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The Effect of Air Pollution on Cancer in the Eastern Mediterranean Region: A Systematic Literature Review

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Abstract This study was conducted to assess the risk of cancer associated with air pollution in Eastern Mediterranean Region (EMR) by summarizing the existing knowledge from previous studies in the region and to identify knowledge and research gaps to support further research efforts. Combinations of search terms from three categories ("country" keywords AND 'air pollution" keywords AND "cancer" keywords) were used to search for the relevant literature published between January 2000 and June 2016 using MEDLINE and other databases. Six case-control studies and three studies of other designs had assessed the association between air pollution and cancer in the EMR and met the inclusion criteria. These studies have assessed the effect of various indoor and outdoor air pollutants on the risk of different types of cancer. In this review, cancers were classified into: lung cancer; nasopharyngeal cancer; urinary bladder cancer; overall incidence of cancer in adults; and childhood cancer incidence. Limited epidemiological studies were found in the literature that properly address cancer incidence and air pollution in the EMR countries. Outdoor air pollution was not properly addressed in the included studies. Studies showed that using fuel for heating and living near an electricity generator and diesel exhaust exposure were significant contributors to lung cancer. NO_2 has been shown to increase the risk of lung and breast cancer incidence. PAHs exposure did not increase the risk of cancer incidence. In conclusion, studies on the link between air pollution and cancer in EMR are limited to few studies in few countries. The reviewed studies have many limitations that make the evidence about the link between air pollution and cancer weak.

Keywords: *air pollution, cancer, eastern mediterranean region, systematic review, mortality*

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1. Introduction

Air pollution is defined as the contamination of either indoor or outdoor environments by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere. Industrialization, economic expansion, urbanization, climate change and increasing of population contribute to increasing levels of air pollution in developing areas [1]. Outdoor air pollution is a complex mixture containing a number of known carcinogens. The body of evidence regarding outdoor and household air pollution indicated that both are associated with lung cancer risk. However, the evidence was considered inconclusive regarding which specific components of the air pollution mixture are driving the increased risk [2,3]. The International Agency for Research on Cancer (IARC) recently concluded that exposure to outdoor air pollution and to particulate matter (PM) in outdoor air is carcinogenic to humans and causes lung cancer [4,5].

Previous studies and reports showed that different cancers are linked to air pollution including lung cancer, head and neck cancer, nasopharyngeal carcinoma, breast cancer and bladder cancer [6,7,8]. Recent meta-analysis studies and reviews showed that ambient exposure to nitrogen oxides, sulfur dioxide, and fine particulate matters significantly increase the risk of lung cancer [9] and childhood leukemia [10], and household air pollution is associated with increased risk for oral, nasopharyngeal, pharyngeal, and laryngeal cancers [11].

The major air pollutants that were investigated in most of worldwide epidemiologic studies and risk assessments of air pollution are particulate matter, sulfur dioxide (SO_2), nitrogen oxides (NOx = NO +NO2), carbon monoxide (CO), and ozone (O3). Of those, PM_{10} has been one of the most important air pollutants with respect to its health effects [12,13].

Major constituents of outdoor air pollutants are derived from common byproducts of traffic emissions, power plants, industrial processes, and black smoke. Solid fuels in cooking or heating, poor ventilation, tobacco products, and other processes that release gases or particles are primary contributors to indoor air pollution in developing countries. Second-hand smoking (SHS) has been seen to increase the risk of different types of cancers such as nasal sinus cavity cancer, nasopharyngeal cancer, lung cancer, and breast cancer in adults, as well as brain tumors, lymphoma, and leukemia in children [14,15]. The risk of developing lung cancer is 20 to 30% higher among SHS compared to none exposed [15]. This study was intended to provide a comprehensive assessment of the risk of cancer associated with air pollution in Eastern Mediterranean Region (EMR) by summarizing the existing knowledge from previous studies in the region and to identify knowledge and research gaps to support further research efforts.

2. Methods

2.1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, PsychINFO, Cochrane Collection, Google scholar, Pubmed, and ISI Web of Knowledge. Key references from extracted papers were also hand-searched. These searches focused upon papers published between January 2000 and June 2016.

2.2. Search Terms

Combinations of search terms from three categories ("country" keywords AND 'air pollution" keywords AND "cancer" keywords) were used to search for the relevant literature.

"Country" keywords

Jordan [Title/Abstract] OR Lebanon OR Libya OR Kuwait OR Bahrain OR Qatar OR Sudan OR Djibouti OR Iran OR Iraq OR Palestine OR Yemen OR Syria OR Emirates OR Somalia OR Tunisia OR Saudi Arabia OR Morocco OR Oman OR Pakistan OR Afghanistan OR Egypt OR Arabian Gulf OR Persian Gulf OR Eastern Mediterranean OR Middle East

"Air pollution" keywords

Nitrogen dioxide OR smoke OR sulphur dioxide OR ozone OR particles OR carbon monoxide OR particulate matter OR reactive nitrogen OR PM_{10} OR $PM_{2.5}$ OR SO_2 OR NO_2 OR gaseous pollutants OR volatile organic compounds OR persistent organic pollutants OR particulate matter OR respirable particles OR chemical emissions OR mold spores OR animal allergens OR combustion gases OR tobacco OR air quality OR aeroallergens OR dust OR air pollution OR outdoor air pollution OR indoor air pollution OR atmospheric pollution

"Health outcomes" keywords

Cancer OR childhood cancer OR lifetime cancer risk OR cancer incidence OR carcinogenic risk.

2.3. Filtering and Study Selection

Literature search using the combinations of keywords and hand search resulted in 634 articles (Figure 1). Two researchers assessed the eligibility of all citations by reviewing the abstract. Where citations could not be excluded based on title or abstract or when there were discrepancies, the full-text paper was retrieved and assessed. Full papers of potentially eligible citations were identified following screening of all titles and abstracts by two study authors. These were further reviewed for eligibility and inclusion in the review by a single author (YK).

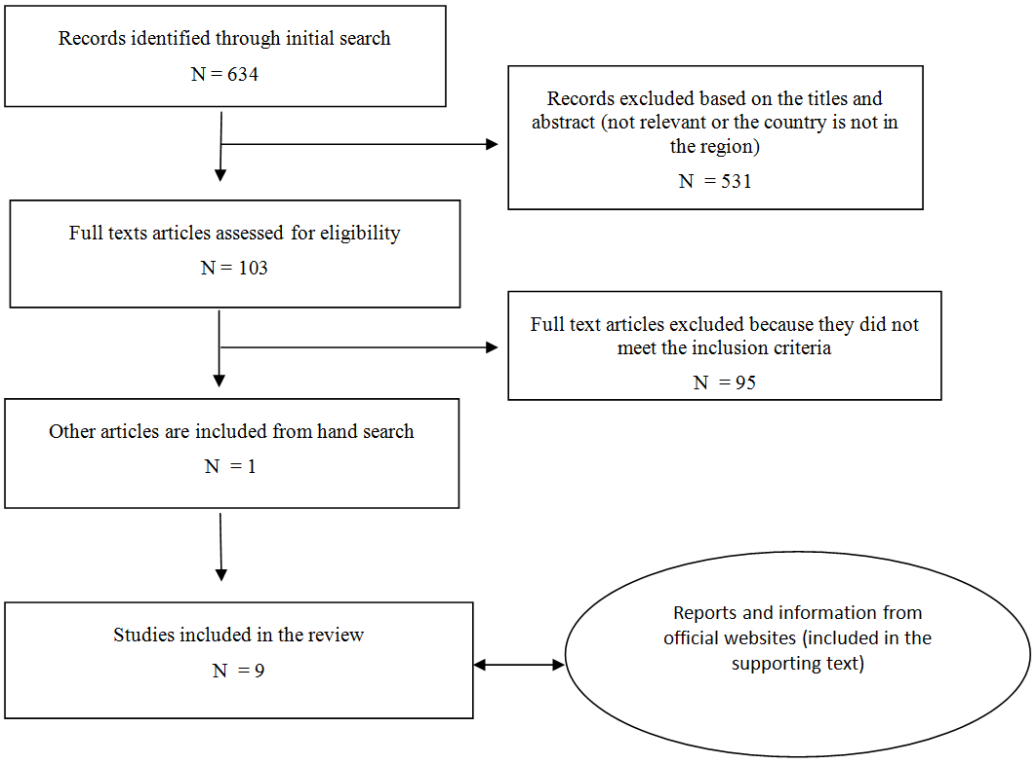

Figure 1. Flowchart of search strategy and selection of studies for inclusion in the systematic review

2.4. Inclusion Criteria and Exclusion Criteria

Literature search was limited to papers and reports published since 2000. Papers and reports that met inclusion criteria were included in this review and were summarized in review tables and discussed in the text. Papers which examined the link between air pollution and human health without explicitly quantifying or qualifying the impact or the link were included in supporting text but not in the tables. Data from unpublished reports and websites were not systematically extracted into review tables, but sources including WHO and CDC were discussed in the accompanying text. Similarly, papers not fulfilling inclusion criteria were sometimes used to give a better contextual outline and are discussed in the relevant sections.

2.4.1. Inclusion Criteria

- Papers presented original data from cohort, case-control, or cross-sectional studies, ecologic studies, case-crossover or time-series studies.
- Studies examining the relations between gaseous air pollutants (carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) or particulate ($PM_{2.5}$ or PM_{10}) or second-hand smoking and clearly defined human cancer
- Conducted in a human population
- Papers published in any country of the region between 1/ 1/ 2000 to 1/6/2016
- Papers published in English.

2.4.2. Exclusion Criteria

- Editorials and letters
- News articles
- Non English language papers
- Papers published before 2000.

2.5. Data Collection and Analysis

Data from scientific papers that met inclusion criteria were extracted systematically using a specially designed data extraction form. Column headings of summary tables included the followings: Study outcome, authors, year of publication, country, study design, population, exposure, study years, main results. Because of the heterogeneity in study designs, exposure, and outcomes, meaningful quantitative summary statistics were not possible. Moreover, quality assessment of the included papers was not undertaken.

3. Results

3.1. Descriptive Summary of Studies from the EMR

Six case-control studies and three studies of other designs [16-24] had assessed the association between air pollution and cancer in the EMR and met the inclusion criteria (Table 1). These studies have assessed the effect of various indoor and outdoor air pollutants on the risk of different types of cancer in Morocco [16], Lebanon [17], Pakistan [18,23], Algeria, Morocco and Tunisia [19], Egypt [20], Saudi Arabia [21], UAE [22], and Iran [24]. In this review, cancers were classified into the following categories: lung cancer; nasopharyngeal cancer; urinary bladder cancer; overall incidence of cancer in adults; childhood cancer incidence.

3.2. Lung Cancer

Three case-control studies in Morocco [16], Lebanon [17] and Pakistan [18] had evaluated different environmental risk factors for lung cancer. Thus, it is difficult to compare the study findings and to reach a meaningful summary conclusion on the effect of air pollution on cancer. The Moroccan study [16] evaluated several environmental risk factors for lung cancer including passive smoking, candle use, poor ventilation of the kitchen, and occupational exposures. Those factors showed a slight, but not significant, increase in the risk of lung cancer after adjusting for smoking status [16]. Although the Lebanese study was a pilot study, with small sample size, several environmental factors were significantly associated with lung cancer risk. Using fuel for heating (Adjusted OR = 9.12, 95% CI: 2.15-44.30, P = 0.003) in females, and living near an electricity generator (Adjusted OR = 13.26, 95% CI: 1.85-95.04, P= 0.010) in males were significant risk factors for lung cancer in the Lebanese study [17]. On the other hand, strong associations were found between lung cancer and diesel exhaust exposure (OR = 3.1, 95% CI: 2.1-4.5) in the Pakistani study [18].

3.3. Nasopharyngeal Cancer

A matched multi-center case-control study was conducted in Algeria, Morocco, and Tunisia to evaluate possible risk factors that are associated with nasopharyngeal cancer [19]. Environmental risk factors for nasopharyngeal cancer that were considered in this study were occupational and domestic fumes. Exposure to occupational fumes was not a significant factor for nasopharyngeal cancer (OR =1.5, 95% CI: 0.8–2.9). Conversely, exposure to domestic fumes during childhood, such as cooking in kanoun oven, was significantly associated with nasopharyngeal cancer risk (OR = 1.96, 95% CI: 1.28, 2.72) after adjustment of socioeconomic status and diet.

3.4. Urinary Bladder Cancer

A multi-center case-control study in Egypt evaluated the risk of urinary bladder cancer from ETS [20]. Interestingly, this study found a positive significant association between ETS and the risk urinary bladder cancer in males only (OR = 2.5, 95% CI: 1.2, 5.1), but not in females (OR = 1.8, 95% CI = 0.8, 3.8). On the other hand, ETS was not significantly associated with squamous cell carcinoma in males (OR =0.9, 95% CI = 0.3, 2.5) and females (OR = 2.1, 95% CI: 1.0, 4.4).

3.5. Overall Adult Cancer

Two ecological studies evaluated different outdoor exposures and the risk of all cancers in general [21,22]. One was carried out in the United Arab Emirates [22] and the other was carried out in Saudi Arabia [21]. The effect of NO_2 on the risk of cancer was assessed ecologically in Saudi Arabia [21]. Separate statistical analysis was done

on regional, governorate, and city levels. Higher coefficients were observed among increased spatial level (i.e. stronger goodness of fit and higher coefficients of variations were seen on regional level, followed by governorate level, and finally by city level). Ordinary least squares showed that lung (R^2 = 0.62), prostate (R^2 = 0.56), Hodgkin's disease (R^2 = 0.55), bladder (R^2 = 0.55) and breast cancers (R^2 = 0.55) were significantly and positively associated with NO_2.

Several outdoor pollutants from clinical waste incinerator and from vehicle emissions were evaluated as risk factors for cancer in the UAE [22]. While there was considerable differences of air pollutants from different sources, the overall cancer risk was extremely low from PAH and other carcinogens [13]. Another study in Pakistan [20] suggested a moderate to potential high cancer risk for adults and children exposed to dust-bound PAHs in both exposure sites, in particular via both dermal and ingestion contact pathways.

Table 1. The characteristics and main findings of the nine studies in the EMR that have examined the impact of air pollution on cancer

Study Outcome	Authors	Year	Country/ Region	Study Design	Population/sample	Study Year	Exposure
Lung cancer	Sasco AJ et al. (16)	2002	Morocco	Hospital-based case–control study	118 lung cancer cases and 235 controls	1996-1998	Second-hand smoking and domestic exposures (cooking practices, use of coal and candles, ventilation).
Exposure to passive smoking (OR =1.36; 95% CI: 0.71–2.62), cooking/heating with coal (OR =0.74; 95% CI: 0.17–3.14), lighting with candles (OR =1.44; 95% CI: 0.42–5.01), and poor ventilation of kitchen (OR =1.22; 95% CI: 0.57–2.58) were not significant contributors to lung cancer in the multivariate analysis.							
Lung Cancer	Aoun J, et al. (17)	2013	Lebanon	A pilot case-control study	Patients were recruited in a tertiary health care centre		Using fuel for heating and living near an electricity generator
Outdoor and indoor pollution factors were potential risk factors of lung cancer. Using fuel for heating (Adjusted OR=9.12) for females and living near an electricity generator (Adjusted OR=13.26) are the main risk factors for lung cancer.							
Lung cancer	Luqman M et al. (18)	2014	Pakistan	Case-control study	400 cases and 800 controls		Pesticide exposure and exposure to diesel exhaust
Strong associations were observed between lung cancer and pesticide exposure (OR=5.1; 95% CI: 3.1-8.3) and exposure to diesel exhaust (OR=3.1; 95% CI: 2.1-4.5). Other factors associated with lung cancer were welding fumes (OR=2.5, 95% CI: 1.0-6.5) and wood dust (OR=1.9; 95% CI: 1.2- 3.1). Strongest dose-response relationships were observed for pesticide exposure (R^2=50.9%) and exposure to diesel exhaust (R^2=51.8%).							
Nasopharyngeal carcinoma	Feng B, et al. (19)	2009	Algeria, Morocco and Tunisia	Multi-centre case–control		2009	Cannabis, tobacco and domestic fumes
Cigarette smoking and snuff (tobacco powder with additives) intake were significantly associated with differentiated nasopharyngeal carcinoma but not with undifferentiated carcinoma, which is the major histological type of nasopharyngeal carcinoma in these populations. Domestic cooking fumes intake by using kanoun (compact charcoal oven) during childhood increased nasopharyngeal carcinoma risk, whereas exposure during adulthood had less effect.							
Urothelial carcinoma (UC) and squamous cell carcinoma (SCC)	Zheng YL et al. (20)	2012	Egypt	A case-control study	Bladder cancer cases and non-cancer controls	2006-2010	Environmental tobacco smoke (ETS)
Exposure to ETS increases the risk of both SCC and UC. Among male, ETS exposure at home and outside the home, was significantly associated with UC (OR = 2.5; 95% CI: 1.2 - 5.1), but not with SCC (OR = 0.9; 95% CI: 0.3 - 2.5). Among women, ETS exposure was not significantly associated with UC (OR = 1.8; 95% CI: 0.8 - 3.8) and borderline significantly associated with SCC (OR = 2.1; 95% CI: 1.0 - 4.4).							
Cancer incidence	Al-Ahmadi K and Al-Zahrani A (21)	2013	Saudi Arabia	National cancer registry data were correlated NO2 atmospheric level	Cancer Registry; 45,532 cancer cases.	1998-2004	Atmospheric NO2
High coefficients of determination were observed between NO_2 concentration and lung and breast cancer incidences, followed by prostate, bladder, cervical and ovarian cancers							
Carcinogenic risk	Wheatley A and Sadhra S (22)	2010	UAE	Modelling risk assessment			Clinical waste incineration and road traffic emissions
Emissions associated with operation of the clinical waste incineration present a negligible contribution to overall cancer risk from polycyclic aromatic hydrocarbons and other carcinogens.							
Lifetime cancer risk	Atif Kamal, et al. (23)	2015	Pakistan	The incremental lifetime cancer risk (ILCR) modeling	Dust samples from residential household cooking areas and professional cooking workplaces		Polycyclic aromatic hydrocarbons (PAHs) in dust samples
The average incremental lifetime cancer risk (ILCR) suggested a moderate to potential high cancer risk for adults and children exposed to dust-bound PAHs in exposure sites, in particular via both dermal and ingestion contact pathways							
Childhood cancer	Edraki M and Rambod M (24)	2011	Iran	Case- control study	98 children newly diagnosed with cancer before the age of 14 years and 100 age- and sex-matched controls.	2007-2008	Parental smoking
Maternal smoking (prior to and during pregnancy and after the birth), and the numbers of maternal cigarettes smoked were not associated with an increased risk of childhood cancer. However, maternal exposure to passive smoke during pregnancy increased the risk of cancer childhood (OR = 3.6; 95% CI: 1.3-5.0). Father's smoking prior to (OR = 1.8; 95% CI: 1.4-6.0) and during pregnancy (OR = 3.0; 95% CI 1.4-5.0) was significantly associated with an increased risk of cancer and this increased with heavy smoking. There were no relationship between an enhanced risk of childhood cancer and father's smoking after the child's birth.							

3.6. Overall Childhood Cancers

One study in Pakistan [23] showed a moderate to potential high cancer risk for adults and children exposed to dust-bound PAHs in both exposure sites, in particular via both dermal and ingestion contact pathways. A case-control study in Iran showed that neither maternal active smoking nor the numbers of cigarettes smoked per day by the mother were significantly associated with increased risk of childhood cancer [24]. Nonetheless, maternal passive exposure prior (OR = 1.8, 95% CI: 1.4, 6.0) and during (OR = 3.0, 95% CI: 1.4–5.0) pregnancy was associated with increases risk of childhood cancer.

4. Discussion

Outdoor exposure to PM or living near air pollution sources such traffic emissions, urban dwelling, or factories can trigger the risk of lung cancer occurrence [25,26,27].

Several indoor pollutant sources have been linked with the increase of lung cancer incidence, those include environmental tobacco smoke [28] and the use of coal and fuel in cooking/heating [29,30].

Limited epidemiological studies were found in the literature that properly address cancer incidence and air pollution in the EMR countries. Outdoor air pollution was not properly addressed in the included studies. The reviewed studies have many limitations that make the evidence about the link between air pollution and cancer weak. The small number of cases with cancer in some of the presented studies can lead to high statistical uncertainty in the estimated associations between exposure and outcome. The inclusion criteria for cancer cases sometimes limit the generalization for the conclusion on the population cancer cases. Recall bias in long retrospective studies affects the accuracy of recalling exposures. Most studies relied on self-reported exposures rather than reliable biomarkers. Outcome misclassification is a concern for studies with self-reported outcome rather than doctor-diagnosed cancer. The exposure and outcome were measured at the same time in some of the presented studies ignoring the fact that cancer usually takes decades to develop, and patterns of air pollution change over time. Furthermore, not all sources of emissions were included in outdoor air pollution studies. Failure to account for important confounders and concurrent exposures in some included studies and the possible selection bias and admission bias in hospital-based case control might affect the association of some factors with the disease.

Information bias, recall bias, and interviewer bias are of concern for administered questionnaires. Some uncertainties in the methodology used to estimate the exposure and model the outcome risk from the exposure with inherit assumptions do exist and can affect the estimate findings of some of the studies.

Using fuel for heating and living near an electricity generator in Lebanon [17] and diesel exhaust exposure in Pakistan [18] were significant contributors to lung cancer. Overall, ETS increased the risk of Urothelial carcinoma, squamous cell carcinoma, Nasopharyngeal carcinoma, but not undifferentiated carcinoma, nor childhood cancer. NO2 has been shown to increase the risk of lung and breast cancer incidence. PAHs exposure did not increase the risk of cancer incidence. While it is considered a rare disease, nasopharyngeal cancer is prevalent in Western North Africa (Algeria, Morocco, and Tunisia) [19]. A matched multi-center case-control study was conducted in Algeria, Morocco, and Tunisia endeavored to overcome some of the limitations of previous studies by increasing the sample size and adjusting for major confounding factors. The study showed that exposure to domestic fumes during childhood, such as cooking in kanoun oven, was significantly associated with nasopharyngeal cancer risk. While IARC has recognized ETS as a possible carcinogen for lung cancer, ETS was not established thus far as a carcinogen for urinary bladder cancer [19]. A multi-center case-control study carried out in Egypt evaluated the risk urinary bladder cancer from ETS and was included in this review [20]. Interestingly, this study found a positive significant association between ETS and the risk urinary bladder cancer in males only.

In an ecological study in Saudi Arabia [21], lung, prostate, Hodgkin's disease, bladder and breast cancers were significantly and positively associated with NO2.

There is controversial evidence for the link of parental smoking with childhood cancer in most studies [31,32]. A case-control study conducted in Iran was included in this review that looked at the association between parental smoking and childhood cancer. Neither maternal active smoking nor the numbers of cigarettes smoked per day by the mother were significantly associated with increased risk of childhood cancer [24]. Nonetheless, maternal passive exposure prior (OR = 1.8, 95% CI: 1.4, 6.0) and during (OR = 3.0, 95% CI: 1.4–5.0) pregnancy was associated with increases risk of childhood cancer. SHS exposure of infants and children was not associated with childhood cancer risk. While it is surprising that SHS rather than active smoking is associated with childhood cancer, this might be due to the heavier style of smoking with fathers compared to mothers.

Many recommendations need to be considered for future research and for policy makers.

At present, epidemiological literature in EMR is limited to a few studies in few countries. Furthermore, ambient outdoor measures were rarely performed. Standardized reliable assessments on the national level for various air pollutants on different regions should be implemented, and publically available for researchers to utilize in research. Advancing and utilizing epidemiological designs is of key importance. Best epidemiological designs to yield strong and valuable information for chronic health outcomes that are rare like cancer are well-designed case-control studies to ascertain the relevance of air toxics and pollutants to health outcomes onset and chronicity. Of course, accurate exposure and outcome assessments, as well as incorporating the appropriate confounders are key factors in designing the study. It is advisable to consider exposures to mixtures especially ones that are emitted together, as well as individual pollutants to fully understand the mechanism of the health outcome.

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