Scoping Review Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2022 (27 Jul);36.84. https://doi.org/10.47176/mjiri.36.84

Scoping Review of 5 Common Occupational Cancers and Their Related Exposures

Ahmad Naghibzadeh-Tahami[1], Yahya Khosravi[2], Mahboubeh Es'haghi[3], Ali-Akbar Haghdoost[4]*

Received: 17 Jan 2022 Published: 27 Jul 2022

Abstract

Background: Occupational cancers can be avoided by removing dangerous chemicals from the workplace or limiting occupational exposure. Approximately, 10 major risk factors account for 85% of all occupational cancers. This scoping review study aimed to determine the most important chemical carcinogens related to 5 known occupational cancers.

Methods: In this scoping review, we followed Arksey and O'Malley's 5-step framework. Four databases (PubMed, Web of Science, Google Scholar, Scopus) were systematically reviewed for relevant published papers from January 2000 to September 2021. Studies were included in this scoping review, which examined the effect of carcinogenic (definite and probable) chemical exposures on 5 known occupational cancers (lung, bladder, laryngeal, leukemia, and liver). We reported the types of occupational carcinogens, the geographical diversity of studies, extraction of relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs), and identified gaps in the existing literature.

Results: The highest number of studies was related to lung cancer (LC) (n = 26), bladder cancer (BC) (n = 11), laryngeal cancer (LaC) (n = 8), leukemia (LeC) (n = 3), and primary liver cancer (PLC) (n = 2), respectively. Most studies were performed in France and Canada (n = 8), Germany (n = 4), Finland (n = 3), Netherlands (n = 2), and Finland (n = 2), respectively. Furthermore, the most common occupational chemical carcinogens associated with the 5 known occupational cancers were asbestos, benzene, crystalline silica, polycyclic aromatic hydrocarbons (PAH), and diesel motor exhausts (DME).

Conclusion: Although the attributable risk of occupational cancers in developing countries is much higher, a small proportion of studies were performed in these countries.

Keywords: Occupational Carcinogens, Cancer, Risk Factor, Developing Countries

Conflicts of Interest: *None declared*
Funding: *The Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences (grant number 98000771).*

Cite this article as: Naghibzadeh-Tahami A, Khosravi Y, Es'haghi M, Haghdoost AA. Scoping Review of 5 Common Occupational Cancers and Their Related Exposures. *Med J Islam Repub Iran.* 2022 (27 Jul);36:84. https://doi.org/10.47176/mjiri.36.84

Introduction

Occupational exposures were among the earliest carcinogens identified (1, 2). The term "occupational carcinogens" refers to occupational exposures, particularly chemical exposures, which are used or released as intermediate compounds during manufacturing and have been proven or suspected to cause cancer (3). According to estimates of the current and future burden of o ccupational diseases, occupational cancers are still a concern and they will continue to be so in the future due to workers being exposed to carcinogens (4).

According to the World Health Organization (WHO) estimates, carcinogen exposures in the environment and

Corresponding author: *Dr Ali-Akbar Haghdoost, Ahaghdoost@kmu.ac.ir*

1. Department of Biostatistics and Epidemiology, School of Public Health, Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
2. Department of Occupational Health and Safety Engineering, School of Health, Research Center for Health, Safety and Environment, Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
3. Department of Occupational Health Engineering, School of Health, Kerman University of Medical Sciences, Kerman, Iran
4. Department of Biostatistics and Epidemiology, School of Public Health, Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

↑What is "already known" in this topic:
Despite the higher burden attributable to occupational carcinogens in developing countries, to estimate the burden attributed to these carcinogens, most studies have been conducted in developed countries.

→What this article adds:
Due to the higher burden of occupational cancers in developing countries, there is a need for more and better-quality studies in these countries.

[DOI: 10.47176/mjiri.36.84]

workplace cause around 19% of cancer diagnoses worldwide, resulting in nearly 1.3 million deaths per year (5). These carcinogens are one of the major categories of risk factors that can be reduced using preventative actions (6). According to the International Agency for Research on Cancer (IARC) classification, carcinogens are divided into 2 categories; Group 1 (known human carcinogen), and Group 2A (probable human carcinogen). The IARC monographs have designated nearly 200 exposures as carcinogenic or probably carcinogenic to humans. A high proportion of these exposures occur in industrial contexts. As a result, the impact of occupational exposure on cancer burden is a major public health concern in many nations (7-9).

BTEXs (benzene, toluene, ethylbenzene, and xylene), asbestos, crystalline silica, heavy metals such as arsenic and its inorganic compounds, beryllium and its compounds, cadmium and nickel compounds, wood dust, and pollution caused by diesel equipment are all known or probable carcinogens for workers in these industries (10). Also, lung cancer (LC), bladder cancer (BC), laryngeal cancer (LaC), primary liver cancer (PLC), and leukemia cancer (LeC) are among the 5 most common occupational cancers globally, according to the Institution of Occupational Safety and Health (IOSH) (11).

However, it does not appear that in the last 30 years in developed countries, including the United States, a coherent study has been conducted to evaluate occupational cancers and provide preventive strategies to control these cancers (12). According to the WHO, initiatives aiming at eliminating or reducing established risk factors for cancer, such as occupational exposures, are the most effective in reducing the global burden of cancer (13).

In total, evidence-based information on carcinogenic agent exposures and cancer risks in workers is needed for national and worldwide efforts to minimize the burden of occupational cancers (14). Furthermore, studies that estimate the number of cancers caused by historical occupational exposures, such as chemical, physical, or circumstantial carcinogens, are critical for guiding public health and prevention priorities, as well as developing and enforcing labor regulations for various occupational exposures (15).

Based on the above, it can be said that occupational malignancies can be avoided by removing harmful compounds or limiting worker exposures. It is vital to understand the types of occupational carcinogens and their prevalence in this regard (14).

In total, despite the extensive scientific work done on occupational carcinogens, it seems that so far, a coherent review study has not been done to identify gaps in scientific evidence related to occupational carcinogens. Scoping reviews are comprehensive studies used to map available literature and to identify potential gaps based on evidence (16). As far as we know, no comprehensive review study based on occupational cancers has ever been done elsewhere in the world. On the other hand, knowing the major occupational carcinogens is critical for estimating the burden of cancers attributable to these exposures and implementing control and preventative measures to limit these exposures. Accordingly, it is necessary to conduct a comprehensive study to identify important occupational carcinogens.

Therefore, the present scoping review aimed to review studies conducted worldwide based on 5 known occupational cancers (LC, BC, LaC, PLC, and LeC) and determine the most common chemical exposures in occupational and industrial environments. Overall, the present study follows 4 objectives: (a) determine the geographical diversity for studies on occupational carcinogens and 5 cancers attributed to these exposures; (b) identify the types of occupational carcinogens associated with these 5 common cancers and the main outcomes (mortality/incidence) that were assessed about these exposures; (c) assess the quality and characteristics of studies in the field of occupational carcinogens; (d) report on the observed associations between occupational carcinogens and 5 known cancers and extraction of relative risks (RRs), hazard ratios (HRs), or odds ratio (ORs) of 5 common cancers attributed to occupational carcinogens; and (e) conduct a thorough examination of the field as a whole and identify gaps in the existing literature. Thus, to achieve the above goals, we conducted a systematic scoping review on occupational carcinogens and 5 common cancers associated with these exposures.

The present study has some implications to provide evidence to pave the path for future estimates of the burden of occupational cancers.

Methods

This scoping review is registered with the research registry (reviewregistry1271). Arksey and O'Malley's published a methodological framework for a scoping review in 2005 (17). The goal of this framework is to map the key concepts underpinning a research area, as well as the main sources and types of evidence available. The framework consists of 5 stages, which are as follows:

Stage 1: Determining the Primary Research Question

Our study query was as follows: What is known about the association between occupational carcinogens and the 5 known occupational cancers?

Our research question was as follows: What is known about the relationship between occupational carcinogens and the 5 known occupational cancers in the literature?

Stage 2: Identifying Relevant Studies

The review's research objectives were to identify occupational carcinogens and cancers in the world. Five cancers of LC, BC, LaC, PLC, and LeC were selected as the main cancers due to occupational exposures based on the literature review and expert opinion; . however, to increase the sensitivity of the search strategy, it did not focus on these cancers, but in the review of the title and abstract and body text for screening articles, only these cancers were considered. Through 4 bibliographic databases, a literature search was done to find papers relevant to occupational cancer worldwide (PubMed, Web of Science, Google Scholar, Scopus) from January 2000 to August 2021. To find relevant papers, the titles, abstracts, and body texts were all searched for specific keywords.

According to the PICOs statement, the search queries

[DOI: 10.47176/mjiri.36.84]

(Table 1) included terms (population: workers, and the world; exposure: carcinogenic occupational exposures; outcomes: cancer; comparison: unexposed/exposed workers) (18). Boolean search operations (AND, OR, NOT) and MeSH terms were used to combine the above terms in the search strategy. We included complete publications from epidemiological studies (cohort and case-control studies on occupational cancers).

Stage 3: Study Selection

We included articles reporting that occupational agents were limited to chemical agents evaluated by the IARC Monograph Programme on the Identification of Carcinogenic Hazards to Humans; that is, group 1 (carcinogenic to humans), group 2A (probably carcinogenic to humans), and group 2B (possibly carcinogenic to humans). Studies conducted before 2000 or other harmful environmental factors, including noise, radiation, and shift work, were excluded.

Duplicates were deleted after importing the identified articles into EndNote reference management. To ascertain potential eligibility, the titles and abstracts of all identified references in the original search were examined. If there was a disagreement between reviewers (A.N.T. and M.E.), the full-text publication was studied and discussed to solve the problem; a third reviewer (AA.H.) was consulted if required to reach a consensus. The full texts of the relevant references were acquired after the primary screening.

If additional information or study procedures were not otherwise available, we made one attempt to contact the authors of the included articles. It should be noted that HRs, ORs, and RRs, as parameters to show effect measures of the associations between carcinogens and studied common cancers, were extracted from the included studies.

Stage 4: Extracting the Data

We did not assess the quality of the individual studies or the risk of bias by scoping review methodology because our goal was to map the evidence and/or summarize the study results (17).

We used a data extraction form developed by Udoh et al (19) to aid our extraction process, as shown in Table 2.

Table 1. Search strategy in this scoping review

1	Occupational exposure* OR job-related exposure OR occupant*OR workplace*OR job
2	Neoplasms OR cancer* OR carcinoma* OR tumor
3	Incidence OR mortality OR risk
4	1 AND 2 AND 3
5	1 AND 2 AND 3 NOT animal

Table 2. Data extraction form adapted from Udoh et al (2020)

Author in chief
Publication date
The study's title
Design of the study
Setting for research (country)
Population under study
Number of participants in the study
Findings from the study
Significant findings
Conclusions

Name of the first author, date of publication, study title, study location, study design (cohort/case-control), names of the exposure agents, population size/sample size (number of workers/samples), outcome (incidence/mortality), and study results were collected from each included article (specific cancer sites).

Two tables were created to summarize the information that was extracted. The first table (Table 3) listed the first author, publication year, country or location where the research was performed, size and description of the study population, cancer site, type of exposure investigated, and controlled confounders. Table 4 includes exposure assessment methods, the examined outcome (Incidence/mortality) main results and conclusions.

Stage 5: Collating, Summarizing, and Reporting the Results

The final stage of a scoping review involves collating, summarizing, and reporting the findings.

According to Arksey and O'Malley, a framework should be used to collate results. We used the Preferred Reporting Items for Systematic Reviews and the Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (20).

For study characteristics, we created a data table. To answer our research questions, we compared characteristics and settings across all studies using these tables. Then, studies were reviewed to examine the most common effect measures. Finally, for the final inference, the conclusions of each study were evaluated.

Results

Figure 1 shows a modified PRISMA flow diagram that displays the publishing selection process. A total of 2349 publications were found during the initial systematic search (922 from PubMed, 1037from Web of Science, and 390 from Google scholar). A total of 1149 publications remained after eliminating the duplicates (n = 1200). By screening the titles and abstracts, 1080 were removed. A total of 24 studies evaluating occupational exposure about health outcomes other than cancer were also eliminated from the remaining 69 full-text articles. In total, 45 relevant publications (10 cohort studies, 35 case-control studies) were retained for data extraction (summarized in Tables 3 and 4, some papers examined more than 1 outcome).

The Geographical Diversity of Studies Conducted Worldwide

Figure 2 shows the geographical distribution of studies worldwide. Eight studies were conducted in France (21-28) and Canada (29-36). There were also 4 papers in Germany (37-40), and 3 in Finland (41-43). Two studies were conducted in the Netherlands (44, 45) and Sweden (46, 47). Poland (48), China (49), the U.S. (50), England (51), Hong Kong (52), Turkey (53), Indonesia (54), Iran (55), and Italy (56) each had 1 article. Also, 9 studies were conducted jointly in several countries (57-65).

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Table 3. The basic information of the studies included in this review

First author /Location/ Date of publication	Population Size/Description	Cancer Sites	Exposure Agents Assessed	Covariates Controlled for in Modeling
Cohort studies				
Sciannameo/ Italy/2019	A cohort of 2991 (790 females & 2201 males) Italian electroplaters, workers who were potentially exposed to the hazards of galvanic production, cases:162	LC [a], BC[b]	Nickel, chromium	Age, sex, calendar period
Liu/China/2013	In a cohort in China (1960–2003), 34018 workers, with an average of 34.5 years of follow-up from seven metal mines and four pottery factories, cases:546, data collection: interviews, exposure assessment: JEM	LC	Silica Exposure	Sex, year of birth, and smoking
Siew/ Finland /2012	Cohort of all Finnish men (born 1906 -1945) (1.2 million) followed up through the Finnish cancer registry (FCR), cases: nose (n = 292), nasopharynx (n = 149), and lung (n = 30,137) 1971–1995. exposure assessment: JEM	LC	Wood dust, formaldehyde	Smoking, socioeconomic status, and exposure to asbestos and/or silica dust
Offermans/Netherlands/2014	Netherlands Cohort Study (NLCS) (58279 males aged 55 - 69), cases: after 17.3 years of follow-up 2324 LC cases available, data collection: self-administered questionnaire, exposure assessment: JEM	LC, LaC[C]	Asbestos	Cigarette smoking, the number of cigarettes smoked per day, years of smoking cigarettes, exposure to crystalline silica, PAH
Lindbohm/Finland/2009	A cohort of economically active Finns (1.2 million) (born 1906 - 1945) was followed up (1.2 million, 1971–1995) by FCR, cases: 2474, exposure assessment : JEM	PLC[d]	Organic solvents and gasoline vapors, Aliphatic and alicyclic HC	Alcohol, smoking, socioeconomic status (SES)
Bourgkard/ France/2009	Historical cohort, all male (1672) and female (959) workers ever employed in a French carbon steel-producing factory, causes of death: via death certificates, data collection: interviews with and a review of historical documentation, exposure assessment JEM.	LC BC	Iron oxide	Asbestos, PAH, silica, smoking
Taeger/Germany /2008	Cases: male workers who died from LC who had a known history of uranium mining, total sample: 8066 uranium miners, where 3174 died from LC exposure assessment: JEM	LC	Arsenic, quartz	Silicosis
Lohi/Finland/2008	A cohort of all economically active Finns was followed up for BC. cases: All cancers diagnosed between 1971 and 1995 (10277) among people born between 1906 and 1945 were extracted from the nationwide FCR. , exposure assessment: JEM.	BC	Chlorinate HC Solvents	Smoking, obesity, social class
Purdue / Swedish /2006	Cases:510 H&NC (171 in the oral cavity, 112 in the pharynx, 227 in the larynx) were identified among 307799 male workers in the Swedish construction industry, exposure assessment: JEM	LaC	Asbestos mineral wool cement dust DME solvents wood dust	Age, smoking

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Table 3. Continued

First author /Location/ Date of publication	Population Size/Description	Cancer Sites	Exposure Agents Assessed	Covariates Controlled for in Modeling
Cohort studies				
Zhao/US/2005	A cohort of 55000 workers employed (1950 - 1993) at several Boeing North America. caces:5049 of workers who were alive and at risk of being diagnosed with cancer. exposure assessment: JEM	LC, BC LeC[e]	PAH, mineral oils, benzene TCE	Age
Case-control studies				
Sce´lo´ın six Central and Eastern Europe countries/2004	Cases:2861, controls: 3118, occupational agents: collected based on detailed occupational questionnaires	LC	Vinyl chloride, acrylonitrile, styrene	Center, gender, age, tobacco consumption
Radoï/France /2019	Cases:2161 H&NC, controls:3555 population controls, data collection: standardized questionnaire and interview, exposure assessment: JEM	LaC	Leather dust	Age sex, area of residence, SES, tobacco smoking status
Warden /Canada/2018	Cases: 733, controls:894 population controls. data collection: obtained via interview	LC	Benzene, toluene, xylene (BTX)	Age, smoking
Latifovic/Canada/2020	Cases: 658, controls:1360 age-frequency matched population control, data collection: self-administered questionnaires, exposure assessment: JEM	BC	Silica, asbestos	Province of residence, age, proxy respondent, cigarette pack-years, DME exposure, ever exposed to mineral/lube oil at work
Suraya/ Indonesia/2020	Cases: 336, controls:360, data collection: questionnaire and interviews, exposure assessment: JEM	LC	Asbestos	Gender, age, ethnicity, education, house ownership, smoking, and environmental asbestos exposure
Hall/ Western Europe12 and Latin America, Germany/2020	Cases: 2256, controls:7857 population controls (1604 females; 6253 males), data collection:. structured questionnaire and interviews, exposure assessment: JEM	LaC	Asbestos, crystalline silica, chromium-VI, chromium-VI and nickel combined	The study, age, alcohol, tobacco smoking
Colin/France /2018	Cohort: included 22795 male workers from six French steel-producing factories, cases:84, controls:251, data collection: face-to-face interviews and questionnaires, exposure assessment: JEM	BC	MWFs (straight, soluble, and synthesized)	Smoking, age
Khedher/ France/2017	Cases: 2926 incident cases with a histologically confirmed (18-75), controls:3555 population controls, data collection: questionnaire. exposure assessment: JEM	LC	Textile dust, cotton fibers	Asbestos, smoking, gender, age, geographic area of residence
Barul/France/2018	Cases: 454 histologically confirmed (18-75) controls :2780 Population controls	LaC	Petroleum-based solvents, oxygenated solvents	Smoking, alcohol
Talibov/Finland, Iceland, Norway, and Sweden/2017	The study was nested in the Nordic Occupational Cancer Study (NOCCA) cohort. Cases: 20615 (diagnosed in 1961-2005), controls:103075 population controls, exposure assessment: JEM	LeC	Occupational solvent exposure	Age, sex, year of birth
Ilar/Swedish/2017	Cases:993, controls :2359 (two groups, population-controls and mortality-matched population controls), data collection: questionnaire and telephone interviews, exposure assessment: JEM	LC	DME	Tobacco smoking, asbestos, residential radon, age, year of study, exposure to air pollution from road traffic
Hadkhale/Finland, Iceland, Norway, and Sweden/2017	NOCCA database, cases: 113343 (1961 -2005), controls: 566715 population controls, exposure assessment: JEM	BC	TCE, benzene, toluene, aromatic HC, aliphatic & alicyclic HC	Age, sex, birth year, country

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Table 3. Continued

First author /Location/ Date of publication	Population Size/Description	Cancer Sites	Exposure Agents Assessed	Covariates Controlled for in Modeling
Case-control studies				
Barul/France/2017	Cases: 1857, controls: 2780 population control, data collection: face to face interviews using a standardized questionnaire, exposure assessment: JEM	LaC	Perchloroethylene (PCE), trichloroethylene (TCE), methylene chloride (MC), chloroform (CF), carbon tetrachloride (CT)	Age, tobacco smoking, alcohol consumption, asbestos exposure,
Switkowska/ Poland/2015	Case-control studies were carried out within a cohort including 7374 former workers of asbestos processing plants (employed 1943 -998), cases:165, controls:825 population control	LC	Asbestos	Cigarette smoking
Matrat/France/2015	Cases :2926 (18 - 75), identified during the study period (2001-2007) , controls:3555 population controls, exposure assessment: JEM	LC	DME	Age, asbestos, silica, residential history, education, occupation, lifelong cigarette smoking, and alcohol consumption
Kachuri/Canada/2014	Cases:1681(1994 -1997), population controls: 2053, data collection: self-administered questionnaire	LC	Crystalline silica	Cigarette smoking, second-handed smoke, DME
Latifovic/Canada/2015	Cases: 658, controls:1360 population, data collection: self-administered questionnaire controls, exposure assessment: JEM	BC	DME	Cumulative silica exposures, cigarette pack-year, sex,5- year age group
Colt/England/ 2014	Cases: 895 histologically confirmed (30 -79) between 2001 - 2004, population controls: 1031, data collection: questionnaire and interviews	BC	MWFs	State, gender, and age at diagnosis (within 5 years), smoking
Pesch⁄Germany/2013	Case-control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC), cases: 754, controls: 833, exposure assessment: JEM	BC	PAH, aromatic amines	Gender, age, smoking cigarettes, smoking of other tobacco types, age, research center
Mo¨hner/ Germany /2013	A cohort study that followed up on approximately 6,000 German potash miners, cases: 68, contrls: 340, exposure assessment: JEM	LC	DME	Cigarette smoking
Guida/ France /2013	Cases:1350 histologically confirmed LC in men (18 - 75), controls:1912 population controls, data collection: face-to-face interviews via standardized questions, exposure assessment: JEM	LC	MWs, asbestos, silica	Age, cigarette smoking, gender, education, lifetime alcohol consumption
Villeneuve/ Canada /2012	Cases: 1,681, controls: 2053 (recruited between 1994 and 1997), data collection: self-reported questionnaires	LC	Asbestos	Age, cigarette smoking, SES, secondhand smoking, occupational exposure to silica, DME
Tse/ Hong Kong/ 2012	Cases: 1208 male, controls: 1069 age-matched male population controls (2004–2006), data collection: face-to-face interviews via standardized questions	LC	Asbestos, silica dust, welding fume, DME, MMMF	Smoking, indoor air sources pollutants, tobacco smoking alcohol, dietary habits, history of diseases
Villeneuve/ Canada /2011	Cases: 1681 (men 40 years of age), 2053 population controls: data collection: self-reported questionnaire	LC	DME	Crystalline silica, asbestos, cigarette smoking
Mannetje/Central Eastern Europe and UK /2011	Cases: 2853, controls: 3104. data collection: face-to-face interviews via a questionnaire	LC	Chromium, cadmium, nickel, arsenic	Cigarette smoking, age, center, sex,

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Table 3. Continued

First author /Location/ Date of publication	Population Size/Description	Cancer Sites	Exposure Agents Assessed	Covariates Controlled for in Modeling
Case-control studies				
Preller /Netherlands/2010	Men (58279) from the NLCS, cases:1667 after 11.3 years of follow-up. data collection: self-reported questionnaire, exposure assessment: JEM	LC	Silica	Age, family history of LC; smoking behavior, fruit/, vegetable, asbestos
Olsson/ seven European countries and Liverpool (UK)/2010	Cases:2852, controls:2936 population or hospital (1998-2002), data collection: questionnaire via interviews	LC	PAH	Age, sex, center, tobacco pack years, occupational exposure to silica, asbestos, metals (arsenic, chromium, cadmium)
Kiran/ Czech Republic, France, Germany, Italy, Ireland, and Spain /2010	Cases: 406, controls:2463population controls, data collection: self-reported questionnaire (between 1998–2004)	LeC	Ethylene oxide	Age, sex, and participating center.
ELCI/ Turkey/ 2009	Cases:189 pathologically confirmed male NSND, controls: 536 NSND hospital-based controls, data collection: face-to-face interviews via a questionnaire	LaC	Silica, grain dust, leather dust, asbestos, wood dust, cotton dust, PAH, DME, formaldehyde, solvent	Age, smoking, alcohol
Richardson /Canada/2007	Cases: 1062 adult male (diagnosed between 1983 and 1990), controls: 8057 population controls, data collection: self-administered questionnaire, exposure assessment: JEM	BC	Coal-tar pitches, mineral oils, Benz (a) anthracene, DME Direct black 38,4-Chloro-ortho-toluidine, ortho-Toluidine	Ethnic origin, marital status, education, alcohol, cigarette smoking
Richiardi/ Germany /2006	Cases: 595 histologically confirmed, controls: 845 population controls. data collection: structured questionnaire and through interviews, exposure assessment: JEM	LC	DME	Sex, smoking
Berrino/ four European countries / 2003	Cases: 315 male of hypopharyngeal/ LaC, controls:819 population controls (during 1979–1982), exposure assessment: JEM	LaC	Asbestos, PAH, chromium, arsenic, and compounds, wood dust, formaldehyde, solvents,	Age, center, tobacco, alcohol, diet, SES
Heinemann/six European countries /2000	Cases: 317 women hospital cases, controls:1789 (1060 hospital controls and 719 population controls), exposure assessment: JEM	PLC	Beryllium, cadmium, formaldehyde, PAH, lead, mercury	Age, center, hepatitis infection, smoking, alcohol, oral contraceptive use
Roussea/ Canada/2007	Cases:3730 Men, controls: 533 population controls were interviewed. data collection: structured questionnaire and interviews	LC	Lead (organic, inorganic, gasoline emissions)	Age, tobacco, SES
Hosseini /Iran /2009	Cases:242 histologically confirmed (178 male, 64 female), controls: two controls for each patient (242 hospital controls and 242 visiting healthy controls), data collection: structured questionnaire and through interviews	LC	Asbestos, heavy metals, coal tar, soot, DME, Inorganic dust, wood dust, cotton dust, silica	Age, sex, place of residence

[a]LC: Lung cancer;[b] BC: Bladder cancer; [c] LaC: Laryngeal cancer; [d] PLC: Primary Liver cancer; [e] LeC: Leukemia

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Table 4. The results of the studies reviewed, about the association between occupational exposures and five common occupational cancers

First author /Location/ Date of publication	Type of assessment	Outcome evaluated	Main results	Conclusion
Suraya/ Indonesia/2020	ever exposure Duration cumulative exposure	LC[a]incidence	Asbestos: risk was elevated forever exposure (OR = 2.04, 95% CI = 1.21–3.42), Exposure ≥10 (OR = 2.31, 95% CI = 1.26–4.26)	Elevated LC risk attributable to asbestos exposure. The disease risk is consistent with a dose-response relationship.
Latifovic⁄Canada/2020	Ever exposure Duration of exposure cumulative exposure	BC[b] incidence	Silica: ever exposure (OR:1.29, 95%CI: 1.00–1.61), for≥27 years 1.41 (95%CI: 1.01–1.98). Asbestos: ever exposure: (OR:1.32,95%CI: 0.98–1.77), exposures ≥20 years ago (OR:2.04, 95%CI:1.25–3.34), < 10 years (OR:1.75, 95%CI:1.10–2.77), lower tertile of cumulative exposure (OR:1.69, 95%CI:1.07 2.65)	Occupational silica and asbestos increase the risk of BC, silica exposure: an exposure-response relationship.
Hall/ Western Europe12 and Latin America/ Western Europe12 and Latin America, Germany/2020	Ever exposure Duration of exposure Cumulative exposure	LaC[c]incidence	Asbestos: at >90 percentile cumulative exposure (OR: 1.3, 95% CI = 1.0, 1.6), Respirable crystalline silica: >30years duration (OR: 1.4, 95% CI = 1.2, 1.7), 75th–90th percentile cumulative exposure (OR: 1.4, 95% CI = 1.1, 1.8), chromium-VI: at >75th percentile cumulative exposure (OR: 1.9,95% CI = 1.2, 3.0), chromium-VI and nickel combined: at 20–29 years duration (OR: 1.5, 95% CI = 1.1,2.2).	Exposure to asbestos, respirable crystalline silica, chromium-IV, and chromium-VI with nickel) increase the risk of LaC
Sciannameo/ Italy/2019	Cumulative exposure	LC & BC mortality	Chromium & LC: Not any association Chromium & BC: Not any association Nickel & LC: Increased risks for a cumulative exposure of (HR:6.03, 95% CI 2.94 -12.37) Nickel & BC: not any association	Exposure to nickel compounds may increase the risk of LC
Offermans/Netherlands/2014	Ever exposure duration of exposure cumulative exposure	LC & LaCincidence	Asbestos & LC: Ever exposure (HR= 1.50; 95% CI: 1.27–1.78) duration of exposure ((Lowest (HR=1.47; 95% CI: 1.15-1.87), Middle (HR=1.58; 95% CI: 1.21-2.07), Highest (HR=1.46; 95% CI: 1.2-1.9)) was associated with LC. The risk of LC increased with cumulative exposure to asbestos ((Lowest HR=1.44; 95% CI: 1.12-1.86), Middle (HR=1.40; 95% CI: 1.09-1.79), Highest (HR=1.76; 95% CI: 1.3-2.38)). Asbestos & LaC: No statistically significant relationship was observed	Asbestos exposure increased risk for LC
Liu⁄China⁄2013	Ever/never exposure cumulative exposure	LC mortality	Silica: Quartiles of cumulative exposure yielded HR of 1.26(0.98, 1.60), 1.54 (1.16, 2.05), 1.68 (1.26, 2.24), and 1.70 (1.23, 2.34), respectively.	Silica exposure is associated with a significant increase in LC risk
Siew/Finnish /2012	Cumulative exposure	LC incidence	Formaldehyde: cumulative exposure to formaldehyde was associated with an elevated risk of LC (RR, 1.18; 95% CI: 1.12–1.25). Wood dust: not any association	Elevated LC risk attributable to cumulative exposure of formaldehyde

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Table 4. Continued

First author /Location/ Date of publication	Type of assessment	Outcome evaluated	Main results	Conclusion
Lindbohm/Finland/2009	Cumulative exposure	PLC[d] incidence	Aromatic HC: the highest exposure category (RR: 1.77;95% CI: 1.30–2.40), Aliphatic/alicyclic HC: the highest exposure category (RR :1.47;95% CI: 0.99–2.18), Chlorinated HC: the highest exposure category (RR:2.65;95% CI: 1.38–5.11) The highest exposure category other solvents" (RR :2.14;95% CI: 1.23–3.71).	Men who are exposed to chlorinated HC have a higher risk of PLC.
Bourgkard/France/2009	Ever exposure Duration of exposure Cumulative exposure	LC & BC mortality	Iron oxide &LC: No excess was observed forever exposure (RR= 0.80, ;95% CI: 0.55 - 1.17) Oil mist & BC; Excess was observed forever exposure: (RR =2.44;95% CI: 1.06 - 5.60), duration of exposure: (RR=1.85;95% CI: 1.07 - 3.19) and cumulative of exposure (RR= 1.69;95% CI: 1.03 - 2.79)	Exposure to Oil mist increases the risk of BC
Taeger/ German /2008	Cumulative exposure	LC mortality	Cumulative exposure to quartz (OR, 1.78; 95%CI, 1.39–2.26) and arsenic (OR, 1.18; 95%CI, 0.99–1.4) were determined as risk factors for LC	Evidence indicated that quartz and arsenic are risk factors for LC
Lohi/Finland/2008	Cumulative exposure	BC incidence	Middle levels of chlorinated HC solvents (1.7; 95% CI:1.2–2.5) and a low level of aromatic HC solvents (1.6; 95% CI:1.3–2.1) were associated with BC	occupational exposure to HC solvents may have an impact on BC risk
Purdue/Swedish/2006	Ever exposure cumulative exposure	LaC incidence	Asbestos: Ever exposure was related to an increased LaC incidence (RR:1.9, 95% CI 1.2–3.1). Mineral wool: excesses of LaC were observed forever exposure (RR:1.6, 95% CI 1.03–2.4) and moderately exposure (RR: 1.7, 95% CI 1.01–2.7) Other exposures did not show a significant association	Asbestos and Mineral wool increases the risk of LaC .
Zhao/America/2005	Cumulative exposure	LC, BC & LeC[e] incidence& mortality	Mineral oils & LC: High levels of exposure increased mortality and incidence ORs (1.56; 1.02–2.39 and 1.99; 1.03–3.85). TCE & LC: was not associated Benzene, PAH & LC: no associations were observed TCE & BC: high exposure levels likely to increase the risk of BC (RR: 1.98;95CI: 0.93–4.22) Mineral oils, PAH & BC: were not associated TCE & LeC: was not associated Mineral oils & LeC: was associated with mortality (RR for high exposure levels: 2.88(1.19–7.0) Benzene, PAH & LeC: No association was found	Mineral oils experienced an increased risk of developing and/or dying from LC and LeC . TCE exposure was probably at increased risk of BC
Sce´lo/in six Central and Eastern Europe countries/2003	Ever exposure Duration of exposure Cumulative exposure	LC incidence	Acrylonitrile: Ever exposure was associated to LC (OR: 2.20;95CI: 1.11–4.36). No association between exposure to styrene, vinyl chloride and LC risk was found	Exposure to acrylonitrile increases the risk of LC

[DOI: 10.47176/mjiri.36.84]

Table 4. Continued

First author /Location/ Date of publication	Type of assessment	Outcome evaluated	Main results	Conclusion
Radoï/France /2019	Ever exposure Cumulative exposure	La Cincidence	Leather dust: Cumulative exposure was associated (OR :2.26;95% CI: 1.07–4.76); ever exposure was not associated (OR :1.40;95% CI: 0.77–2.56)	Increased cases of LaC attributable to leather dust
Warden/Canada/2018	Ever exposure duration of exposure	LC incidence	Benzene: Ever exposure (OR: 1.35 ;95% CI 0.99 - 1.84) and exposure>10 years (OR: 1.44 ;95% CI 0.94 -2.21) were associated with LC Toluene: Ever exposure increased risk of LC (OR=1.31; 95% CI 0.99 - 1.74), Exposure>10 years was not associated with LC (OR=1.12; 95% CI 0.78 to 1.60). Xylene: Ever exposure increased risk for LC (OR=1.44; 95% CI 1.03 - 2.01), exposure>10 years was not associated with LC (OR=1.43; 95% CI 0.89 2.31)	Exposure to one or more of the BTX agents may be associated with LC
Colin/France /2018	Duration of exposure, Cumulative exposure	BC incidence	MWFs: Duration of exposure to straight MWFs (≥25 years) was associated with BC (OR=1.13 (1.02–1.25). exposure to synthetic MWFs: not any association	Exposure to MWFs increases the risk of BC
Khedher/ France/2017	Ever exposure	LC incidence	Textile dust: Inverse association between working in textile dust and LC, although this relationship was not statistically significant (OR = 0.84, 95%CI 0.67-1.07). Cotton fibers: LC was significantly decreased among workers exposed (OR = 0.70, 95%CI 0.48-0.97).	Decreased risk of LC associated with exposure to textile dust, particularly cotton.
Barul/France/2018	Ever exposure Cumulative Exposure	LaC incidence	Benzene: No significant association was found forever (OR:0.94 ;95%CI: 0.71–1.24) and cumulative exposure to low, medium and high	Exposure to petroleum-based or oxygenated solvents is not a substantial role in LaC risk
Talibov/Finland, Iceland, Norway, and Sweden/2017	Cumulative Exposure	LeC incidence	Perchloroethylene: Significantly risks were observed for cumulative exposure (OR =1.61, 95% CI:1.01-2.56) among women non-significant associations were observed forever exposure to methylene chloride, perchloroethylene, and 1,1,1-trichloroethane in both sex	There is not any association between solvent exposure and adult LeC
Ilar/Swedish/2017	Ever exposure Duration exposure Cumulative Exposure	LC incidence	DME: OR forever exposure was 1.15 (95% CI:0.94–1.41). duration; OR in the highest quartile of exposure duration ≥34 years) was 1.66 (95% CI:1.08–2.56)	Elevated risk for LC attributable to DME exposure
Hadkhale/Finland, Iceland, Norway and Sweden/2017	Cumulative Exposure	BC incidence	Increased risks for TCE (HR=1.23; 95% 95% CI :1.12-1.40), toluene (HR= 1.20, 95% CI: 1.00-1.38), benzene (HR= 1.16; 95% CI: 1.04-1.31), aromatic HC solvents (HR= 1.10; 95% CI: 0.94-1.30) and aliphatic & alicyclic HC solvents (HR =1.08;95% CI :1.00-1.23) at high exposure level	Exposure to TCE, perchloroethylene, aromatic hydrocarbon solvents, benzene and toluene and an elevated risk for BC
Barul/France/2017	Ever exposure cumulative exposure	LaC incidence	The OR for LaC was 3.86 (95% CI = 1.30 - 11.48) for those exposed to the highest levels of PCE. There was no increased risk of exposure to TCE MC, CF, CT, and LaC	High exposure to PCE increases the risk of LaC
Swiatkowska/ Poland/2015	Cumulative Exposure	LC incidence	Risk in the group with the highest exposure was two times higher (OR= 1.99; 95%CI: 1.22–3.25)	LC risk is associated with asbestos exposure and it increases along with the increasing exposure.

[DOI: 10.47176/mjiri.36.84]

Table 4. Continued

First author /Location/ Date of publication	Type of assessment	Outcome evaluated	Main results	Conclusion
Matrat/France/2015	Ever exposure duration of exposure cumulative exposure	LC incidence	DME: Ever exposure was associated with LC (OR = 1.3;95%: CI 1.1–1.6). The more the cumulative exposure increases, the more the risk of LC increases (OR= 1.4; 95% CI: 1.1–1.6) for the highest IEC	DME exposure as a risk factor of LC
Offermans/Netherlands/2014	Ever exposure duration of exposure cumulative exposure	LaC incidence	LaC showed a positive association after prolonged higher asbestos exposure (HR per10 years increment, 1.95[95% CI: 1.36 - 2.80].	Asbestos levels may be associated with an increased risk of LaC
Kachuri/Canada/2014	Ever exposure duration of exposure cumulative exposure	LC incidence	Silica: Increasing duration of exposure was associated with a significant risk to LC (OR≥30 years: 1.67; 95% CI: 1.21 2.24), cumulative exposure was associated with LC risk (OR=1.81; 95% CI: 1.34–2.42), ever exposure was related to LC (OR=1.20; 95% CI: 1.0–1.43)	occupational exposure to silica is a risk factor for LC
Latifovic/Canada/2015	Ever exposure duration of exposure cumulative measure	BC incidence	DME: Ever exposed was not associated with BC; duration >10 years of exposure had a greater than two-fold increase in the risk of BC (OR = 2.45; 95% CI: 1.04–5.74)	Exposure to high concentrations of DME may increase the risk of BC
Colt/England/ 2014	Ever exposure Cumulative exposure	BC incidence	Ever exposure: risk was elevated among men who reported using straight MWFs (OR=1.7; 95% CI: 1.1–2.8) .Cumulative exposure to straight MWFs: was associated with BC (OR=2.2; 95% CI: 1.02–4.8)	MWFs exposure was associated with a significantly increased BC risk
Pesch/German/2013	Cumulative exposure	BC incidence	Exposure to aromatic amines and PAH was associated with an increased BC risk (highest exposure: OR=1.37; 95% CI: 1.02–1.84, and OR=1.50; 95% CI: 1.09–2.05, respectively)	Excess risks of BC are associated with occupational exposure to aromatic amines and are supportive of the role of PAHs in the development of BC
Mo¨hner/ German /2013	Cumulative reparable elemental carbon (REC) exposure as a continuous variable	LC mortality	Introducing cumulative REC exposure as a continuous variable yielded an odds ratio of 1.04 [0.70–1.53]	LC was not associated with DME exposure
Guida/ France /2013	Ever exposure Cumulative exposure	LC incidence	MWs :Ever and cumulative exposure was not associated with LC Asbestos: ever exposure was associated with significantly increased risk of LC (OR = 1.46; 95% CI: 1.17 -1.83). Crystalline silica: ever expose was related to LC (OR = 1.35; 95% CI: 1.03 - 1.77)	Crystalline silica & asbestos were associated with an increased risk of LC. no firm evidence that MWs was not associated with LC
Villeneuve/ Canadian /2012	Ever exposure Cumulative exposure duration of exposure	LC incidence	Asbestos: cumulative exposure to medium or high concentrations of had OR for LC of 2.16 (95% CI=1.21-3.88, ever exposure increased risk of LC (OR = 1.28; 95% CI: 1.02 to 1.61)	Exposure to asbestos has contributed to an increased risk of LC
Tse/ Hong Kong /2012	Ever/never exposure, duration of exposure	LC incidence	Significantly elevated risk for ever exposure to silica dust (1.75; 95% CI: 1.16–2.62), welding fumes (1.74; 95% CI: 1.13–2.68), DME (2.18; 95% CI: 1.23–3.84), and MMMF (7.45; 95% CI: 1.63–34.00), significantly reduced risk of LC (OR = 0.67; 95% CI: 0.47–0.95) was linked to ever exposure to cotton dust, ever exposure to asbestosis showed no association with LC	Silica dust, welding fumes, DME, AMMMF were at significantly increased risks of LC, while long-term exposure to cotton dust seemed to be protective

[DOI: 10.47176/mjiri.36.84]

Table 4. Continued

First author /Location/ Date of publication	Type of assessment	Outcome evaluated	Main results	Conclusion
Villeneuve/ Canada /2011	Ever exposure cumulative exposure	LC incidence	DME: Ever exposure (OR = 1.06; 95% CI: 0.89–1.25) and cumulative exposure Lowest ((OR=0.93; 95% CI: 0.75-1.17), Middle (OR=1.03; 95% CI: 0.83-1.29), Highest (OR=1.12; 95% CI: 0.89-1.10) were not associated with LC	The findings of this study suggest that exposure to DME may increase the risk of LC
Mannetje/Central Eastern Europe and UK /2011	Ever exposure duration of exposure cumulative exposure	LC incidence	Arsenic: Ever exposure was associated with an increased LC risk (OR= 1.65;95% CI:1.05–2.58). Cadmium fumes: highest category of cumulative exposure was associated with LC (OR=2.04; 95% CI: 1.07–3.90). No increased risk was observed for inorganic acid mist, inorganic pigment dust, Chromium, or nickel	Occupational exposure to metals is an important risk factor for LC.
Preller /Netherlands/2010	Ever exposure duration of exposure cumulative exposure	LC incidence	Silica: Ever exposure was not associated with LC (RR=1.06; 95% CI: 0.84-1.39). Elevated risks for LC were observed for exposure duration (RR=1.65; 95% CI: 1.14 - 2.41 for 26-51 and cumulative exposure (RR= 1.47;95% CI: 0.93 2.33).	Elevated LC risk attributable to crystalline silica exposure
Olsson/ seven European countries and Liverpool (UK)/2010	Ever exposure cumulative exposure	LC incidence	PAH: Ever exposure, duration of exposure, and cumulative exposure were not associated with LC in the CEE countries. The OR forever PAH exposure in the UK was 1.97 (95% CI 1.16 -3.35)	Occupational PAH exposure may contribute to the burden of LC in some countries
Kiran/ Czech Republic, France, Germany, Italy, Ireland, and Spain /2010	Ever exposure Duration Cumulative exposure	LeC Cincidence	The OR forever exposure to ethylene oxide and LeC was 2.0 (95% CI= 0.8–4.1), and for medium/high duration of exposure was 6.2(1.3–29.3). Cumulative exposure was not related to LeC	ethylene oxide is a risk factor for LeC
ELCI/ Turkey/ 2009	Ever exposure	laC incidence	An excess of LaC occurred with silica (OR, 1.7; 95%CI: 1.1–3.0) and PAH (OR,1.5; 95%CI:1.1–2.2). Other exposures did not show a significant relationship	The excess risk from silica and PAH exposure and LaC
Richardson / Canada/2007	Ever exposure cumulative exposure	BC incidence	Ever exposure to Mineral oils (OR, 1.16; 95%CI, 1.01–1.32), Benz(a)anthracene (OR, 1.92; 95%CI, 1.02–3.61), and DME (OR, 1.18; 95%CI, 1.04–1.35) were associated with BC. Also, cumulative use of DME was related to BC (OR, 1.25; 95%CI, 1.04–1.49)	Several specific chemical agents were significantly associated with the risk of BC
Richiardi/Italy/2006	Ever exposure Duration of exposure cumulative exposure	LC incidence	The OR forever exposure to DME and LC was 1.04 (95% CI: 0.79–1.37). no association was found with cumulative and duration of exposure	NO statistically significant relationship between occupational exposure to DME and LC risk.
Berrino/South Europe/ 2003	Ever exposed Duration of exposure	LaC incidence	A positive association between ever exposure to wood dust (OR 1.7, 95% CI: 1.2–2.6), organic solvents (OR:1.7, 95% CI: 1.1–2.5), and asbestos (OR= 1.6;95% CI:1.0–2.5) and LaC was observed. The duration of formaldehyde exposure was also associated with an increased risk of LaC (OR:2.3, 95% CI: 1.1–4.6) No association was found for exposure to arsenic, chromium, and PAH	Occupational exposure to solvents and asbestos was associated with an increased risk of LaC
Heinemann/six European countries and covered the period July 1990 to June 1996/2000	Ever exposure	PLC incidence	None of the beryllium, cadmium, Lead, Mercury, and PAHs were not associated with PLC. Although Formaldehyde (OR: 3.36, 1. 2–9.35) was associated with PLC	No consistently and significantly increased PLC risk concerning with the mentioned exposures
Roussea/ Canada/2007	Ever exposure	LC incidence	Ever exposure to lead was not associated with an increase in the odds of LC(OR:1.4, 95%CI: 0.6–3.2)	Little evidence for an association between lead and LC
Hosseini /Iran /2009	Ever exposure	LC incidence	Occupational exposures to inorganic dust (OR 4.2, 95% CI = 2.8–6.7), chemical compounds (OR= 3.4, 95% CI = 2.1–5.6), and heavy metals (OR 3.0, 95% CI = 1.3–7.0) were all found to be independent risk factors for LC	Inorganic dust, chemical compounds, and heavy metals were associated with LC etiology

[a]LC: Lung cancer ;[b] BC: Bladder cancer; [c] LaC: Laryngeal cancer; [d] PLC: Primary Liver cancer; [e] LeC: Leukemia

[DOI: 10.47176/mjiri.36.84]

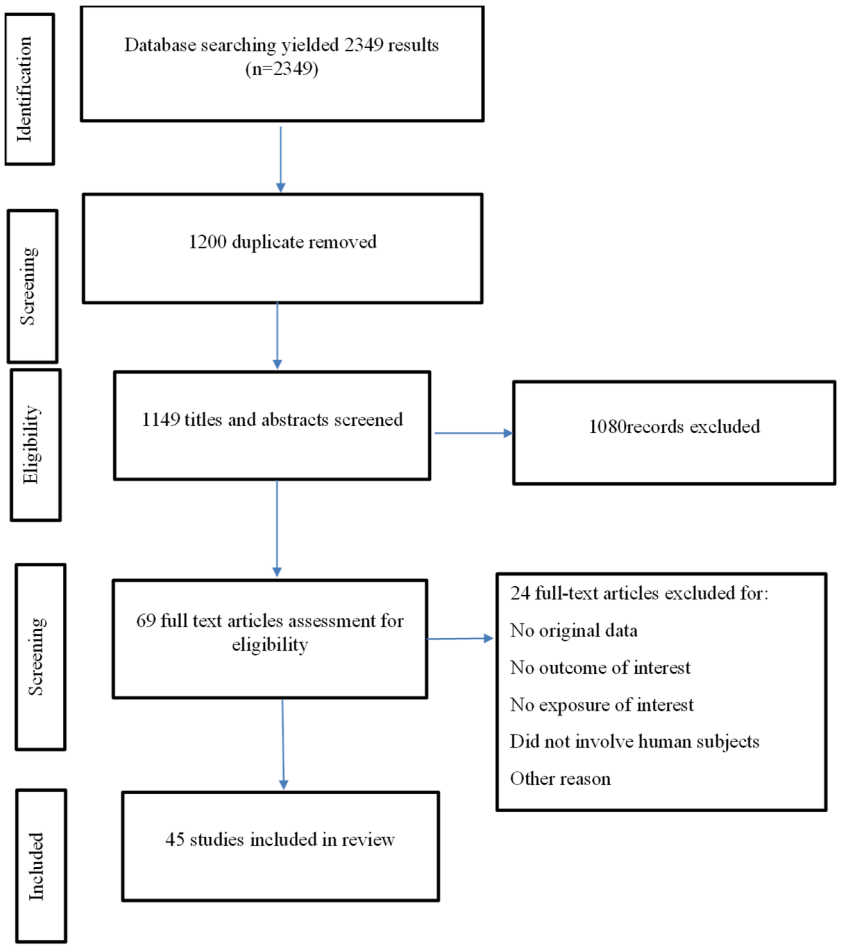

Fig. 1. PRISMA flow diagram

The Types of Occupational Carcinogens

One study examined the effects of nickel and/or chromium (56). The effect of diesel motor exhausts (DME) was investigated in 5 studies (27, 33, 37, 40, 47). Silica and/or asbestos (31, 49) polycyclic aromatic hydrocarbons (PAH), and/or aromatic amines (39, 65) were examined in 2 studies. Furthermore, 2 studies examined metalworking fluids (MWFs) (23, 51).

Wood dust and/or formaldehyde (41), arsenic and/or quartz (38), textile dust and/or cotton fibers (24), benzene and/or gasoline (25), iron oxides (21), ethylene oxide (64), lead (35), leather dust (22) chlorinated hydrocarbon solvents (43) vinyl chloride, acrylonitrile and/or styrene (57), and oil mist (21) were examined in a separate study. A study also examined the effects of co-exposure to benzene, toluene, and xylene (BTX) (29).

The effect of asbestos has been studied in 4 studies (32, 44, 48, 54). Other studies investigated the impact of multiple exposures (26, 28, 42, 46, 50, 52, 53, 55, 59-63). All exposures are shown in Table 3.

The Main Outcome Evaluated

Five studies evaluated the mortality of cancer (21, 38, 40, 49, 56), 1 study evaluated the incidence or mortality (50), and other studies considered the incidence (occurrence) of cancer as the outcome (Table 4).

Characteristics and Quality of Studies

Cohort studies

Sciannameo et al (56) who evaluated the 2 outcomes of lung and bladder cancers, had a relatively small sample size but the potential confounders were almost controlled.

Confounders were successfully controlled in the analyses of Liu et al and Offermans et al (44), in addition to the large sample size.

Although the outcome was recorded and collected by the Finnish Cancer Registry (FCR) in the research of Lindbohm et al (42), Siew et al (38), and Lohi et al (43), in addition to having a large sample size and thorough management of confounders, this contributed to minimizing selection bias in these investigations. In the study by Bourgkard et al (21), the sample size was relatively small, but potential confounders, especially socioeconomic status (SES), were largely controlled. Although the study by Taeger et al (38) had a middle sample size, the control of potential confounders was relatively weak, and only exposure to silica was considered a potential confounder.

Case-control Studies

In studies by Sce´lo et al (57), as well as Radoï et al (22), in addition to having a large sample size, potential confounding factors were also well controlled. However, the choice of control in the first study was individually and

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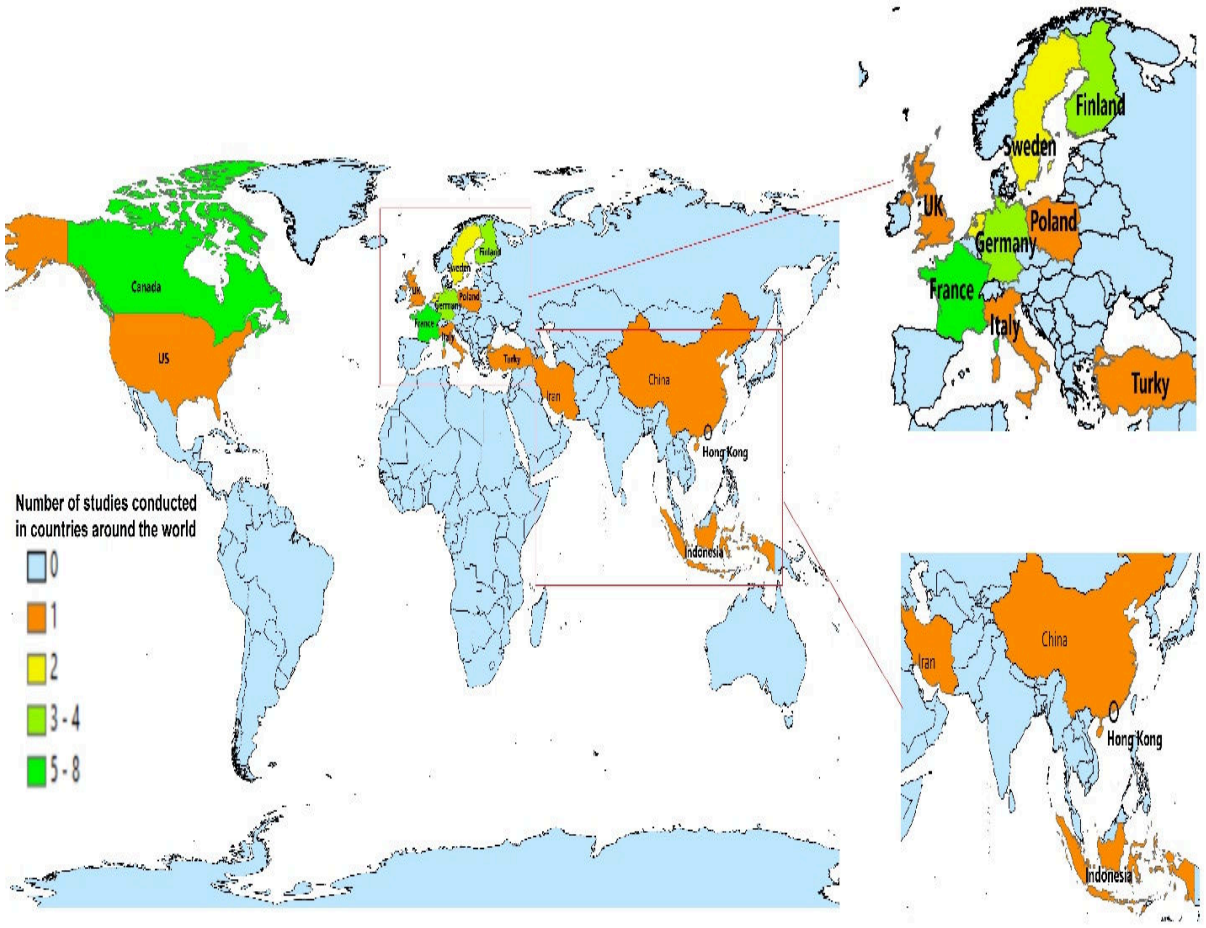

Fig. 2. The geographic diversity of studies across the world

population-based, but in the second study, it was frequency matching. Warden et al (29) conducted a study with a relatively high sample size and population control selection.

Only 2 variables, smoking and age, were controlled, and other confounding factors were not considered.

In the studies of Latifovic et al (31), Suraya et al (54), Hall et al (63), Ilar et al (47), Barul et al (26), Matrat et al (27), Mannetje (60), Kachuri et al (30), Latifovic et al (36), Villeneuve et al (33), Olsson et al (65), and Kiran et al (64), in addition to large sample sizes, detailed information on lifelong occupational histories was available and the dose-response rate was assessed; also the impact of other occupational carcinogens as potentially confounding agents was controlled.

The studies by Colin et al (23), Pesch et al (39), Talibov et al (58), and Mohner et al (40) were nested case-control studies with large sample sizes. In these studies, potentially confounding factors were collected, cumulative exposure over a lifetime was collected, and the incidence and dose-response could be estimated.

Switkowska et al (48) conducted their case-control study on a cohort of employees with large sample size. Because the exposure was already recorded, the possibility of information bias was minimized; however, only smoking was controlled as a cofounding factor and the effect of other possible confounders was not considered.

Khedher et al (24), Barul et al (26), Colt et al (51), Guida et al (28), Richiardi et al (37), and Hosseini et al (55) studies were based on histopathologically confirmed cases, and this prevented the occurrence of selection bias. However, the studies of Richiardi et al (37), as well as Hosseini et al (55), had a smaller sample size than other studies, it seems that even these studies have good statistical power for statistical analysis.

A case-cohort study by Preller et al (45) provided a direct estimation of incidence; however, this study had a large sample size, and potentially confounding factors were well controlled.

Overall, one of the most important limitations of case-control studies is the use of job exposure matrices (JEM) that increased the occurrence of differential misclassification (26).

Main carcinogens, associations, and the strength of associations between common occupational carcinogens and 5 related occupational cancers.

LC

Among the cohort studies, 7 studies examined the effects of occupational carcinogens on LC (21, 38, 41, 44, 49, 50, 56). Also, out of 34 case-control studies, 19 studies related to LC (24, 27, 29, 30, 32, 33, 35, 37, 40, 44, 45, 47, 48, 52,

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54, 55, 57, 60, 65). The most important exposures were asbestos (28, 32, 44, 48, 52-55), silica (28, 30, 45, 49, 52, 53, 55), DME (27, 33, 37, 40, 47, 52, 55), cotton dust (24, 52, 55), benzene (29, 50), PAH (50, 65) , wood dust (41, 55), nickel (56, 60), chromium (56, 60), and arsenic (38, 60), respectively. Other exposures each included a study (Table 3).

Except for 2 studies (52, 55), all findings showed a significant association between exposure to asbestos and LC. Also, the effect of exposure to silica was not shown in 1 study (55). The relationship between occupational exposure to DME was not seen in 2 studies (33, 55), and *in* 4 other studies, a statistically significant relationship was observed.

In 2 studies (38, 60) conducted to investigate the effect of arsenic, both studies showed a statistically significant relationship. Only 1 of 2 studies on the effect of benzene (29), PAH (65), and nickel (56) was significant. Also, 2 studies (41, 55) conducted to investigate the effect of wood dust and chromium (56, 60) did not show any statistically significant relationship. In 2 studies (24, 52), exposure to cotton dust reduces the risk of LC; however, 1 study showed an increased risk, and this association was not significant (55). Other occupational exposures that elevated the incidence of LC include quartz (38), iron oxide (21), acrylonitrile (57), mineral oil (50), xylene and toluene (29), cadmium fumes (60), and inorganic dust, chemical compounds, and heavy metals (55). The strength of all associations and other results are shown in Table 4.

BC

Among the cohort studies, 4 studies were related to BC (21, 43, 50, 56). There were also 7 case-control studies for occupational carcinogens and BC (23, 31, 34, 36, 39, 51, 59). The most important occupational carcinogens included solvents (43, 50, 59), PAH (39, 50), mineral oils (34, 50), and DME (34, 36). Other occupational exposures are listed in Table 3.

The results of the studies suggest that exposure to solvents in 2 studies (43, 59) increased the risk of BC, although 1 study (50) showed no association. One study (39) also showed an association between PAH and BC, although another study (50) did not show this association.

Two studies (34, 36) showed that DME increases the risk of BC. In 1 study mineral oils (50) did not show a significant relationship with increased risk of BC; however, another study (34) found an increased risk of BC associated with mineral oils.

For other exposures, MWFs (23), aromatic amines (39), Benz(a)anthracene (34), oil mist (21), silica (49), and asbestos (31) increased the risk of BC. Strength of all associations and exposures that showed no association is listed in Table 4.

LaC

The effect of occupational carcinogens on LaC was evaluated in 2 cohort studies (44, 46). Also, 6 case-control studies examined the effect of occupational carcinogens on LaC (22, 25, 26, 44, 53, 61, 63). The most common occupational exposures were asbestos (44, 46, 53, 61, 63), solvent (25, 26, 46, 53), wood dust (46, 53, 61) , PAH (53, 61), DME(46, 53), leather dust (22, 53), chromium (61, 63), silica (53, 63), and formaldehyde (53, 61). Other occupational carcinogens are listed in Table 3.

The effect of asbestos on the increased risk of LaC was seen in 4 studies (44, 46, 61, 63); however, no statistically significant relationship was observed in 1 study (53).

Solvents showed a significant relationship with increased risk of LaC only in 1 study (26), and in the other 3 studies, no association was found (25, 46, 53). One study (53) found a significant relationship between PAH and LaC, although this relationship was not significant in another study (61). The 2 studies on the effect of DME on LaC were not statistically significant (46, 53).

One study (61) *showed* an increased risk of LaC due to occupational exposure to wood dust, but no statistically significant relationship was observed in the other 2 studies (46, 53).

Of the 2 studies investigating the relationship between exposure to leather dust and LaC, only 1 study (22), showed a statistically significant association. One study (63) found an association between chromium and LaC, although no statistically significant association was found in another study (61).

Of the 2 studies to investigate the effect of formaldehyde on LaC, only 1 study (61) showed a significantly increased risk. Exposure to silica in 1 study (63) increased the risk of LaC; however, no significant relationship was observed in another study (53).

Mineral wool (46) and the combination of nickel and chromium (63) increased the risk of LaC. The complete results are shown in Table 4.

LeC

A cohort study (50) and 2 case-control studies (58, 64) examined the effect of occupational carcinogens associated with LeC. The most common exposure was solvents (50, 58). Other exposures included PAH, benzene, mineral oils, and ethylene Oxide (50, 58, 64).

According to Table 4, in 2 studies (50, 58) there was no statistically significant association between exposure to solvents and LeC. Occupational exposure to mineral oils in 1 study (50) increased the risk of LeC, although benzene and PAH were not associated with an increased risk of LeC in this study. Exposure to ethylene oxide (64) shows an increased risk of l LeC in exposed individuals. Other results and the strength of the observed associations are presented in Table 4.

PLC

A cohort study (42) and 1 case-control study (62) examined the effect of occupational carcinogens on PLC. The most important exposures that have been evaluated for PLC include solvents (42, 62), beryllium, cadmium, formaldehyde, PAH, lead, mercury (62), and gasoline vapors, aliphatic, and alicyclic hydrocarbons (HC) (42).

Based on the results of Table 4, in 1 study (42), organic solvents (aliphatic and alicyclic) were associated with an increased risk of PLC. However, gasoline vapors were not significantly associated with PLC. Occupational exposure to formaldehyde (62) was significantly associated with an

[DOI: 10.47176/mjiri.36.84]

increased risk of PLC, but beryllium, cadmium, lead, mercury, and PAHs were not significantly associated with PLC. Table 4 shows the strength of associations observed in studies and other results.

Discussion

Summary of Findings

Our review found 45 papers on occupational exposure to carcinogens and cancer risk. The findings of this review strongly suggest that occupational exposures were associated with an increased risk of LC, BC, LaC, LeC, and PLC. The present review also appears to be the first study based on 5 common occupational cancers.

In this review, of the 7 cohort studies that assessed the effects of occupational carcinogens on LC, 6 studies showed a positive association between occupational exposure and LC. In addition, 3 out of 4 cohort studies on BC were associated with an increased risk of BC. In the other 3 cohort studies, the incidence of LaC, LeC, and PLC increased because of carcinogenic exposures.

Of the 19 case-control studies evaluating the effect of occupational carcinogens on LC, only 5 studies showed no statistically significant relationship. Also, all 7 case-control studies that examined the effect of occupational exposure on BC showed a statistically significant increase in the risk of BC, and this suggests that occupational carcinogen exposures strongly influence this cancer. Also, of 5 case-control studies related to occupational carcinogens and LaC, 4 studies were significant. One out of 2 case-control studies related to occupational carcinogens and LeC showed a statistically significant relationship. There were 2 case-control studies on occupational carcinogens and PLC, one of which showed an association with these carcinogens.

Interpretation Concerning Other Literature

According to previous studies, LC was the main cancer attributed to occupational exposure, followed by BC (9, 15). Among the studied exposures in this study, asbestos, silica, DME, benzene, formaldehyde, and PAH were ranked first to fifth, respectively. Previous studies have shown that crystalline silica, DME, wood dust, formaldehyde, benzene, solvents, and asbestos are the most common occupational exposures (3).

This review provides critical information for selecting carcinogenic occupational exposures and risk estimates; it is the first step in estimating the cancer burden associated with various exposures through nationwide studies, however, the methodologies, statistical approaches, and confounders used in the research evaluated were all highly diverse, which explains some of the differences in the results.

The present review study showed that developing countries have the highest exposure to occupational carcinogens but have the least published studies. Most studies were conducted in developed countries, especially in Western countries. Also, studies conducted in low- and middle-income countries had a poor methodology. Most of these studies were conducted by local authorities or by small industries. Their main goal was not to estimate the cancer burden resulting from these occupational exposures (66, 67). On the other hand, few studies conducted in developing countries have incomplete reports, and the force of association has not been well demonstrated. Even studies conducted in developed countries have high heterogeneity in controlling potential confounders and reporting other influencing factors. This heterogeneity has reduced the ability to pool the results of these studies.

Also, the present review found that a single occupational carcinogen may be linked to multiple cancer sites, and a single cancer site may be linked to multiple occupational carcinogens. According to this, in the future, the less developed countries are expected to focus more on designing studies with a stronger methodology, emphasizing common occupational carcinogens in the industries in these countries. It is also recommended that more emphasis be placed on occupational carcinogens approved by the IARC in these countries. Furthermore, policymakers should evaluate the possibility of occupational carcinogens being related to cancer sites, as even minimal exposure to some of these agents' increases cancer risk significantly (15).

Evidence Gaps and Implications for Future Surveys

Interviews and self-reporting of jobs and/or occupational exposures were used to acquire occupational information in case-control studies, and no effort was made to assign occupational exposures. Some of the case-control studies had problems in their design (eg, choice of controls, potential confounding, and power) that limited the interpretation of the results (14). According to this, it is recommended that in the future in developed and high-income countries, where the registration and quality of occupational carcinogens are higher than the registration and quality of information collected in developing countries, the emphasis be on conducting studies with stronger methodologies, including historical cohorts with higher sample sizes.

Strengths and Limitations

Overall, almost all of the studies included in this review were methodologically strong, and the few weaknesses of these studies did not affect the outcome evaluation of these studies. RRs, ORs, HRs, prevalence, and type of exposure are needed to estimate the burden attributed to cancers. The present study, which focused on 5 occupational malignancies and identified the key carcinogens linked to these cancers, appears to be a suitable reference for future studies estimating the burden of occupational cancers. The absence of carcinogenic exposures described in non-cancer research is this review's major limitation. Furthermore, researches that were not published in studies indexed by the searched databases may have been overlooked. Some investigations were not sufficiently comprehensive to obtain all essential data. "Questionnaires evaluated occupational exposures," for example, although the sort of exposure was not specified.

Conclusion

The findings of this study revealed that cancers caused by industrial chemical exposures place a significant financial burden on developed and developing countries alike.

[DOI: 10.47176/mjiri.36.84]

Furthermore, occupational carcinogens of asbestos, benzene, crystalline silica, PAH, and DME were among the most common exposures associated with the 5 known occupational cancers (LC, BC, LaC, LeC, and PLC).

The present review also found that although the number of published studies related to occupational carcinogens is high, the majority of these researches have been performed in both high-income and low-income nations. The number of research has been quite low in areas where these exposures are significantly more common. In the future, more high-quality research should be undertaken in developing countries, with a focus on approved occupational cancers. In developed countries, where occupational exposures and malignancies are well documented and collected, historical cohort studies should be conducted.

Ethics Approval

The ethics committee of Kerman University of Medical Sciences (KUMS) approved this study with ID number IR.KMU.REC.1399.407.

Acknowledgment

The authors would like to thank the Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran (KUMS) for financially supporting this research (grant number 98000771).

Conflict of Interests

The authors declare that they have no competing interests.

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[DOI: 10.47176/mjiri.36.84]

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[DOI: 10.47176/mjiri.36.84]