a full work shift	Elevated ELCR attributable to duration of chloride vinyl exposure
Mazinani/Tehran, Iran/study year is unknown [48]	Manufacturing of plastics products	54 samples from 4 workshops in different units including cutting, stoning, pressing, and packing	Formaldehyde	Stationary air sampling over a full work shift. Indoor air temperature, pressure, and relative humidity used in analyses	Elevated risk of cancer attributable to formaldehyde exposure in all units; the highest level of exposure was in stoning and pressing units
Azari/Iran/study year is unknown [25]	Manufacturing of shoes	Sample from 48 workers in 12 workshops including cutting, modelling, fitting, and finishing tasks	Benzene, toluene	Personal air sampling, once a month during 3 consecutive months, details on sampling duration were not provided	Elevated risk of leukemia attributable to benzene and toluene exposure in shoemakers; the level of exposure was higher than the threshold limit value (TLV)
Sanjari/Iran/study year is unknown [51]	Aluminum rolling	103 samples from different units including slabbing, production, painting, and washing workshops	Chemical exposure including aluminum products, silica, rock wool, iron oxide, manganese, sulfuric acid, benzene, ethylbenzene, toluene and xylene	Stationary air sampling; details on sampling duration were not provided; indoor air temperature, pressure, and humidity used in analyses	Elevated ELCR attributable to benzene exposure; level of exposure to sulfuric acid in washing lines and manganese in the manufacturing unit were higher than in other units
Zarei/Tehran, Iran/2017 [40]	Foundry	Sampling of breathing zone of 55 workers from different units including machine operator, painting, furnace, and cleaning; information on number of samples was not provided	Crystalline silica	Stationary air sampling, 4 h during a work shift	Elevated lung ELCR attributable to crystalline silica exposure; All workers exposed to a higher level than the definite acceptable limit recommended by OSHA 7

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Omidianidost/Tehran, Iran/2011 [52]	Foundry	80 samples of 80 workers from workshops used for 29 small foundries including 10 iron cast, 3 brass, and an aluminum foundry	Crystalline silica	Personal air sampling over a full work shift	Elevated risk of lung cancer mortality; 50 percent of workers exposed to greater than the acceptable threshold limit value by OSHA
Omidi/Iran/study year is unknown [36]	Steel manufacturing	50 samples from the breathing zone of 372 workers in energy and biochemistry units, benzol refinement and experimental furnace units	BTEXs	Stationary air sampling over a full work shift	Elevated cancer risk attributable to benzene exposure; exposure to BTEX components in the benzol refinement unit was higher than in other units
Normohammadi/Tehran, Iran/2010–2011 [42]	Construction	60 demolition workers from 4 demolition sites; 15 samples from each site	Crystalline silica	Personal air sampling over a full work shift, meteorological parameters including air temperature and wind speed were used in the analysis	Elevated ELCR of lung cancer attributable to crystalline silica exposure in workers
Tavakol/Tehran, Iran/study year is unknown [43]	Construction	85 samples from 85 construction workers including supervisors, stonemason, batching and concrete workers, and labors	Crystalline silica	Personal air sampling over a full work shift	Elevated ELCR of lung cancer attributable to crystalline silica exposure in construction work; batching and concrete workers had the highest average exposure that was greater than the threshold limit recommended by OSHA
Moghadam/Neyshabour, Iran/2015 [53]	Concrete manufacturing	Sampling of breathing zone of 72 workers from autoclave units, wing tube and cutter line, mixing, packing, and quality control units; information on number of samples was not provided	Crystalline silica	Stationary air sampling; information on sampling duration was not provided	Elevated ELCR for lung cancer attributable to crystalline silica exposure

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Azari/Tehran, Iran/study year is unknown [44]	Stone cutting and milling, foundry work, glass manufacturing, asphalt, construction, sand and gravel mining, sand blast, ceramics, bricks and cement	200 workers from 50 workplaces (4 workers in each) including stone cutting and milling, foundry, glass manufacturing, asphalt preparation, ceramic, brick and concrete manufacturing, and construction	Crystalline silica	Personal air sampling over a full work shift	Elevated lung ELCR attributable to cumulative exposure of crystalline silica (direct correlation between the level of exposure and lung cancer risk)
Mohammadi/Markazi, Iran/2015 [41]	Ceramic pin insulator manufacturing	60 samples from 5 units including pressing, production, coating, furnace, and packing (12 samples in each unit)	Crystalline silica	Stationary air sampling; information on sampling duration was not provided	The highest mortality risk of lung cancer attributable to crystalline silica exposure was estimated for furnace workers
Yahyaei/Rasht, Iran/2018 [47]	Hospital	65 employees in pathology labs including pathologist, lab technician, office worker, service workers	Formaldehyde	Personal air sampling during direct exposure to formaldehyde (8:00 and 12:00 a.m.); 25 min for each task; stationary air sampling during a full work shift	Elevated individual lifetime cancer risk 100–1000 times higher than the acceptable cancer risk in all exposed laboratory staff; exposure level in all staff members was higher than the acceptable level by OSHA
Pourtaghi/Tehran, Iran/2018 [46]	Hospital	68 samples from the breathing zone of 72 hospital staff	Formaldehyde	Stationary air sampling during one full work shift	Elevated LCR attributable to intensity of formaldehyde exposure greater than the recommended acceptable limit by OSHA
Jalali/Iran/2019 [45]	Hospital	Sampling of breathing zone of 60 pathology laboratory staff members; information on number of samples was not provided	Formaldehyde	Stationary air sampling during one full work shift	Highest LCR attributable to formaldehyde in lab technicians

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Zarei/Tehran/Iran/ 2010 [29]	Brake shoe and clutch disk manufacturing	61 workers including weighing, mixing, pressing, and finishing occupations	Asbestos	Personal air sampling; 4 h over a full work shift	Elevated risk of lung cancer ELCR attributable to cumulative exposure of asbestos; exposure levels for all workers far greater than the occupational exposure limits recommended by OSHA
Jafari/Isfahan, Iran/ study year is unknown [54]	Asbestos-cement products manufacturing	97 workers from 4 units including milling, cutting, and cutting	Asbestos	Personal air sampling; samples collected from different units of the factory over a full work shift	Elevated risk of lung, mesothelioma, and gastrointestinal cancer mortality after 20 years of exposure; greater risk in the dry cutting unit than the wet cutting unit
Harati/Iran/2015 [37]	Automobile manufacturing	46 samples from 20 workers	BTEXs, Silica	Personal air sampling (2 times for each worker over a full work shift), and 6 stationary air samples over a full work shift	Elevated hematological cancer risk corresponding to cumulative exposure to benzene and crystalline silica
Dehghani/Iran/2016 [38]	Automobile manufacturing	34 samples from breathing zones of workers: cabin maker, pre-paint, and painting units	BTEXs	Stationary air sampling over a full work shift	Elevated risk of cancer in painting unit workers attributable to benzene and ethyl benzene with 30 years of exposure
Baghani/Ardabil, Iran/2017 [31]	Beauty salons	50 beauty salons across the Ardabil Province	BTEXs	Stationary air sampling; indoor air temperature, pressure, and relative humidity were used in the analysis, samples taken during the afternoon (14:00 to 19:00)	Elevated LTCR ⁸ attributable to BTEX components

Table 3. Cont.

Reference/Location/ Study Year	Industry	Population/Sample Size/Description	Exposure Agents Assessed	Type of Assessment/Frequency of Measurement	Outcome/Results
Hadei/Tehran, Iran/2016–2017 [30]	Beauty salons	360 samples from 20 beauty salons, 180 samples each for indoor and outdoor; (3 samples for each component including BTEXs, formaldehyde, and acetaldehyde)	BTEXs, formaldehyde, and acetaldehyde	Stationary air sampling; over a full work shift during 3 consecutive months; air temperature, pressure, and relative humidity were used in the analysis	Elevated risk of cancer attributable to benzene, formaldehyde, and acetaldehyde exposure; exposure to different components affected by tasks: benzene and toluene (hair dyeing), formaldehyde (hair style and nail treatments), and xylene (hair styling)
Hazrati/Ardabil, Iran/study year is unknown [32]	Waterpipe café	87 samples from 81 waterpipe cafés	BTEXs	Stationary air sampling; each sample duration lasted for 50 min; sampling from 14:00 to 19:00; 6 additional samples taken directly from the smoke mainstream of the waterpipe (4 from fruit flavored tobacco and 2 from regular tobacco).	Elevated long-term exposure cancer risk attributable to benzene exposure
Rostami/Ardabil, Iran/2018 [33]	Waterpipe café	51 samples from 51 waterpipe cafés	PAHs ⁹	Stationary air sampling; from breathing zone of smokers and employees; air temperature, pressure, and relative humidity were used in the analysis	Elevated risk of cancer attributable to PAH component inhalation

¹ Benzene, Toluene, Ethylbenzene and Xylenes; ² Excess Lifetime Cancer Risk; ³ Volatile Organic Compound; ⁴ Lifetime Cancer Risk; ⁵ Incremental Lifetime Cancer Risk; ⁶ Compressed Natural Gas; ⁷ Occupational Safety and Health Administration; ⁸ Inhalation Lifetime Cancer Risk; ⁹ Polycyclic Aromatic Hydrocarbons (PAH), 16 PAH compounds including Naphthalene (Naph), Acenaphthylene (Acy), Acenaphthene (Ace), Fluorene (Flu), Phenanthrene (Phen), Anthracene (Anth), Fluoranthene (Fit), Pyrene (Pyr), Benzo[a]anthracene (BaA), Chrysene (Chr), Benzo[b]fluoranthene (BbF), Benzo[k]fluoranthene (BkF), Benzo[a]pyrene (BaP), Dibenzo[a,h]anthracene (DahA), Benzo [ghi]perylene (BghiP), and Indeno[123-cd]pyrene (Ind).

3.3. Burden of Cancer Studies

In addition, there were three relevant publications that used secondary data to project occupational cancer risk [55–57]. Of these, two publications by Mosavi-Jarrahi et al. projected the fraction of leukemia and lung cancer incidence in Iran attributable to exposure to occupational carcinogens, e.g., benzene, ionizing radiation, and ethylene oxide for leukemia, and silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium, and asbestos for lung cancer [55,56]. Both publications applied available country-specific workforce survey data from the International Labour Organization (ILO) and estimated the proportion of exposed workers in each industry using the European CARcinogen Exposure (CAREX) database and relative risk estimates from the literature to predict the burden of occupational cancer [58]. The authors reported that 0.08% of male workers and 0.02% of female workers were exposed to the major occupational lung carcinogens (silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium, and asbestos), resulting in an attributable fraction of lung cancer due to occupational exposures of 12% in men and 1.5% in women [55], and that 0.016% of male workers and 0.02% of female workers were exposed to leukemogens (benzene, ionizing radiation, and ethylene oxide), estimating that 7.6% of leukemia in men and 3.6% in women were attributable to occupational exposures [56].

Abtahi et al. [57], estimated age-, sex-, and cause-specific mortality attributable to occupational risks for the years 1990, 2005, and 2015 using the methods provided in the Global Burden of Disease project (GBD) 2015 [57]. The occupational carcinogens included in the projections were asbestos, arsenic, benzene, beryllium, cadmium, chromium, diesel exhaust engine, formaldehyde, nickel, polycyclic aromatic hydrocarbons, second-hand smoke, silica, and sulfuric acid. Information on industry patterns was extracted from National Population and Housing censuses in 1986, 1996, 2006, 2011, and 2016, and exposures by industry were derived primarily from the European CAREX database [59,60]. The results of this study showed that exposure to particulate matter, gases, and fumes, and asbestos was among the highest contributions to the national attributable DALYs in 2015 among occupational risks. In addition, from 1990 to 2015, the increase in total DALYs attributable to occupational carcinogens (112%) was higher than that for other occupational risks.

3.4. Publications over Time and Location

There were no relevant publications before 2009; in the subsequent years, the trend fluctuated between two to four publications per year until 2015. In 2016 to 2021, the trend was between five to seven publications per year. Only a few epidemiological studies per year were published between 2009 and 2021. Figure S1 provides a full summary of the time trends.

In terms of the geographical trend of publications, the greatest number ($n = 15$ or 31%) were at the national level or in non-specified areas of Iran in various manufacturing industries. The second most frequent geographical area was Tehran 11 (22%), the capital of Iran with a population of around 9 million, including multiple types of economic activities. Studies in Tehran were conducted across diverse workplaces such as manufacturing of plastic products, manufacturing of parts and accessories for motor vehicles, hairdressing and other beauty treatment, hospitals, and the construction industry. Studies conducted in the central part of Iran (Isfahan, Arak, Yazd, and Kashan; $n = 8$) included mostly heavy industries such as casting of iron and steel ($n = 2$), the manufacture of basic metals including iron and steel, and plastic products ($n = 6$) (Figure S1).

4. Discussion

This review identified 49 articles on occupational exposure to carcinogens and associated cancer risk in Iran. The studies consisted of one cohort study and 11 case-control studies directly investigating the association between occupational exposures and the risk of various cancers, as well as 34 studies with exposure monitoring including projections of associated cancer risks, and three studies investigating the burden of cancer

related to occupational carcinogen exposure based on secondary national and international survey data.

The first relevant article published in 2009 indicates that occupational cancer epidemiology is a relatively new topic in Iran, with the number of publications increasing in recent years. The relatively low number of published articles on occupational cancers overall may be due to several reasons including (1) occupational physicians and hygienists focusing on acute effects of occupational exposure rather than cancers that take many years to develop, (2) limited tradition of collaboration across disciplines, e.g., hospitals, cancer registries, universities, and relevant ministries, (3) it may be that some research is conducted but not published in national and international journals, and (4) a lack of training and capacity in this particular area of research.

Even though the petroleum industry is a major industry in Iran [1], only six publications focused on this industry. This could be due to confidential matter and safety precautions in this industry that would require permission and special security training for external researchers [61].

Regarding the epidemiological studies, the only identified prospective cohort study with a long-term follow-up examined cancer incidence in relation to a single exposure to sulfur mustard in military service personnel in the Iran–Iraq war (which has been evaluated by IARC monograph as an occupational exposure agent with sufficient evidence for lung cancer) [62]. This cohort study also included volunteers who joined the armed forces temporally to defend their cities with unknown job histories, so it is not a classical occupational cohort with precise exposure information.

In case–control studies, occupational information was collected via interviews, by self-reporting of jobs and/or occupational exposures, with no further attempt to assign occupational exposures. Some of the case–control studies featured design aspects (e.g., choice of controls, potential confounding, and power) that will have led to limitations in the interpretation of the results. One of the case–control studies appeared to have selected controls in an inappropriate way (by selecting them based on the absence of exposure), but could be related to authors' uncertainty about the study design or mistranslation from Farsi to English in the English publication [11].

This review found that exposure monitoring studies in Iran mostly focused on the projection of cancer risk based on a limited number of exposure measurements (personal and stationary air sampling). Thirteen out of 34 studies assessed the exposure through stationary measurements that provide only a very crude indication of personal exposure. Moreover, exposure agents such as BTEXs, crystalline silica, formaldehyde, and chromium in the workplaces were mostly measured on single occasions, although it is well known that exposure levels often differ between and within workers from day-to-day and are not constant over time (months, seasons, and years) [63,64]. Estimating the risk of cancer based on the exposure level derived from a single (personal) exposure measurement may over- or underestimate risk as this value may not be representative for the individual's exposure over time [63]. A few of the studies used previously established exposure databases, e.g., CAREX to project the occupational cancer burden [58]. CAREX is a database which contains estimates of numbers of workers occupationally exposed to carcinogens by European industries (exposure data from 1990–1993). As shown by the two studies applying CAREX and GBD data to estimate the occupational cancer burden in Iran, the burden appears relevant, but these estimations have large uncertainties and do not provide insight into targeted prevention measures, as they are based on extrapolating exposure from other countries, workforce, and risk data instead of structured representative (exposure and risk) data from Iran.

This review provides the first overview of the status of occupational cancer research in Iran. A major limitation of the review is that carcinogenic exposures summarized in non-cancer studies are not captured here. Further, studies that have not been published in journals indexed by the searched databases might have been missed. Some studies were

not sufficiently detailed to retrieve all relevant information, e.g., “questionnaires assessed occupational exposures” but did not indicate the type of exposure.

5. Conclusions

Identifying the burden of occupational cancers is an important step to identify the extent of a problem and develop prevention measures to reduce risks [2]. Since industrial and regulatory circumstances vary across countries, well-designed occupational cancer studies of sufficient size that include relevant exposure assessment methods for each study design are needed in Iran. Enhanced collaboration, between, e.g., occupational physicians, cancer researchers, industrial hygienists, and workplace representatives, as well as collaborations and participation in international conferences [65], would be an asset to conduct informative studies.

Additionally, further systematic exposure monitoring surveys will help to identify potential high-risk occupational environments for future risk management planning and facilitate and can inform the exposure assessment and assignment of future epidemiological studies [64,66].

We recommend that further work be focused in three key areas. First, given that there are large-scale ongoing cancer epidemiology studies in Iran (for example, the Persian cohort study [67] and the IROPICAN case-control study [68]), proper occupational exposure assessment and assignment should be included in these studies, which requires the development of valid job-exposure matrices specifically for Iran. Second, large-scale cohort studies in major industries should be initiated to inform cancer control in Iran and efforts on a global scale, as data from emerging economies are lacking worldwide [69]. Third, occupational exposure monitoring needs to be more systematic, with data made (centrally) available for (epidemiological) research and to develop risk reduction measures.

All these efforts will support the ultimate goal of occupational cancer prevention in Iran. Further, the documentation of exposure levels, contexts, and cancer risks in Iran will contribute to the scientific understanding of occupational cancers and related exposure factors on a global scale.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/cancers13143581/s1>, Figure S1: Temporal trend of publications on cancer research in occupational settings in Iran, Table S1: Search query used in PubMed to retrieve relevant publications from initiation up to January 2021, Table S2: Search query used in Web of Sciences to retrieve relevant publications from initiation up to January 2021.

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Supplementary Figures and tables

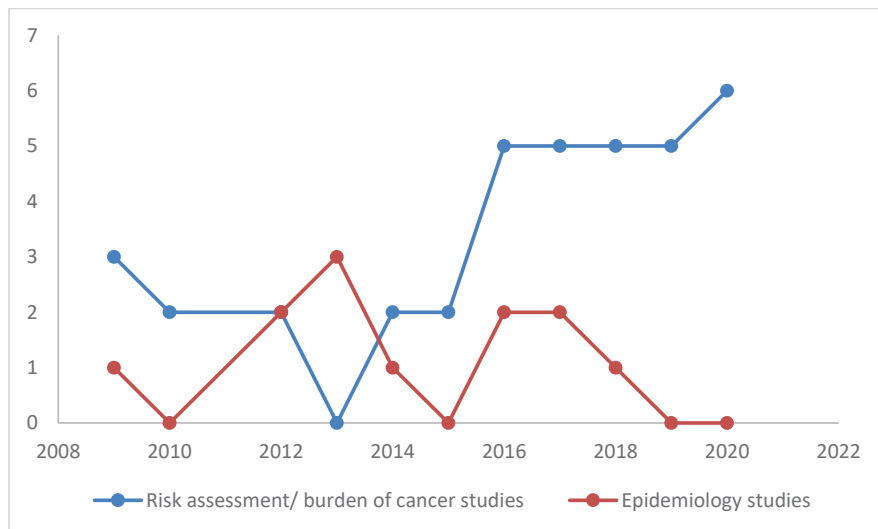
Supplementary Table S1. Search query used in PubMed to retrieve relevant publications from initiation up to January 2021

	Search	Query	Items found
		Cancer	
#1	#1	neoplasms[MeSH Terms]	2481403
#2	#2	(cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan*)	3695197
		Occupational exposure	
#3	#3	Occupational exposure[MeSH Terms]	59375
#4	#4	(Occupational hazard* OR workplace hazard* OR hazard*)	316470
#5	#5	Industry[MeSH Terms]	249120
		Iran	
#6	#6	Iran[MeSH Terms]	26189
#7	#7	(Iran* OR Tehran* OR Shiraz OR Mazandaran OR Esfahan OR Kerman* OR Yazd OR Arak)	191212
#8	#1 OR #2	(neoplasms[MeSH Terms]) OR ((cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan*))	3872610
#9	#3 OR #4	(Occupational exposure[MeSH Terms]) OR ((Occupational hazard* OR workplace hazard* OR hazard*))	368083
#10	#9 OR #5	((Occupational exposure[MeSH Terms]) OR ((Occupational hazard* OR workplace hazard* OR hazard*))) OR Industry[MeSH Terms]	597564
#11	#7 OR #8	(iran[MeSH Terms]) OR ((Iran* OR Tehran* OR Shiraz OR Mazandaran OR Esfahan OR Kerman* OR Yazd OR Arak))	191212
#14	#9 AND #10 AND #11	((neoplasms[MeSH Terms] AND (1990:2020[pdat])) OR (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* AND (1990:2020[pdat]))) AND (((Occupational exposure[MeSH Terms] AND (1990:2020[pdat])) OR (Occupational hazard* OR workplace hazard* OR hazard* AND (1990:2020[pdat]))) OR (Industry[MeSH Terms] AND (1990:2021[pdat]))) AND ((Iran[MeSH Terms] AND (1990:2020[pdat])) OR (Iran* OR Tehran* OR Shiraz OR Mazandaran OR Esfahan OR Kerman* OR Yazd OR Arak AND (1990:2020[pdat])))	726
#15	#14 NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))	((((neoplasms[MeSH Terms] AND (1990:2020[pdat])) OR (cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan* AND (1990:2020[pdat]))) AND (((Occupational exposure[MeSH Terms] AND (1990:2020[pdat])) OR (Occupational hazard* OR workplace hazard* OR hazard* AND (1990:2020[pdat]))) OR (Industry[MeSH Terms] AND (1990:2020[pdat]))) AND ((Iran[MeSH Terms] AND (1990:2020[pdat])) OR (Iran* OR Tehran* OR Shiraz OR Mazandaran OR Esfahan OR Kerman* OR	718

		Yazd OR Arak AND (1990:2020[pdat]))) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]) AND (1990:2020[pdat]))	
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Supplementary Table S2. Search query used in Web of Sciences to retrieve relevant publications from initiation up to January 2021

	Search	Query	Items found
#1	#1	TS=(cancer* OR carcinoma* OR neoplas* OR tumor* OR tumour* OR malignan*)	3,764,615
#2	#2	TS=(Occupational hazard* OR workplace hazard* OR hazard*)	382,311
#3	#3	TS=(industr*)	1,278,655
#4	#4	#3 OR #2	1,634,769
#5	#5	TS=(Iran* OR Tehran* OR Shiraz OR Mazandaran OR Esfahan OR Kerman* OR Yazd OR Arak)	122,013
#6	#6	#5 AND #4 AND #1	391



Supplementary Figure S1. Temporal trend of publications on cancer research in occupational settings in Iran

Chapter 3: Occupational lung cancer in Iran

In this chapter, the risk of lung cancer in relation to major International Standard Classification of Occupations (ISCO-68), and selected high-risk occupations held in a large nationwide case-control study (IROPICAN) in Iran [112] has been investigated. For the selected occupations with evidence based increased risk and large enough numbers, the duration of employment and risk by lung cancer subtypes further analysed.

3.1 RATIONALE

By far lung remain the most important targeted organ of occupational carcinogens. A substantial proportion of human carcinogens had been classified in the IARC monographs program occur mostly in occupational settings [113]. Globally it has been estimated that approximately 15% of lung cancers can be attributed to occupational environment exposures but varied greatly by geographical region.

Iran is the most industrial country in the Middle east region, workers may expose to variety of carcinogens in the occupational settings. Nevertheless, majority of our understanding about lung cancer raised from workplace exposures, mainly comes from High-Income countries (HICs) but a few attempts have been made to estimate the risk of lung cancer associated with occupations in LMICs including Iran [35]. There has been an estimation of lung cancer attributable to occupational exposure to silica, cadmium, nickel, arsenic, chromium, diesel fumes, beryllium, and asbestos

in Iran was 12%. However, this estimation is based on available data from HICs [33, 34], that resulting in large uncertainties.

Although, previously occupational exposures have been strongly associated with an increased risk of lung cancer in various countries, still, we are facing a huge uncertainty related to occupational lung cancer in Iran. Therefore, in this study, available collected information on 658 lung cancer cases and 3477 controls from a national case-control study that collected good quality information on occupational history to assess the risk of lung cancer in relation to occupations in Iran was used. The study population and the methods in detail described in section 1.5, and 1.6.

3.2 MAIN FINDINGS

Negative association of lung cancer risk has been found in the first two major occupation groups of ISCO-68 including professional, technical and related workers (OR= 0.6; CI: 0.4,0.9); administrative and managerial workers (0.4; CI: 0.2,0.7) in the baseline model but not significant by adjusting for smoking and opium consumption (fully adjusted). the risk of lung cancer military service workers remained reversely associate even in the fully adjusted model (0.5; CI: 0.2, 0.9); compared to the positive association in workers of elementary occupations (1.4; CI: 1.2, 1.7) in the baseline model. The only adjusted association were seen in women 's agricultural workers (2.6; CI: 1.3, 5.3). Remaining major groups showed varying odds ratios with wide confidence intervals due to small numbers.

Table 9 shows further results on specific high-risk occupations, increased risk of lung cancer was observed among construction workers (1.4; CI: 1.0,1.8), and petroleum industry workers (3.2; CI: 1.1, 9.8) in men. Table 10 shows the results in women, the association revealed among farmers (2.6; CI: 1.3, 5.3) and bakers (5.5; CI: 1.0, 29.8), although the latter was based on small numbers.

Table 9: Risk of lung cancer associated with ever having worked in the selected specific occupations (ISCO-68) in men

ISCO-68 major groups	Ever worked N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
Textile industry workers	5/ 49	0.6 (0.1, 2.0)	0.4 (0.1, 1.2)	0.6 (0.3, 1.6)
Painters	7/31	1.1 (0.5, 2.7)	0.7 (0.3, 2.0)	0.7 (0.3, 2.0)
Construction workers	95/ 318	1.6 (1.2, 2.1)	1.5 (1.1, 1.9)	1.4 (1.0, 1.8)
Drivers	53/ 250	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	0.9 (0.6, 1.2)
Road drivers	46/ 190	0.9 (0.7, 1.3)	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)
Heavy vehicles drivers	9/ 69	0.6 (0.3, 1.2)	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)
Welders	16/ 53	1.5 (0.8, 2.7)	1.2 (0.6, 2.4)	1.0 (0.5, 2.0)
Farmers	161/ 678	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)
Only field farmers	130/ 576	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)
Only animal farmers	16/ 60	1.4 (0.8, 2.5)	1.2 (0.6, 2.2)	1.0 (0.5, 2.0)
Petroleum industry workers	5/ 13	1.7 (0.6, 4.8)	2.5 (0.8, 7.6)	3.2 (1.1, 9.8)
Bakers	8/ 24	1.8 (0.8, 4.0)	1.8 (0.8, 4.3)	1.4 (0.5, 3.7)
Rubber industry workers	3/ 9	1.7 (0.4, 6.7)	2.5 (0.5, 11.0)	2.7 (0.6, 12.6)

Note: ISCO-68, International Standard Classification of Occupations; N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

Table 10: Risk of lung cancer associated with ever having worked in the selected specific occupations (ISCO-68) in women

ISCO-68 major groups	Ever worked N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
	Female	Female	Female	Female
Textile industry workers	6/ 58	0.8 (0.3, 2.3)	0.9 (0.4, 2.4)	0.4 (0.1, 1.1)
Farmers	18/ 69	2.3 (1.2, 4.5)	2.4 (1.2, 4.6)	2.6 (1.3, 5.3)
Only field farmers	14/63	2.0 (1.0, 4.0)	2.0 (1.0, 4.1)	2.4 (1.1, 5.1)
Only animal farmers	3/ 5	3.1 (0.6, 14.4)	3.0 (0.7, 14.8)	3.9 (0.8, 19.7)
Bakers	3/ 5	5.0 (1.1, 22.2)	5.0 (1.1, 23.2)	5.5 (1.0, 29.8)

Note: ISCO-68, International Standard Classification of Occupations; N, number; OR, odds ratio; CI, confidence interval

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

The risk of lung cancer in relation to the duration of work experience as construction worker by treating the duration continues variable in equal categories (10-years intervals) was (1.1; CI: 1.1, 1.2); Table 11.

Table 11: Risk of lung cancer associated with the duration of employment as a construction worker, in men

Duration of employment as a construction worker (years)	N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
Never being employed		ref	ref	ref
≤28	48/ 190	1.4 (1.0, 2.1)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)
>28	47/ 128	1.8 (1.3, 2.5)	1.7 (1.2, 2.4)	1.6 (1.1, 2.4)
Continues duration of employment (P value trend)		1.2 (1.1, 1.2) (<0.001)	1.1 (1.0, 1.2) (<0.001)	1.1 (1.0, 1.2) (<0.001)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

Reported P-value for trend were not shown significant effect of farming duration on lung cancer risk in both sexes Table 12 and Table 13.

Table 12: Risk of lung cancer associated with the duration of employment as a male farmer

Duration of employment as a farmer (years)	N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
Never being employed	342/ 1,734	ref	ref	ref
≤35	56/ 251	1.1 (0.9, 1.7)	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)
>35	103/ 413	1.2(0.9, 1.5)	1.2 (0.9, 1.5)	1.1 (0.8, 1.4)
10 years interval (P value trend)		1.1 (0.9, 1.3) (0.10)	1.1 (0.9, 1.3) (0.10)	1.1 (0.97, 1.3), (0.10)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

Table 13: Risk of lung cancer associated with the duration of employment as a female farmer

Duration of employment as a farmer (years)	N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
Never being employed	139/ 1,010	ref	ref	ref
≤35	12/ 31	4.3 (1.9, 9.7)	4.5 (2.0, 10.0)	4.7 (1.9, 11.6)
>35	6/ 38	1.2 (0.4, 3.1)	1.2 (0.5, 3.2)	1.5 (0.6, 4.1)
10 years interval (P value trend)		1.0 (0.99, 1.1) (0.10)	1.0 (0.98, 1.1) (0.20)	1.0 (0.96, 1.1) (0.50)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

By histological subtypes, SCC lung cancer subtype showed an elevated risk of (1.9; CI, 1.2- 3.0) in male construction workers and increased risk of both adenocarcinoma (3.8; CI: 1.4, 9.9) and SCC (4.3; CI: 1.1, 17.2) subtypes in fully adjusted model for female farmers.

3.3 CONCLUSION

The inverse association of lung cancer risk was observed for two ISCO-68 major groups of white-collar occupations (professional, technical and related workers; administrative and managerial workers), and military service workers compare to elevated risk for “elementary occupations” and “plant and machine operators and assemblers”. All associations attenuated after adjusting for smoking and opium consumption. Various lifestyles pattern across groups may lead to more frequent lung cancer risk factors e.g., tobacco smoking, and opium consumption in some occupations.

Although an association in some high-risk occupations were not observed, such as painters, welders, and rubber industry workers, who are consistently exposed to a variety of lung cancer carcinogens, our study supported the association between some occupations, such as construction workers and petroleum industry workers in men and women, farmers, and bakers with lung cancer risk. The small sample size may explain why no association was found, although most associations were derived from a small number of cases. Accordingly, these results came from occupations that may involve a wide range of tasks with exposure to different types and amounts of carcinogenic chemicals. For example, we studied lung cancer risk for all types of painters, e.g., construction painters and automotive painters, which may obscure the true association, as we combined varies types and tasks in a single occupation title as a painter. In this regard, conducting studies capable of assessing the risk of specific tasks of occupations is necessary for the identification of carcinogenic chemicals in order to develop evidence-based action plans to reduce exposure in occupational settings.

3.4 PUBLICATION II

Title: Lung Cancer Risk in Relation to Jobs Held in a Nationwide Case-Control Study in Iran

Status: published in Occupational and Environmental Medicine Journal, August 2022.





This paper provided new and more reliable results about the risk of lung cancer associate to occupations in Iran and refined the risk of lung cancer that arising from high-risk occupations for lung cancer while adjusting for sex, age, geographic region, and personal substance use, it also showed that opium (and smoking) are confounders for occupations.



OPEN ACCESS

Original research

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.

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



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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 LMICs⁸ 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.

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

Study participants' characteristics	Male n (%)		P value*	Female n (%)		P value*
	Cases 501 (17.3)	Controls 2398 (82.7)		Cases 157 (12.7)	Controls 1079 (87.3)	
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 (%)		P value*	Female n (%)		P value*
	Cases 501 (17.3)	Controls 2398 (82.7)		Cases 157 (12.7)	Controls 1079 (87.3)	
Missing, students, jobless	1 (0.2)	9 (0.4)		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.

Workplace

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

ISCO-68 major groups	Ever worked N (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
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

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 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.

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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Supplementary Materials

The following are available at the supplementary materials, Table S1: The 5-digit ISCO-68 codes corresponding to each specific selected job, Table S2: Risk of lung cancer associated with the duration of employment as a construction worker, in male, Table S3: Risk of lung cancer associated with the duration of employment as a farmer, stratified sex.

Table S1: The 5-digit ISCO-68 codes corresponding to each specific selected job

Selected specific occupations from (ISCO-68)	Five-digits codes
Textile industry workers	7-00.70, 7-51.10 to 7-59.90, 7-91.00 to 7-91.90, 7-93.00 to 7-99.90, 8-35.60
Painters	9-31.00 to 9-39.90
Construction workers	9-51.00 to 9-52.90, 9-55.00 to 9-59.99, 9-75.24 to 9-74.40, 9-72.20, 9-73.35, 9-99.10
Drivers	6-28.20, 6-31.40, 9-83.20 to 9-83.90, 9-85.20 to 9-85.90, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90, 9-85.00 to 9-85.90, 9-89.90
Road drivers	9-85.20 to 9-85.50, 9-85-70, 9-85-90
Heavy vehicles drivers	6-28.20, 6-31.40, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90, 9-85-60, 9-89.90
Welders	8-72.10 -8-72.90
Farmers	6-11.00 to 6-49.90
Only field farmers	6-11.00 to 6-12.30, 6-12.70, 6-12.90, 6-21.05 to 6-23.90, 6-28.20 to 6-28.90, 6-29.40 to 6-29.60, 6-29.90, 6-31.10 to 6-32.90
Only animal farmers	6-12.40 to 6-12.60, 6-12.90, 6-24.10 to 6-26.90, 6-29.20 to 6-29.30, 6-29.90, 6-41.00 to 6-49.90
Petroleum industry workers	7-13.20 to 7-13.90, 7-43.50, 7-45.20 to 7-45.90, 9-69.40, 9-72.50
Bakers	7-76.10 to 7-76.90
Rubber industry workers	7-49.90, 9-01.20 to 9-01.50, 9-02.20 to 9-02.90

Note: ISCO-68, International Standard Classification of Occupations.

Table S2: Risk of lung cancer associated with the duration of employment as a construction worker, in males.

Duration of employment as a construction worker (years)	N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)
Never being employed		ref	ref	ref
≤28	48/190	1.4 (1.0, 2.1)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)
>28	47/128	1.8 (1.3, 2.5)	1.7 (1.2, 2.4)	1.6 (1.1, 2.4)
Continues duration of employment (P value _{trend})		1.2 (1.1, 1.2) (<0.001)	1.1 (1.0, 1.2) (<0.001)	1.1 (1.0, 1.2) (<0.001)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

Table S3: Risk of lung cancer associated with the duration of employment as a farmer, stratified by sex.

Duration of employment as a farmer (years)	N (Cases/Controls)		Model 0 ^a OR (95% CI)		Model 1 ^b OR (95% CI)		Model 2 ^c OR (95% CI)	
	Male	Female	Male	Female	Male	Female	Male	Female
Never being employed	342/1,734	139/1,010	ref	ref	ref	ref	ref	ref
≤35	56/251	12/31	1.1 (0.9, 1.7)	4.3 (1.9, 9.7)	1.1 (0.8, 1.6)	4.5 (2.0, 10.0)	1.0 (0.7, 1.4)	4.7 (1.9, 11.6)
>35	103/413	6/38	1.2 (0.9, 1.5)	1.2 (0.4, 3.1)	1.2 (0.9, 1.5)	1.2 (0.5, 3.2)	1.1 (0.8, 1.4)	1.5 (0.6, 4.1)
10 years interval (P value _{trend})			1.1 (0.9, 1.3), (0.10)	1.0 (0.99, 1.1) (0.10)	1.1 (0.9, 1.3), (0.10)	1.0 (0.98, 1.1) (0.20)	1.1 (0.97, 1.3), (0.10)	1.0 (0.96, 1.1) (0.50)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption.

Chapter 4: Occupational Bladder Cancer in Iran

This chapter describes the design adopted by this research to achieve the aims and objectives stated in (section 1.6.2) of Chapter 1, to assess the risk of bladder cancer related to occupations and industries in Iran. (Section 4.1) rationale of conducting the study; (section 4.2) details the main finding of the study; (section 4.3) conclude the results; and (section 4.4) includes the publication of section.

4.1 RATIONALE

Overall, estimated around 15–20% of all bladder cancer in men could be attributed to occupation [26, 114, 115]. Occupational carcinogen exposure accounted for second commonest risk factor of bladder cancer following tobacco smoking, several exposures, occupations, and industries have been associated with increased bladder cancer risk [116]. Exposure to some of the aromatic amines in dye manufacture, rubber and other industries, hairdresser, and painters are specific agents in the workplace which have been associated with bladder cancer [11, 56, 85, 117, 118], and exposure to PAHs in aluminium process workers and other industries has also been associated with bladder cancer [56, 119].

Iran as an industrial country has many large industries in which workers may expose to variety of bladder carcinogens. Nevertheless, we do not know much about the bladder cancer raised from workplace exposures, except evidence mainly from HICs. Although, a few studies had been carried out to estimate the risk of bladder cancer associated with occupations in Iran

but still did not achieve certain results, (refer to the publication 1 in chapter 2) [120-123].

To identify potential high risk occupational for bladder cancer, we conducted a study using IROPICAN case-control study to evaluate the risk of bladder cancer associate with occupations while adjusting for personal substance use (e.g., smoking, opium).

4.2 MAIN FINDINGS

As 85% of women's cases were housewives, therefore you excluded them from the analysis. The results revealed inverse association between bladder cancer risk and workers in second and third ISCO-68 major group of occupations including administrative and managerial workers (0.4; CI: 0.2, 0.9), and clerks (0.6; CI: 0.4, 0.9). Elevated risk has been observed in the baseline model for plant and machine operators (1.4; CI: 1.0, 1 .8), and elementary occupations (1.3; CI: 1.0, 1.5) but no longer remained significant by adjusting for smoking, opium consumption and urinary tract disease.

Further findings in Table 14 on high-risk occupations, shows increased risk of bladder cancer among metal processors (5.8; CI: 1.4, 25.2) based on a small number of cases, and workers in occupations with the high-risk of exposure to aromatic amines (2.1; CI: 1.2, 3.8). In addition, nonsignificant elevated risk of bladder cancer has been observed among construction workers, road drivers, welders, electronic workers, and glass industry workers.

Table 14: Risk of bladder cancer associated with ever having worked in the selected specific occupations (ISCO-68)

ISCO-68 major groups	Ever worked N (Cases/Controls)	Model 0 ^a OR (95% CI)	Model 1 ^b OR (95% CI)	Model 2 ^c OR (95% CI)	Model 3 ^c OR (95% CI)
	Male	Male	Male	Male	Male
Textile industry workers	12/ 49	1.0 (0.5, 1.8)	0.9 (0.4, 1.7)	0.6 (0.3, 1.6)	1.0 (0.5, 2.0)
Painters	3/31	0.4 (0.1, 1.5)	0.3 (0.1, 1.2)	0.3 (0.1, 1.3)	0.4 (0.1, 1.4)
Construction workers	90/ 316	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
Road drivers	54/ 188	1.2 (0.8, 1.6)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)	1.1 (0.8, 1.5)
Heavy vehicles drivers	26/ 69	1.7 (1.1, 2.7)	1.4 (0.9, 2.4)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Welders	16/ 53	1.3 (0.7, 2.4)	1.3 (0.7, 2.5)	1.1 (0.6, 2.1)	1.1 (0.6, 2.2)
Plumber	3/21	0.7 (0.2, 2.3)	0.7 (0.2, 2.4)	0.5 (0.1, 1.8)	0.4 (0.1, 1.8)
Petroleum industry workers	4/ 13	1.2 (0.4, 3.7)	1.9 (0.6, 6.9)	2.3 (0.7, 7.5)	2.0 (0.6, 6.7)
Rubber industry workers	3/ 17	0.7 (0.2, 2.6)	0.7 (0.2, 2.5)	0.8 (0.2, 2.9)	0.8 (0.2, 3.1)
Hairdresser/ barbers	5/32	0.7 (0.3, 1.9)	0.6 (0.2, 1.8)	0.5 (0.2, 1.5)	0.5 (0.2, 1.5)
Metal processors	5/4	4.1 (1.0, 16.1)	3.8 (0.8, 16.5)	5.4 (1.3, 23.4)	5.8 (1.4, 25.2)
Leather goods makers	4/7	1.9 (0.5, 6.7)	1.5 (0.4, 5.6)	1.1 (0.3, 4.2)	0.9 (0.2, 3.5)
Mechanics	18/55	1.4 (0.8, 2.4)	1.4 (0.8, 2.5)	1.1 (0.6, 2.0)	1.0 (0.5, 2.0)
Electronic workers	10/40	1.2 (0.6, 2.5)	1.2 (0.5, 2.5)	1.2 (0.5, 2.6)	1.1 (0.5, 2.5)
Glass industry workers	7/15	1.9 (0.7, 4.9)	1.6 (0.6, 4.2)	1.8 (0.6, 5.0)	1.7 (0.6, 4.9)
Workers exposed to some aromatic amines	21/48	1.7 (1.0, 3.0)	1.9 (1.1, 3.3)	2.2 (1.2, 4.0)	2.1 (1.2, 3.8)

Note: ISCO-68, International Standard Classification of Occupations; N, number; OR, odds ratio; CI, confidence interval; —, no data.

^a Model 0 (M0) is adjusted for age categories (5-year categories) and residence (provinces)

^b Models 1 (M1) is adjusted for M0 plus cigarette smoking status and intensity.

^c Model 2 (M2) is adjusted for M1 plus opium consumption

^d Model 3 (M3) is adjusted for M2 plus urinary bladder infection and urinary bladder stone.

Table 15 shows the joint effect of smoking and opium consumption with some occupations with the high-level of exposure to some aromatic amines were evaluated, the result did not revealed interaction between this group of occupations and individual substance uses. No significant deviations from an additive or multiplicative scale were observed. Interactions on a multiplicative scale were assessed using an interaction term between occupation as exposed workers to the aromatic amines (never vs ever) and smoking status (never vs ever) or opium consumption status (never vs ever) in logistic regression models. Interactions on an additive scale were assessed by fitting linear OR models and calculating the relative excess risk due to interaction (RERI), in order to test the departure from additivity of the effects of both risk factors (occupations exposed to aromatic amines and smoking/ or opium consumption). RERI estimates along with 95% CIs based on the delta method are reported [124]. Never smokers and never

workers were considered as the reference category. The RERI measures the extent to which the effect of both exposures combined exceeds the sum of the effects of each considered separately and is thus given by $OR_{11} - OR_{10} - OR_{01} + 1$, where OR_{ij} is the OR for bladder cancer comparing the group with exposures i and j to the reference category. A $RERI > 0$ indicates a positive additive interaction where the effect of both exposures together exceeds the sum of the two exposures considered separately.

To compute summary estimates and 95% CIs comparing 'ever' with 'never' work in occupations exposed to aromatic amines across studies and to explore heterogeneity between studies, expressed as a percentage (I^2). The I^2 statistic quantifies the amount of inconsistency between studies and estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 ranges from 0% and 100%; a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity [125].

Table 15: Effect modification between smoking or opium consumption; and employment in high-risk occupations for aromatic amines exposure

Exposure status to cigarette smoking	N Case/Controls	OR a (95% CI)
Never-smoker and aromatic amines exposed worker	173/ 1273	ref
Never smoker and aromatic amines exposed worker	9/ 27	2.5 (1.1, 5.7)
Ever-smoker and never aromatic amines exposed worker	430/ 1073	3.3 (2.7, 4.0)
Ever-smoker and ever aromatic amines exposed worker	12/ 21	5.0 (2.3, 10.6)
P value multiplicative interaction		0.9
RERI a		0.1 (-4.1, 3.0)
Exposure status to opium consumption		
Never-opium user and never aromatic amines exposed worker	290/ 1801	ref
Never-opium user and aromatic amines exposed worker	15/ 40	2.3 (1.2, 4.4)
Ever- opium user and never aromatic amines exposed worker	313/ 545	4.5 (3.7, 5.6)
Ever- opium user and ever aromatic amines exposed worker	6/ 8	6.8 (2.2, 20.4)
P value multiplicative interaction		0.8
RERI b		09 (-6.7, 8.4)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Adjusted odds ratio for age categories (5-year categories), and residence (provinces)

^b RERI: biological interaction on an additive scale: relative excess risk due to interaction

4.3 CONCLUSION

This study found that occupations including administrative and managerial workers decrease the risk of bladder cancer while working as plant and machine operators, and elementary occupation elevated the risk. Moreover, excess risk of bladder cancer has been observed among metal processing workers and a group of occupations with the high probability of exposure to aromatic amines.

Unexpectedly, association for some high-risk occupations for bladder cancer (i.e., painters, plumbers, hairdressers, and rubber industry workers) has not been found but increased risk have been observed in some of the occupations (e.g., construction workers, road drivers, welders, electronic workers, and glass industry workers).

One explanation could be due to the small sample size that were not provided enough power to detect potential associations. Also, likely could be due to different chemical used and various level of exposure to those chemicals in Iran in compared to the other countries. Our study confirmed the previous findings on increased risk of bladder cancer associated with exposure to aromatic amines. Therefore, conducting large epidemiological studies in high-risk occupations with the high level of exposure to aromatic amines, is necessary to provide stronger evidence for developing of workplace legislation in order to decrease exposure in occupation settings.

4.4 PUBLICATION III

Title: Bladder Cancer Risk in Relation to Jobs Held in a Nationwide Case-Control Study in Iran

Status: paper has been submitted to the International Journal of Cancer

This paper is provided new and more reliable results about the risk of bladder cancer associated to occupations, and refined exposure assessment techniques (i.e., combining occupations by exposure likelihood) in Iran, while adjusting for sex, age, geographic region, and personal substance use.



Bladder Cancer Risk in men in Relation to Occupations Held in a Nationwide Case-Control Study in Iran

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Key Words:	Occupational cancer, Bladder cancer, Occupational exposure, Carcinogen, Iran

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Bladder Cancer Risk in men in Relation to Occupations Held in a Nationwide Case-Control Study in Iran

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Keywords: Occupational cancer, Bladder cancer, Occupational exposure, Carcinogen, Iran

Abbreviations:

CI	Confidence Intervals
IARC-WHO	International Agency for Research on Cancer- World Health Organization
ICD-O	International Classification of Diseases for Oncology
IROPICAN	The Iranian nationwide case-control study of Opium and Cancer
ISCO-68	International Standard Classification of Occupations
NIMAD	National Institute for Medical Research Development
ORs	Odds Ratios
RERI	Relative Excess Risk due to Interaction
UTIs	Urinary Tract Infections
UTSs	Urinary Tract Stones
4-APB	4-aminobiphenyl
2-NA	2-naphthylamine

Novelty and Impact

Metal processor workers and workers exposed to aromatic amines had an increased risk of bladder cancer, also in Iran. In addition, we found that the opium consumption may have been a confounding factor. The results showed that the risk of bladder cancer was reduced in several major groups of the International Standard Classification of Occupations after adjustment for the opium use.

Categories: Cancer Epidemiology

Abstract:

Globally, bladder cancer has been identified as one of the most frequent occupational cancers, but our understanding of the risk of occupational bladder cancer in Iran is less advanced. This study aimed to assess the risk of bladder cancer in relation to occupation in Iran. We used the IROPICAN case-control study data including 624 incident cases and 2392 controls. We assessed the risk of bladder cancer in relation to ever working in major groups of the International Standard Classification of Occupations (ISCO-68) while controlling for cigarette smoking, opium consumption, and urinary tract infections/stones. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) were calculated. Decreased ORs for bladder cancer were observed in administrative and managerial workers (OR 0.4; CI: 0.2, 0.9), and clerks (OR 0.6; CI: 0.4, 0.9). Elevated ORs were observed in metal processors (OR 5.8; CI: 1.4, 25.2), and workers in occupations exposed to aromatic amines (OR 2.1; CI: 1.2, 3.8). There was no evidence of interactions between working in aromatic amines-exposed occupations and tobacco smoking or opium use. Elevated risk of bladder cancer in metal processors and workers exposed to aromatic amines aligns with associations observed outside Iran. Other previously confirmed associations between high-risk occupations and bladder cancer were not observed, possibly due to small numbers or lack of details on exposure. Future epidemiological studies in Iran would benefit from the development of exposure assessment tools such as job exposure matrices, generally applicable for exposure assessment of epidemiological studies.

Introduction

Bladder cancer is one of the most common cancers among Iranian men (4th in prevalence, and 5th in incidence), with an ascending incidence trend observed over the past decade¹. Worldwide, half of bladder cancers are attributed to tobacco smoking, followed by 5 to 20% attributed to occupational exposure to chemicals²⁻⁷. Various occupations, industries, and agents encountered in occupational environments have been classified as carcinogenic to humans (Group 1) for bladder cancer by the International Agency for Research on Cancer-World Health Organization (IARC-WHO) Monographs⁸. An elevated risk of bladder cancer has also been observed among occupations such as rubber industry workers, painters, hairdressers drycleaners, transportation workers⁹⁻¹¹. Further, exposure to aromatic amines including 2-naphthylamine (2-NA), 4-aminobiphenyl (4-APB), and benzidine, is an established occupational carcinogen for bladder cancer and usually occurring in certain jobs/ industries such as textile, dye, rubber, leather, paint, and printing industries, may increase the risk of bladder cancer¹². In addition to tobacco smoking and some occupational exposures, recently, opium consumption has been classified as carcinogenic to humans (Group1) for bladder cancer risk¹³. Several other risk factors

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3 have been suspected to be associated with bladder cancer risk e.g., schistosomiasis infection ^{14, 15}, and
4 genetic susceptibility that most of significant variants are located in the genes belonging to the chemical
5 carcinogenesis, DNA repair, and cell cycle pathway including *GSTM1-null*, *NAT2-slow*, *APOBEC-*
6 *rs1014971*, *CCNE1-rs8102137*, *SLC14A1-rs10775480*, *PSCArs2294008*, *UGT1A-rs1189203*, and
7 *TP63-rs35592567* ¹⁶⁻¹⁸,
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11 To date, most studies examining bladder cancer risk in occupational settings have been conducted
12 in high-income countries. Information on occupational bladder cancer risk in Low- and Middle-income
13 countries, including Iran, is limited. Few case-control studies have estimated the risk of bladder cancer
14 associated with occupation in Iran ¹⁹⁻²², with results based on few cases (less than 300) in single-centre
15 studies. Further, few of these studies adjusted for the effects of tobacco smoking. Therefore, we took
16 advantage of a large, nationwide case-control study (IROPICAN) using available detailed data to
17 investigate relationships between occupation and bladder cancer in Iran, while adjusting for tobacco
18 smoking and opium consumption.
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27 Materials and Methods

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29 The IROPICAN nationwide multicentre hospital-based case-control study of various cancers (lung,
30 urinary bladder, colorectal, and head and neck), in individuals over 18 years of age, with a total of 3299
31 cancer cases. Cases and controls were recruited from 27 hospitals in ten provinces across Iran between
32 2016 and 2020. Iran has a total of 31 provinces, but the 10 selected ones were chosen as considered
33 representative for the entire country and include 42.5% of the total Iranian population. The main
34 objective of IROPICAN was to investigate the cancer risks associated with opium consumption. More
35 details on the design and study objectives have been described elsewhere ²³. This study was approved
36 by the Institutional Review Boards of the National Institute for Medical Research Development
37 (NIMAD). Informed consent was obtained from eligible participants prior to study enrolment.
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46 Study population

47 While the total number of bladder cancer cases was 717, only the 624 cases in men were used for
48 this study because the vast majority of women were housewives and therefore not informative for an
49 occupational cancer study. All histologically confirmed (ICD-O: C67), according to the International
50 Classification of Diseases for Oncology (ICD-O-3) were included. Only cases with newly diagnosed
51 bladder cancer (less than a year before the interview) were eligible to participate in the study ²⁴.
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57 For each case, a cancer-free control, frequency-matched by sex, 5-year age group, and place of
58 residence, was selected from visitors to the same hospital. Controls were hospital visitors who were
59 relatives or friends of hospitalized patients in non-oncology wards, excluding emergency rooms and
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3 maternity wards. In the current analysis, we included the 2392 male controls (of the 3477 total controls)
4 from the main study, i.e., controls that initially were recruited for all cancers, to increase sample size.
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9 Data collection

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11 Information was gathered from eligible participants by trained interviewers via a semi-structured
12 questionnaire during a face-to-face interview. Participants reported up to three jobs or other types of
13 work circumstance longer than a year in their lifetime, (to capture housewives, etc.) including job title,
14 industry or company title, job tasks, and age at start and end of each job. Three jobs were sufficient to
15 capture the entire lifetime occupational history for the vast majority of Iranians.
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20 Data on demographics (age, sex, place of residence), clinical history of urinary tract stones (UTSs),
21 urinary tract infections (UTIs), exposure to environmental tobacco smoke, and individual consumption
22 history of tobacco smoking, opium, and water-pipe smoking were collected. For each individual
23 substance status, duration, frequency, and amount was recorded by time.
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27 All occupation titles were coded using International Standard Classification of Occupations (ISCO-
28 68) at the 5-digit level ²⁵. A binary variable (ever/never) was created for each ISCO-68 major group
29 (nine major groups including military), and each selected potential high-risk occupation for bladder
30 cancer (ever/never) in the workers' lifetime career. The selected high-risk occupations were either
31 classified by IARC-WHO Monographs programme, e.g. metal industry workers, rubber industry
32 workers, chemicals and dyes manufacturing, painters, and occupations that routinely applying some of
33 the aromatic amines explicitly; such as 2-NA, 4-APB, and benzdine ²⁶; or the excess risk of bladder
34 cancer has been reported previously, such as print workers, textile industry workers, welders, petroleum
35 industry workers, hairdressers, leather goods makers, electronic workers, glass industry workers, and
36 plumbers ^{4,6}. In addition, we included some occupations including drivers (road drivers, heavy vehicle
37 drivers), and farmers (field farmers, animal farmers), with sufficient sample size and adequate power
38 in the current study, as there were observed excess risks of bladder cancer in previous studies carried
39 out in Iranian farmers and drivers ^{19,22}. The list of high-risk occupations and the associated ISCO-68
40 codes (based on 5-digit codes) are listed in Table S1. On the other hand, we excluded hairdressers from
41 the list of high-risk occupations for bladder cancer. Beauty salons in Iran are gender -specific in which
42 the male hairdressers have different tasks in comparison to the female hairdressers in beauty salons;
43 normally they cut, style, and trim hair or shaving or trimming of beards and moustaches. Therefore,
44 commonly used cosmetic products are not routinely applied in male beauty salons.
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56 Variability in tasks and potential exposures within a specific occupation is well understood ²⁷;
57 therefore, we decided to combine occupations in which workers potentially are exposed to some
58 aromatic amines (i.e. 4-APB, benzdine and metabolites, and 2-NA that have been identified as a Group
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3 1 carcinogen for bladder cancer)²⁸. Exposure to aromatic amines occurs mainly during their production
4 or use (i.e., chemical engineering technician and chemical processors workers, rubber and plastic
5 industry workers, and metal processors including workers in aluminium production industries). Some
6 occupations with high exposure to aromatic amines, such as those in auramine production, magenta
7 production, launderers and dry-cleaners, and print workers were not represented in the current study,
8 The list of high-risk occupations (using 5-digit ISCO 68 codes) is presented in Table S2.
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16 Statistical analysis

17 The Chi-square test for categorical variables was applied to assess potential differences between
18 cases and controls regarding distributions of age groups, individual substance use (e.g., tobacco, opium,
19 water-pipe), personal history of urinary tract infections, UTIs, UTSSs, and environmental tobacco smoke.
20 Two-sided p-values were used with a 5% nominal statistical significance.
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24 To investigate associations between occupation and bladder cancer, odds ratios (ORs) and 95%
25 confidence intervals (CIs) were computed using unconditional logistic regression models as detailed
26 below.
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29 Four models were fitted to assess the risk of bladder cancer associated with ISCO 68 major groups
30 and selected occupations (based on 5-digit codes); classifying the remaining study population as non-
31 exposed. Model 1 was adjusted for age (5-years categories) and residential areas (10 provinces), The
32 provinces were however chosen in a way to represent the different geographical and cultural areas of
33 the country and included the capital of Iran(no adjustment for sex needed as only males were analysed)
34 In model 2, cigarette smoking status (never/former/current) and intensity (never smokers/ <10/ 10-20/
35 >20 pack years) was added Model 1 variables. Model 3 included model 1 and model 2 variables plus
36 opium consumption (never users; <1 time day; 1-2/day; >2/day). Model 4 additionally adjusted for
37 UTIs, and UTSSs. In the text we refer to the fully adjusted model (model 4) unless otherwise mentioned.
38 Water-pipe smoking (never/ever) and environmental tobacco smoke exposure (never/ever) did not
39 change effects observed in the models so were not retained in the final analyses.
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48 The interaction between occupational exposure to aromatic amines and smoking has been reported
49 previously²⁹. Thus, this interaction was examined on an additive scale by calculating the relative excess
50 risk due to interaction (RERI), and on a multiplicative scale using an interaction term between exposed
51 workers to aromatic amines (never vs ever) and smoking status (never vs ever smoker) in logistic
52 regression models³⁰. This was also done with opium consumption (never vs ever) instead of smoking
53 to test for potential interaction between exposure to aromatic amines and opium consumption.
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58 Statistical analyses were conducted using the statistical package STATA 15.1 (StataCorp. 2017.
59 Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, licensed to IARC – CIRC).
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Results

Characteristics of the 624 male cases and 2392 male controls are presented in Table 1. The mean age for cases was 63.4 years and 57.9 years for controls, with 3.8 controls per case. Cigarette smoking, opium consumption, history of urinary tract infection and urinary tract stone was more frequent among cases compared to controls. Out of 3016 participants, only 1066 (35.3%) had held a second occupation, while few-only only 170 (5.4%) - of them held a third occupation in their lifetime career.

Table 2 presents information on the risk of bladder cancer by ever having worked in ISCO-68 major occupational groups as described in the Methods. An inverse association was observed in the fully adjusted model for administrative and managerial workers (OR 0.4; CI: 0.2, 0.9), and clerks (OR 0.6; CI: 0.4, 0.9). An increased risk of bladder cancer was observed in the baseline model for plant and machine operators (OR 1.4; CI: 1.0, 1.8), and elementary occupations (OR 1.3; CI: 1.0, 1.5), however this effect was attenuated in subsequent adjusted models. No other significant associations were observed for other major groups.

The risk of bladder cancer associated with ever having worked in selected high-risk occupations for bladder cancer are shown in table 3. An elevated risk of bladder cancer was observed among metal processors (OR 5.8; CI: 1.4, 25.2), however this estimate was based on small numbers of exposed subjects (5 cases; 4 controls). Also, increased risk observed in occupations with exposure to aromatic amines (OR 2.1; CI: 1.2, 3.8). An elevated risk of bladder cancer was observed among heavy vehicles drivers in the baseline model (OR 1.7; CI: 1.1, 2.7) which became nonsignificant when adjusting for potential confounders.

These results did not indicate associations with occupations linked to increased bladder cancer risk in other studies (i.e., painters, plumbers, hairdressers, and rubber industry workers). However, non-significant increased risk has been observed in some other occupations (e.g., construction workers, road drivers, welders, electronic workers, and glass industry workers)

Table 4 shows the joint effects of smoking tobacco or opium use and having worked in occupations with exposure to aromatic amines. No significant deviations from an additive or multiplicative scale were observed.

Discussion

This study examined the risk of bladder cancer in various occupations in Iran, and is the largest epidemiological study to date; with detailed collected occupational history data³¹. Inverse associations were observed in two major ISCO-68 groups of white-collar occupations including administrative and

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3 managerial workers, and clerks, while adjusting for tobacco smoking, opium consumption, and urinary
4 tract disease including UTIs and UTSSs. Elevated risks of bladder cancer were observed in the major
5 ISCO-68 groups of plant and machine operators, and elementary occupation workers, with attenuated
6 associations when adjusted for potential confounders.
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10 Further analyses of specific occupations revealed increased risk of bladder cancer in metal processors,
11 and in workers with high probability of exposure to aromatic amines. A positive association was also
12 observed in heavy vehicle drivers in which the association attenuated when fully adjusted for
13 confounders.
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17 The reduced risk of bladder cancer among white-collar workers may be explained by healthier
18 lifestyle and higher socio-economic status in this group compared to other occupations. Previous studies
19 have shown that smoking prevalence is higher among some “elementary occupations”³²⁻³⁴; for this
20 reason, adjustment is very important for individual substance use habits including smoking. Adjustment
21 for opium consumption, which was recently classified as carcinogenic to humans, (including for urinary
22 bladder cancer) by the IARC monograph programme¹³, is also important since over 40 percent of
23 worldwide opium consumption occurs in Iran³⁵.
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29 Metal processing is an occupation in which workers may have concomitant exposure to a variety of
30 chemical agents, some of which (such as aromatic amines and PAHs) are established carcinogens linked
31 to bladder cancer. In this study, metal processors were found to have excess risk of bladder cancer,
32 although based on small numbers of subjects. This finding is consistent with the result of previous
33 studies³⁶. Increased risk of bladder cancer in these occupations is most likely attributable to some
34 aromatic amines.
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39 Occupational exposure to aromatic amines i.e., 4-APB, 2-NA, benzidine and its metabolites have
40 been classified as carcinogenic to humans and have been strongly and consistently associated with the
41 development of bladder cancer³⁷. On the other hand, tobacco smoking is known as a source of exposure
42 to the mixture of potential carcinogenic chemicals including aromatic amines that may lead to excess
43 risk of bladder cancer in smokers. However, aromatic amines has been detected in urine of non-smokers
44 as well, suggesting a role of occupational exposure^{38,39}. In this study, an elevated risk of bladder cancer
45 was observed in a group of occupations with potentially high levels of exposure to aromatic amines
46 (i.e., chemical engraving technician and chemical processors workers, rubber and plastic industry
47 workers, and metal processors including workers in aluminium production industries). Since there are
48 no exposure measurements data available to characterize exposures for potential high-risk occupations
49 in Iran³¹, it is unclear if the observed association is related to occupational exposure to aromatic amines
50 or to other carcinogenic agents, for example: PAHs or PAH derivatives (i.e., 2-nitronaphthalene which
51 can be metabolized to 2-NA of aromatic amines)^{40,41}.
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3 An excess risk of bladder cancer in heavy vehicle drivers was observed, which the result is consistent
4 with some of previous findings ⁴², but the association was rather weak and not statistically significant
5 in fully adjusted model. Nevertheless, finding of a meta-analysis shows the increased risk of bladder
6 cancer in motor vehicle drivers, especially truck drivers, which presumably linked to PAHs exposure
7 from diesel engine exhaust emission ⁴³.
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11 In this study, associations were not observed for known high-risk occupations linked to bladder
12 cancer such as rubber industry workers, painters, and workers exposed to benzidine-based dyes
13 (manufacture of textile, workers of leather and products industry, plastic manufacture workers) ^{4, 6, 28, 44}.
14 A possible explanation is the small sample size, which provided insufficient statistical power to detect
15 associations. Another explanation may be that exposure circumstances differ in Iran compared to other
16 countries. For instance, previous studies in rubber industry have indicated correlations between
17 increased risk of bladder cancer and exposure to some aromatic amines e.g. 2-NA in those units of rubber
18 industry manufacture that have been used 2-NA more than other units ^{45, 46}, but the quantity of exposure
19 to aromatic amines in various units of rubber industries in Iran is not known.
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26 The results of this study did not show joint effects between occupational exposure to aromatic
27 amines and individual substance use including tobacco smoking and opium consumption, even though
28 this association has been reported previously ⁴⁷.
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32 Although the IROPICAN study was not specifically designed to evaluate the effects of occupation on
33 cancer, the available information on occupational history is rich, including the duration of employment
34 in each held occupation. Approximately only 5 percent of participants held a third job, so the rest of
35 participants held one or two job in their life, therefore; we assume this study has covered life-time career
36 job history of the vast majority of participants.
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40 There are nevertheless limitations to this work. First, various occupations were merged into
41 groupings that may not have reflected exposures unique to specific occupations or occupational tasks,
42 thus potentially masking effects in certain subpopulations. Job titles were used as a surrogate indicator
43 of occupational exposure to aromatic amines to detect the risk of bladder cancer in workers who
44 possibly were exposed to the aromatic amine components in workplace environment.
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49 In conclusion, our findings show associations between increased bladder cancer risk and working
50 as metal processor and working in occupations with high-level of exposure to aromatic amines, after
51 controlling for smoking and opium consumption. This suggests that exposure to aromatic amines
52 contribute to the bladder cancer burden also in Iranian industries, that need control measures to reduce
53 exposures and protect workers. Further priority work should be to develop a specific job-exposure-
54 matrix (JEMs) specialized for the Iranian working population that allows investigations of specific
55 chemical agents and occupational cancer risk in the country.
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Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views often International Agency for Research on Cancer /World Health Organization

Contributions statement

A.O., J.S., K.Z., B.H., had substantial contributions to the design and conduct of the work. B.H., A.O., drafted and prepared the manuscript. B.H., A.O., and L.B. conducted the statistical analyses. A.L.H. consulted in occupational data processing. The final version of the manuscript has been approved by A.O., J.S., K.Z. The remaining authors contributed to the main case-control study and ensured the quality of the original data and ensuring that questions related to the accuracy of any part of the work are appropriately investigated. All authors contributed to the interpretation of the results, revising it critically for important intellectual content. A.O., contributors as being responsible for the overall content as guarantors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

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

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Tables

Table 1: Characteristics of the study population by case-control status.

Study participants' characteristics	N (%)		*p-value
	Cases 624 (100.0)	Controls 2,392 (100.0)	
Age categories, years	n (%)	n (%)	<0.001
<35	4 (0.6)	73 (3.0)	
35-39	6 (0.9)	87 (3.6)	
40-44	14 (2.4)	138 (5.8)	
45-49	29 (4.6)	219 (9.2)	
50-54	65 (10.4)	324 (13.5)	
55-59	101 (16.2)	422 (17.6)	
60-64	126 (20.2)	430 (18.0)	
65-69	110 (17.6)	331 (13.8)	
70-74	68 (10.9)	206 (8.6)	
75- 79	62 (9.9)	99 (4.1)	
80- 84	19 (3.0)	47 (1.2)	
85+	20 (3.2)	16 (0.7)	
Cigarette smoking status			<0.001
Never smokers	194 (31.1)	1,438 (60.1)	
Former smokers	145 (23.2)	383 (16.0)	
Current smokers	285 (45.7)	571 (23.9)	
Intensity of smoking (pack/year) in ever smokers			<0.001
< 10	83 (13.3)	359 (15.0)	
10 to 20	88 (14.1)	207 (8.6)	
> 20	259 (41.5)	388 (16.2)	
Opium consumption status (times/day)			<0.001
Never	330 (52.9)	1,966 (82.2)	
<1/day	123 (19.7)	294 (12.3)	
1-2/day	115 (18.4)	99 (4.1)	
>2/day	56 (9.0)	33 (1.4)	
Water-pipe smoking			0.1
Never	573 (91.8)	2,239 (93.6)	
Ever	51 (8.2)	153 (6.4)	
Environmental tobacco smoke			0.9
Never	457 (73.2)	1,749 (73.1)	
Ever	167 (26.7)	643 (26.9)	
History of urinary tract infection			<0.001
Never	577 (92.5)	2,338 (97.7)	
Ever	47 (7.5)	54 (2.3)	
History of urinary tract stone			0.07
Never	483 (77.4)	1,930 (90.7)	
Ever	141 (22.6)	462 (19.3)	
The longest occupation held (major groups of ISCO-68)			<0.001
0/1: Professional, Technical and Related Workers	58 (9.1)	266 (11.1)	
2: Administrative and Managerial Workers	7 (1.1)	61 (2.5)	
3: Clerical and Related Workers	30 (4.8)	211 (8.8)	
4: Sales Workers	59 (9.5)	182 (7.6)	
5: Service Workers	25 (4.0)	125 (5.2)	
6: Agricultural, Animal Husbandry and Forest	152 (24.4)	541 (22.6)	
7: Craft and related trades workers	36 (5.8)	147 (6.1)	
8: Plant and machine operators	48 (9.6)	172 (7.2)	
9: Elementary occupations	152 (30.3)	554 (23.1)	
X: Military Force	9 (1.8)	130 (5.4)	
Missing, students, unemployed	1 (0.2)	9 (0.4)	

Note: ISCO-68, International Standard Classification of Occupations; OR, odds ratio; CI, confidence interval; N, number.

*p-value for heterogeneity

Table 2: Risk of bladder cancer related to ever having worked in ISCO-68 major occupational groups stratified

ISCO-68 major groups	Ever worked (Cases/Controls)	Model 1 ^a OR (95% CI)	Model 2 ^b OR (95% CI)	Model 3 ^c OR (95% CI)	Model 4 ^d OR (95% CI)
0/1: Professional, technical, and related workers	71/ 318	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
2: Administrative and managerial workers	10 / 93	0.4 (0.2, 0.8)	0.4 (0.2, 0.8)	0.4 (0.2, 0.9)	0.4 (0.2, 0.9)
3: Clerical and related workers	36/ 252	0.5 (0.4, 0.7)	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)
4: Sales workers	81/ 282	1.1(0.8, 1.4)	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
5: Service workers	36/ 173	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)
6: Agricultural, animal husbandry and forest	191/ 676	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
7: Craft and related trades workers	56/ 196	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.2 (0.8, 1.6)	1.2 (0.9, 1.7)
8: Plant and machine operators	68/ 229	1.4 (1.0, 1.8)	1.2 (0.9, 1.7)	1.1 (0.7, 1.4)	1.0 (0.7, 1.4)
9: Elementary occupations	206/ 717	1.3 (1.0, 1.5)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)
X: Military force	24/ 148	0.6 (0.4, 0.9)	0.7 (0.4, 1.1)	0.8 (0.5, 1.3)	0.7 (0.5, 1.2)

Note: Each occupational group is individually compared to the respective remaining group of samples. ISCO-68, International Standard Classification of Occupations; OR, odds ratio; CI, confidence interval; N, number.

^a Model 1 (M1) includes age categories (5-year categories) and residence (provinces)

^b Model 2 (M2) includes M1 variables plus cigarette smoking status and intensity.

^c Model 3 (M3) includes M2 variables plus opium consumption.

^d Model 4 (M4) includes M3 variables plus urinary bladder infection and urinary bladder stone.

Table 3: Risk of bladder cancer associated with ever having worked in the selected specific occupations (ISCO-68)

ISCO-68 selected occupations	Ever worked N (Cases/Controls)	Model 1 ^a OR (95% CI)	Model 2 ^b OR (95% CI)	Model 3 ^c OR (95% CI)	Model 4 ^d OR (95% CI)
	Male	Male	Male	Male	Male
Textile industry workers	12/ 49	1.0 (0.5, 1.8)	0.9 (0.4, 1.7)	0.6 (0.3, 1.6)	1.0 (0.5, 2.0)
Painters	3/31	0.4 (0.1, 1.5)	0.3 (0.1, 1.2)	0.3 (0.1, 1.3)	0.4 (0.1, 1.4)
Construction workers	90/ 316	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
Road drivers	54/ 188	1.2 (0.8, 1.6)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)	1.1 (0.8, 1.5)
Heavy vehicles drivers	26/ 69	1.7 (1.1, 2.7)	1.4 (0.9, 2.4)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Welders	16/ 53	1.3 (0.7, 2.4)	1.3 (0.7, 2.5)	1.1 (0.6, 2.1)	1.1 (0.6, 2.2)
Plumber	3/21	0.7 (0.2, 2.3)	0.7 (0.2, 2.4)	0.5 (0.1, 1.8)	0.4 (0.1, 1.8)
Petroleum industry workers	4/ 13	1.2 (0.4, 3.7)	1.9 (0.6, 6.9)	2.3 (0.7, 7.5)	2.0 (0.6, 6.7)
Rubber industry workers	3/ 17	0.7 (0.2, 2.6)	0.7 (0.2, 2.5)	0.8 (0.2, 2.9)	0.8 (0.2, 3.1)
Hairdresser	5/32	0.7 (0.3, 1.9)	0.6 (0.2, 1.8)	0.5 (0.2, 1.5)	0.5 (0.2, 1.5)
Metal processors	5/4	4.1 (1.0, 16.1)	3.8 (0.8, 16.5)	5.4 (1.3, 23.4)	5.8 (1.4, 25.2)
Leather goods makers	4/7	1.9 (0.5, 6.7)	1.5 (0.4, 5.6)	1.1 (0.3, 4.2)	0.9 (0.2, 3.5)
Mechanics	18/55	1.4 (0.8, 2.4)	1.4 (0.8, 2.5)	1.1 (0.6, 2.0)	1.0 (0.5, 2.0)
Electronic workers	10/40	1.2 (0.6, 2.5)	1.2 (0.5, 2.5)	1.2 (0.5, 2.6)	1.1 (0.5, 2.5)
Glass industry workers	7/15	1.9 (0.7, 4.9)	1.6 (0.6, 4.2)	1.8 (0.6, 5.0)	1.7 (0.6, 4.9)
Workers exposed to some aromatic amines	21/48	1.7 (1.0, 3.0)	1.9 (1.1, 3.3)	2.2 (1.2, 4.0)	2.1 (1.2, 3.8)

Note: ISCO-68, International Standard Classification of Occupations; N, number; OR, odds ratio; CI, confidence interval.

^a Model 1 (M1) is adjusted for age categories (5-year categories) and residence (provinces)

^b Model 2 (M2) is adjusted for M1 plus cigarette smoking status and intensity.

^c Model 3 (M3) is adjusted for M2 plus opium consumption.

^d Model 4 (M4) is adjusted for M3 plus urinary bladder infection and urinary bladder stone.

Table 4: Effect modification between smoking or opium consumption; and employment in high-risk occupations for aromatic amines exposure

Exposure status to cigarette smoking	N Case/Controls	OR ^a (95% CI)
Never-smoker and aromatic amines exposed worker	173/ 1273	ref
Never smoker and aromatic amines exposed worker	9/ 27	2.5 (1.1, 5.7)
Ever-smoker and never aromatic amines exposed worker	430/ 1073	3.3 (2.7, 4.0)
Ever-smoker and ever aromatic amines exposed worker	12/ 21	5.0 (2.3, 10.6)
P value multiplicative interaction		0.9
RERI a		0.1 (-4.1, 3.0)
Exposure status to opium consumption		
Never-opium user and never aromatic amines exposed worker	290/ 1801	ref
Never-opium user and aromatic amines exposed worker	15/ 40	2.3 (1.2, 4.4)
Ever- opium user and never aromatic amines exposed worker	313/ 545	4.5 (3.7, 5.6)
Ever- opium user and ever aromatic amines exposed worker	6/ 8	6.8 (2.2, 20.4)
P value multiplicative interaction		0.8
RERI b		0.9 (-6.7, 8.4)

Note: N, number; OR, odds ratio; CI, confidence interval.

^a Adjusted odds ratio for age categories (5-year categories), and residence (provinces)

^b RERI: biological interaction on an additive scale: relative excess risk due to interaction

Chapter 5: Conclusion

The chapter contains a summary of study finding, discussion of any limitations of the research project and ends up with final recommendations – practical suggestions for implementation of the findings for future research.

5.1 SUMMARY OF FINDINGS

This Ph.D. thesis was initially conducted to provide a pattern of occupational characteristics and examine the risk of lung and bladder cancer arising from occupational settings in Iran, using available databases, IROPICAN nationwide case-control study.

In the early stages of this thesis, the literature review conducted to understand the pattern of occupational epidemiological and exposure assessment studies in Iran. The finding of our review revealed this field of research has been started early last decade. Studies had been done in small samples which did not lead to the strong evidence. The studies were not considered specific know high-risk industries/ occupations or carcinogenic chemicals for occupational cancer. Also, we found exposure monitoring studies in Iran mostly focused on the projection of cancer risk based on a limited number of exposure measurements. Although, a few epidemiological studies have been done so far but still the status of exposure to carcinogenic agents and their assignment to the occupations is not clear. Therefore, to provide strong evidence on excess risk of occupational cancer; further

epidemiological studies need to be focus on specific occupations/ exposure agents.

Following the systematic review, analysis to evaluate the risk of occupational lung and bladder cancer using IROPICAN study was performed. We evaluated the risk base on major groups of ISCO-68 classification, afterwards some high-risk occupations for lung and bladder cancer risk selected to access the risk of these two cancer sites.

Overall, in this analysis significant association of lung cancer risk for major groups of occupations has not been observed. The reduced risk of lung cancer for some major groups of white-collar workers, and excess risk for blue collars workers were attenuated after adjustment for tobacco smoking and opium consumption that were more common in certain categories of workers, therefore acted as confounders. Further, we observed elevated risk of lung cancer for construction workers, and petroleum industry workers in men and women farmers and bakers. Construction workers experienced slightly elevated risk associate with the duration of employment, but no significant trends for duration of employment as a female farmer. Previously, crystalline silica, diesel fumes, and asbestos have been known as responsible carcinogen exposures in construction workers[126-128].

To complement the thesis project, the risk of bladder cancer associated with occupations using IROPICAN data, were evaluated. Preventive effect in some major groups of white-collar workers while adjusting for smoking, opium consumption, and urinary tract diseases (UTI, UTS) were observed. The excess risk of bladder cancer in plant and machine operators, and elementary occupations attenuated following adjustment for mentioned confounders. We also observed elevated risk in high-risk occupations including metal processor workers and a group of occupations with the high probability of exposure to some aromatic amines (i.e., 4-APB, Benzidine and

metabolites, 2-NA, and ortho-toluidine that has been identified as a group 1 of carcinogens for human bladder cancer).

Regarding other risk factors, tobacco smoking is one of the most important risk factors for many cancers including lung and bladder cancers. Studies revealed the prevalence of smoking is higher among blue collar workers e.g., metal, construction, and mining workers compare to the other occupations. That confirm various lifestyles pattern across occupational groups may leads to more frequent cancer occurrence among occupations with higher prevalence of smoking [129, 130]. Even though there has been limited studies on opium consumption distribution among various occupational classes, but due to high prevalence of opium consumption among Iranian population, the joint effect of opium consumption and smoking with some high-risk occupations for the risk of these cancers, also has been evaluated. The joint effect of smoking with occupational exposure has been previously associated, but we did not detect any synergic effect neither for smoking nor opium consumption for lung and bladder cancer risk [86, 126-128, 131-133].

To date, many chemical agents have been identified to be responsible to elevate the risk of lung and bladder cancer for several occupations. The significant elevated risks of lung cancer have been observed for mining workers, furnace workers, welders, agricultural workers, drivers, mechanics, painters, rubber industry workers, construction workers. These occupations are at high-risk as workers are exposed to many known or suspected carcinogens, including silica, asphalt fumes, PAHs, diesel exhaust, paints, asbestos, lead, metal fumes, and solvents [134-136].

Excess risks of bladder cancer also have been observed among painters, metal workers, textile industry workers, printers, hairdressers, dry cleaners, and transport workers [20, 115]. Workers in these occupations/

industries has been exposed to PAHs, industrial oils/cutting fluids, diesel engine exhaust, paints, dyes, chlorinated hydrocarbon solvents, and some aromatic amines (2-NA, benzidine, 4-APB, b-naphthylamine, ortho-toluidine) [20, 56, 84].

Even though, high-risk occupations for lung and bladder cancer risk according to the IARC Monograph programme have been evaluated, but only association in some occupations (excess risk of lung cancer for construction workers, and petroleum industry workers in men and women farmers and bakers, and elevated risk of bladder cancer for metal processor workers and high-risk occupations for aromatic amines exposure) were detected, small sample size could be a reason we could not find association. As due to the small samples we had to combine different tasks in a group of occupation that possibly includes various tasks with different levels of exposure to the carcinogens which could lead to attenuating the association.

The interpretation of epidemiological studies of occupational cancer related to occupations is complicated by the wide variety of chemical mixtures, whose compositions change over time, and the great variability and complexity of working environments. Although there was not enough information in this study provided to assess the association of lung and bladder cancer with specific chemical agents encountered, the robustness of the risk estimates by controlling for sex, region, smoking and opium consumption) support the conclusion that occupational exposures elevate the risk of lung and bladder cancer in Iran.

Occupational exposure to carcinogens is a major cause of death worldwide, therefore identifying occupational carcinogens is an important research topic relevant to public health [137]. Since industrial and regulatory circumstances vary across countries, likely chemical used in Iran might be vary compared to the occupational exposure pattern in other

countries, subsequently occupational cancer risk might be varied. Therefore, well-designed occupational cancer studies of sufficient size that include relevant exposure assessment methods are needed to understand the type and level of exposure to the carcinogenic agents in Iran. To achieve that, interdisciplinary collaboration between experts in national and international levels such as hospitals, cancer registries, universities, and relevant ministries are inevitable [77]. Additionally, further systematic exposure monitoring will be needed to identify potential high-risk occupational environments, for future risk management planning in workplaces, also exposure assessment and assignment of future epidemiological studies [138, 139].

In summary, this thesis identified some high-risk occupations including construction and petroleum industry workers in men, and farmers, and bakers in women for excess lung cancer risk, and metalworking and a group of occupations with exposure to some aromatic amines to increase the risk of bladder cancer. Therefore, this thesis suggests a new hypothesis concerning the important of occupational exposures and needs for more detailed exposure assessment in high-risk occupations environment along with future epidemiological studies in industrial settings e.g., adapting existing job-exposure-matrices (JEMs).

5.2 STRENGTH AND LIMITATIONS

This thesis project provides the first overview of the status of occupational cancer research in Iran and recognized this topic as an important area of research to improve and further develop in the Iran industrial context. Also, our findings highlighted high-risk occupations for excess risk of lung and bladder cancer in Iran which are the most frequent occupational cancer worldwide. In addition, the methods applied in this

study will be a pathfinder of further investigations to identifies occupations/industries where more detailed studies are needed. We were also able to adjust for opium consumption (recently has been classified as group 1 of carcinogenic agents for lung and bladder cancer by IARC monographs working groups). To my knowledge, this is the first occupational epidemiological studies adjusting for opium consumption in addition to tobacco smoking. This study revealed that the pattern of opium consumption differs within occupational groups and so may have acted as a confounder and contributed to different risks between occupations.

There are some limitations to bear in mind. First, the information on occupational history were only a qualitative data of held occupation. Therefore, the risk estimates were based on occupational title or major occupational groups rather than tasks. Accordingly, risks were averaged among workers within large groups of occupations, which may have hidden at-risk occupations. Second, the purposes of the main study were not to for collecting occupational information to identifying the risk of occupational cancer. Third, even though we used a relatively large case-control study for the current thesis project; but due to the extremely wide number of occupations held by study participants, were not possible to assign enough number of participants to each occupation. Therefore, potential association in most of single high-risk occupations were not detected. Finally, we could not adjust for radon exposure in this study to assess the risk of lung cancer related to occupation. This was due to a lack of data on radon exposure in Iran, although radon exposure is one of the most important risk factors for lung cancer.

5.3 RECOMMENDATIONS AND IMPLICATIONS

Acquire knowledge of cancer risk from occupational exposure supports prevention activities, as well as compensation of exposed workers would be possible through regulatory action taken by the national authorities. There are very first steps in the process of cancer prevention which comprises risk identification, risk quantification, and risk reduction. These steps have been taken in many HICs, particularly for many of the known occupational risks of lung and bladder cancer, eventually leading to preventive measures and legislation to compensate exposed workers. This requires risk identification in LMICs, including Iran.

Accordingly, it is recommended that future investigations should be focused on applying proper occupational exposure assessment methods to the ongoing large-scale cancer epidemiology studies in Iran e.g. Persian cohort study [140], which requires the development of valid job-exposure matrices for Iran. In addition, large-scale industrial cohort studies in major industries detected by our study should be initiated to inform cancer control in Iran and efforts on a global scale, as data from emerging economies is lacking worldwide [141].

Additional studies are necessary to confirm the association of many suspicious agents, occupations and industries with lung and bladder cancer, in which major confounders such as tobacco smoking and opium consumption, must be adjusted for, as most occupations are associated with lifestyle habits.

The most notable risk factor for the development of bladder cancers is occupational exposure to some aromatic amines, therefore the industries should be encouraged to develop or improve policies to reduce exposure to aromatic amines or replace these chemicals if it is applicable. In addition

since there is evidence that smoking acts synergistically to increase the risk of lung and bladder cancer, workers should be encouraged to quit smoking.

For future plans to reduced occupational cancer in Iran, holding workshop with Iranian and international expertise have to be prioritized to identify potential sources of exposure data in Iran industries (e.g., petroleum industry, metal processing industries, construction industry and high-risk occupation for aromatic amines exposure), and possibly develop a job-exposure-matrix (JEMs) for Iran which it very fundamental method in exposure assessment of future epidemiological studies. Hence, some important JEMs would be helpful in developing the JEM in this study like, Finnish job-exposure matrix FINJEM, which covers a large selection of exposures, including carcinogens, the other example those in Sweden, Norway, Denmark, and Iceland, which were used in the Nordic Occupational Cancer Study (NOCCA -JEMs) [142]. Forasmuch as the JEMs would be helpful to cover the intensity and duration of occupational exposures in the individual life time exposure [143, 144], as aligned with developing a national JEM, we have a comprehensive picture of occupational exposure in Iranian workforces. In addition, the JEM would be used as a valuable tool to utilize in occupational cancer investigations in Iran[145].

Moreover, further discussions about the feasibility to establish prospective large-scale epidemiological studies among construction workers and petroleum workers is recommend. Subsequent attempts to systematic exposure monitoring of some occupations that it supposes workers to be exposed to high-level of exposure to some aromatic amins including.

Appendices

Appendix A: IROPICAN occupation history questionnaire

To develop job questions section, we used standard occupational classification 2010. First, we ask information about their job and collect exposure history in the three last jobs they worked for more than one year (Table 1). Then we collect information about job classes in five categories using standard occupational classification 2010 (Table 2). Groups are presented below.

Table 1: Questions: Part one

Your occupational status from childhood to the present:

	This information are about three occupations lasts for more than one year in your life time		
	current job	previous Job	previous Job 2
Industry or factory title			
Job or occupation title
Age of onset
Age of ending
Month a year			
Days a week
Hours per day
What did the factory/organization you worked for mainly make or do (at the place where you worked)?
What did you mainly do in your job?
Please name materials you were exposed to at work
How long have you been in contact with those materials?

Table 2: Questions: part two

Please answer the questions about a job you have been employed for most years of your life.

	Participant information	Head of household information
1. Job or occupation title
2. Were you working as an employee? (if "employee" please go to question 3 otherwise to question 5)	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
3. How many people worked for your employer at the place where you worked?
4. In your job, did you have any formal responsibility for supervising the work of other employees?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
5. Did you employ somebody else to work for you?(If you had employee please go to question 6)	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
6. How many people did you employ?
Note: If respondent is a female, please ask these questions about the head of household		

Appendix B: The dictionary of occupation history datasets

Question	Glossary	Label variable in the dataset output	Data	The nature of the data
89(J1)	Recent job title	LastJobName	Text	Textual
	Recent industry title	LastJobIndustryName	Text	Textual
	Recent job output (product/ services)	LastJobMainServiceName	Text	Textual
	Recent job task	LastJobMainActivityName	Text	Textual
	Recent job exposures	LastJobFacingMaterialsName	Text	Textual
	How old was the participant at the starting of the recent job?	LastJobStartAge	Age (number)	continues
	How old was the participant at the end of the recent job?	LastJobEndAge	Age (number)	continues
	Months per year (Recent job)	LastJobMonthInYear	Months per year (number)	continues
	Days per week (Recent job)	LastJobDayInWeek	Days per week (number)	continues
	Hours per day (Recent job)	LastJobHoursInDay	Hours per day (number)	continues
	Duration of recent job	LastJobFacingDuration	Years (number)	continues
	Last industry title	PreviousJob1IndustryName	Text	Textual
	Last job title	PreviousJob1Name	Text	Textual
	Last job output (product/ services)	PreviousJob1MainServiceName	Text	Textual
	Last job task	PreviousJob1MainActivityName	Text	Textual
	Last job exposures	PreviousJob1FacingMaterialsName	Text	Textual
	How old was the participant at the starting of the Last job?	PreviousJob1StartAge	Age (number)	continues
	How old was the participant at the end of the Last job?	PreviousJob1EndAge	Age (number)	continues
	Months per year (Last job)	PreviousJob1MonthInYear	Months per year (number)	continues
	Days per week (Last job)	PreviousJob1DayInWeek	Days per week (number)	continues
	Hours per day (Last job)	PreviousJob1HoursInDay	Hours per day (number)	continues
	Duration of Last job	PreviousJob1FacingDuration	Years (number)	continues
	Second last industry title	PreviousJob2IndustryName	Text	Textual
	Second last job title	PreviousJob2Name	Text	Textual
	Second last job output (product/ services)	PreviousJob2MainServiceName	Text	Textual
	Second last job task	PreviousJob2MainActivityName	Text	Textual
	Second last job exposures	PreviousJob2FacingMaterialsName	Text	Textual
	How old was the participant at the starting of the second last job?	PreviousJob2StartAge	Age (number)	continues
	How old was the participant at the end of the second last job?	PreviousJob2EndAge	Age (number)	continues
	Months per year (Second last)	PreviousJob2MonthInYear	Months per year (number)	continues

	Days per week (Second last)	PreviousJob2DayInWeek	Days per week (number)	continues
	Hours per day (Second last)	PreviousJob2HoursInDay	Hours per day (number)	continues
	Duration of second last job	PreviousJob2FacingDuration	Years (number)	continues
				Textual
90(J2)	The job title that participant was occupied longer on it.	ParticipantJobTitle	Text	Textual
	The job title that participant 's spouse was occupied longer on it.	HouseholdJobTitle	Text	Textual
	If the participant is an employee of a company?	ParticipantWorkForOther	1: Yes 2: No	Ordinal
	If the participant 's spouse is an employee of a company?	HouseholdWorkForOther	1: Yes 2: No	Ordinal
	How many worker/ employees working in the participant workplace/company/organization?	ParticipantPeopleNumberInWorkPlace	Number of employees in the workplace (Participant)	continues
	How many worker/ employees working in the participant 's spouse workplace/company/organization?	HouseholdPeopleNumberInWorkPlace	Number of employees in the workplace (Participant 's spouse)	continues
	If the participant is a supervisor in a company/ organisation and managing others?	ParticipantControlOtherWerker	Participant 's supervises(number)	continues
	If the participant 's spouse is a supervisor in a company/ organisation and managing others?	HouseholdControlOtherWerker	Participant 's spouse supervises(number)	continues
	If the participant is an employer?	OtherPeopleWorkForParticipant	1: Yes 2: No	Ordinal
	If the participant 's spouse is an employer?	OtherPeopleWorkForHousehold	1: Yes 2: No	Ordinal
	How many employees the participant has?	OtherPeopleNumberWorkForParticipant	Employees of participant (number)	continues
	How many employees the participant 's spouse has?	OtherPeopleNumberWorkForHousehold	Employees of participant's spouse (number)	continues

Appendix C: The list of high-risk occupations for lung and bladder cancer according to the IARC Monograph programme

Table S1: The 5-digit ISCO-68 codes corresponding to each specific selected high-risk occupations for lung cancer

Selected specific occupations from (ISCO-68)	Five-digits codes
Textile industry workers	7-00.70, 7-51.10 to 7-59.90, 7-91.00 to 7-91.90, 7-93.00 to 7-99.90, 8-35.60
Painters	9-31.00 to 9-39.90
Construction workers	9-51.00 to 9-52.90, 9-55.00 to 9-59.99, 9-75.24 to 9-74.40, 9-72.20, 9-73.35, 9-99.10
Drivers	6-28.20, 6-31.40, 9-83.20 to 9-83.90, 9-85.20 to 9-85-90, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90
Road drivers	9-85.20 to 9-85-50, 9-85-70, 9-85-90
Heavy vehicles drivers	6-28.20, 6-31.40, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90, 9-85-60, 9-89.90
Welders	8-72.10 -8-72.90
Farmers	6-11.00 to 6-49.90
Only field farmers	6-11.00 to 6-12.30, 6-12.70, 6-12.90, 6-21.05 to 6-23.90, 6-28.20 to 6-28.90, 6-29.40 to 6-29.90
Only animal farmers	6-12.40 to 6-12.60, 6-12.90, 6-24.10 to 6-26.90, 6-29.20 to 6-29.30, 6-29.90, 6-41.00 to 6-41.90
Petroleum industry workers	7-13.20 to 7-13.90, 7-43.50, 7-45.20 to 7-45.90, 9-69.40, 9-72.50
Bakers	7-76.10 to 7-76.90
Rubber industry workers	7-49.90, 9-01.20 to 9-01.50, 9-02.20 to 9-02.90

Note: ISCO-68, International Standard Classification of Occupations.

Table S 2: The 5-digit ISCO-68 codes corresponding to each specific selected high-risk occupations for bladder cancer

Selected specific occupations from (ISCO-68)	Five-digits codes
Textile industry workers	7-00.70, 7-51.10 to 7-59.90, 7-91.00 to 7-91.90, 7-93.00 to 7-99.90, 8-35.60
Painters	9-31.00 to 9-39.90
Construction workers	9-51.00 to 9-52.90, 9-55.00 to 9-59.99, 9-75.24 to 9-74.40, 9-72.20, 9-73.35, 9-99.10
Drivers	6-28.20, 6-31.40, 9-83.20 to 9-83.90, 9-85.20 to 9-85-90, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90
Road drivers	9-85.20 to 9-85-50, 9-85-70, 9-85-90
Heavy vehicles drivers	6-28.20, 6-31.40, 9-79.30 to 9-79.90, 9-83.00 to 9-83.90, 9-85-60, 9-89.90
Welders	8-72.10 -8-72.90
Farmers	6-11.00 to 6-49.90
Only field farmers	6-11.00 to 6-12.30, 6-12.70, 6-12.90, 6-21.05 to 6-23.90, 6-28.20 to 6-28.90, 6-29.40 to 6-29.90
Only animal farmers	6-12.40 to 6-12.60, 6-12.90, 6-24.10 to 6-26.90, 6-29.20 to 6-29.30, 6-29.90, 6-41.00 to 6-41.90
Petroleum industry workers	7-13.20 to 7-13.90, 7-43.50, 7-45.20 to 7-45.90, 9-69.40, 9-72.50
Rubber industry workers	7-49.90, 9-01.20 to 9-01.50, 9-02.20 to 9-02.90
Hairdressers	5-70.20, 5-70-30, 5-70-40
Metal processors (including Aluminium production)	7-20.00 to 7-29.00 (PAH related exposures)
Petroleum industry workers	7-13.20 to 7-13.90, 7-43.50, 7-45.20 to 7-45.90, 9-69.40, 9-72.50

Note: ISCO-68, International Standard Classification of Occupations.

Table S 3: specific occupations with the high-level of exposure to aromatic amines (4-Aminobiphenyl, Benzidine and metabolites, 2-Naphthylamine, and ortho-TOLUIDINE with the strong association with urinary bladder cancer)

Selected specific occupations from (ISCO-68)	Five-digits codes
Chemist	0-11.10 to 0-11.90, 0-14.20, 0-36.10 to 0.36.90, 7-00.40, 7-00.60
Launderer, dry-cleaner	5-60.10 to 5-60.90
Metal processors	7-20.00 to 7-29.90
Chemical processers workers	7-40.00 to 7-49.90
bleachers, Dyers and Textile Product Finishers	7-56.00 to 7-59.90
Tanners and pelt dresser	7-61.00 to 7-61.90, 7-62.50 to 7-62.90
Plumber	8-71.00 to 8-71.90
Painters	9-31.00 to 9-39.90, 8-95.50
Rubber and plastic industry workers	7-41.90, 7-00.60, 7-49.90, 9-01.20 to 9-01.50, 9-02.20 to 9-02.90

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