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Outdoor Air Pollution and Cancer: An Overview of the Current Evidence and Public Health Recommendations

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Abstract

Outdoor air pollution is a major contributor to the burden of disease worldwide. Most of the global population resides in places where air pollution levels, due to emissions from industry, power generation, transportation and domestic burning, considerably exceed the World Health Organization's health-based air quality guidelines. Outdoor air pollution poses an urgent worldwide public health challenge because it is ubiquitous and has numerous serious adverse human health effects including cancer. Currently, there is substantial evidence from studies of humans and experimental animals, as well as mechanistic evidence to support a causal link between outdoor (ambient) air pollution, and especially particulate matter (PM) in outdoor air,

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with lung cancer incidence and mortality. It is estimated that hundreds of thousands of lung cancer deaths annually worldwide are attributable to PM air pollution. Epidemiological evidence on outdoor air pollution and risk of other types of cancer, such as bladder cancer or breast cancer is more limited. Outdoor air pollution may also be associated with poorer cancer survival though further research is needed. This report presents an overview of outdoor air pollutants, sources and global levels, as well as a description of epidemiological evidence linking outdoor air pollution with cancer incidence and mortality. Biological mechanisms of air pollution-derived carcinogenesis are also described. This report concludes by summarizing public health/policy recommendations, including multi-level interventions aimed at individual, community, and regional scales. Specific roles for medical and healthcare communities with regard to prevention and advocacy, and recommendations for further research are also described.

Keywords

particulate matter; lung cancer; cancer survival; bladder cancer; breast cancer

Introduction

Outdoor air pollution is a major contributor to the burden of disease worldwide.[1] Most of the global population currently resides in places where air pollution levels, due to emissions from major sources such as industry, power generation, transportation and domestic burning, considerably exceed the World Health Organization's (WHO) health-based air quality guidelines. This report presents an overview of outdoor air pollutants, sources and global levels, as well as a description of epidemiological evidence linking outdoor ambient air pollution with lung cancer incidence and mortality, followed by studies of other types of cancers in adults as well as childhood cancers, and biological mechanisms of air pollution-derived carcinogenesis. This report concludes by summarizing public health/policy recommendations, including multi-level interventions aimed at the individual, community, and regional scales. The specific role for the medical and healthcare community regarding prevention and advocacy, and recommendations for further research are also described.

Sources and Levels of Outdoor Air Pollution

Exposure to outdoor air pollution poses an urgent public health challenge worldwide because it is ubiquitous, affecting everyone, and has numerous serious adverse human health effects including cancer.[2] Major primary air pollutants, those emitted directly into the environment largely as a result of combustion of fossil and biomass fuels, include gaseous pollutants (such as sulfur dioxide: SO_2, nitrogen dioxide: NO_2, carbon monoxide: CO, and volatile organic compounds: VOCs) and particulate matter (PM) (including carbonaceous aerosol particles, such as black soot). While CO is often low outdoors in the developed world today (due to the use of emissions controls such as catalytic converters on automobiles), high levels can be experienced near biomass burning sources, including wildfires.[3] In addition, secondary air pollutants are formed in the atmosphere from primary pollutants, and include gaseous ozone (O_3), a major component of photochemical smog, formed in the atmosphere when nitrogen oxides (NO_x) and hydrocarbons such as VOCs

react in the presence of sunlight. Similarly, particulate sulfate (e.g., sulfuric acid (H_2SO_4)) and nitrate (e.g., ammonium nitrate (NH_4NO_3)) aerosols are commonly created in the atmosphere from SO_2 and NO_x, respectively. Primary combustion particles and secondary particles are small in diameter, and are often referred to as fine particulate matter, or $PM_{2.5}$ (particles ≤ 2.5 μm in aerodynamic diameter). Submicron combustion-related $PM_{2.5}$ are of particular health concern because they contain numerous toxic compounds (e.g., acids and heavy metals) and can penetrate deeper into the lung than the larger PM generated by natural processes, such as most windblown soil particle mass.[4]

Air pollutants are emitted and/or formed both outdoors and indoors, resulting in personal pollutant exposure levels that can differ from levels measured by routine ambient air pollution measurements at centrally located air monitoring stations. The most common health-related air pollutants of greatest concern are summarized in Table 1 and are categorized into three classes: 1) pollutants primarily emitted into the outdoor environment; 2) pollutants primarily emitted into the indoor environment; and, 3) pollutants emitted into both outdoor and indoor environments. These pollutants and their typical sources are noted, including: $PM_{2.5}$, SO_2, NO_2, O_3, and CO. Subsequent discussions herein will focus on outdoor air pollutants that are associated with cancer, especially PM and its constituents.

PM represents a broad class of chemically and physically diverse aerosols comprised of solid particles or liquid droplets suspended in the air. Such aerosols can be characterized by their size (discussed below), formation mechanism, origin, chemical composition, atmospheric behavior and method of measurement. The concentration of particles in the air varies across space and time and reflects the source of the particles and the pollutant transformations that occur in the atmosphere. PM air pollution can also be viewed in two major components: “primary” PM, including “soot” emitted directly into the atmosphere by combustion pollution sources such as industry, electric power plants, diesel buses, and automobiles, and; “secondary” PM, formed in the atmosphere from primary gaseous pollutants, such as SO_2 and NO_x gases (discussed above). Other primary sources include non-exhaust traffic emissions and windblown dusts from roadways, construction sites, agriculture, and deserts. Desert dust clouds have been documented to be capable of impacting population centers by being transported long distances.[5]

PM is commonly characterized according to the following size fractions:

- PM_{10} (PM ≤ 10 μm in aerodynamic diameter) are the largest inhalable particles. Particles larger than 10 μm are generally not inhaled past the trachea, and are caught in the nose and throat, and not deposited in the lung. PM_{10} also includes all the fractions described below;
- $PM_{2.5–10}$, also known as coarse fraction particles (PM with an aerodynamic diameter > 2.5 μm, but ≤ 10 μm); and
- $PM_{2.5}$, also known as fine particles (PM with an aerodynamic diameter ≤ 2.5 μm), can be inhaled into the deepest recesses of the lung, including to the alveoli sacs, where oxygen exchange to the bloodstream occurs. As such, $PM_{2.5}$ has increasingly become a major research focus of adverse human health impacts of outdoor air pollution exposure over recent decades.

- The smallest fraction of $PM_{2.5}$ are nanoparticles, also known as ultrafine particles (UFPs), generally defined as particles ≤ 0.1 μm in aerodynamic diameter.

The mass concentration (as $\mu g/m^3$) is the common metric used to evaluate and regulate PM pollution, though some constituents, such as lead (Pb) concentration, have been separately regulated. While UFPs usually make up only a small fraction of $PM_{2.5}$ mass, UFPs commonly account for a majority of the number concentration of particles in $PM_{2.5}$. It has been hypothesized based on toxicological studies that UFPs may be an especially toxic component of $PM_{2.5}$ because of their small size, large numbers, and large surface area to mass ratio, but epidemiological evidence is currently sparse.[6]

$PM_{2.5}$ is directly emitted from combustion sources, and is also formed from gaseous precursors, such as SO_2 and NO_x, or organic compounds (discussed above). In some areas and under some conditions, these secondary particles make up a substantial proportion of the $PM_{2.5}$ mass. Secondary fine particles are commonly composed of sulfate, nitrate, chloride and ammonium compounds, organic carbon, and condensed metals. Combustion of fossil fuels, and especially coal, further results in $PM_{2.5}$ that is highly enriched in multiple moderately volatile, and potentially toxic elements. These include the chalcophile elements such as zinc (Zn), arsenic (As), selenium (Se), molybdenum (Mo), and cadmium (Cd).[7] Indeed, coal combustion has been found to account for approximately one-quarter of the world's emissions of both As and mercury (Hg).[8,9] $PM_{2.5}$ can remain in the atmosphere for days to weeks, and travel through the atmosphere hundreds to thousands of kilometers;[5] conversely most coarse particles typically deposit to the earth within minutes to hours and travel within only tens of kilometers from the emission source.

The global population-weighted mean annual average $PM_{2.5}$ concentration was 46 $\mu g/m^3$ in 2017, four-fold greater than the WHO's health-based world air quality guideline of 10 $\mu g/m^3$ (Figure 1).[10] Ninety-two percent of the global population worldwide lives in areas where ambient $PM_{2.5}$ concentrations exceed the WHO guideline and large percentages of the populations of China, Bangladesh, India, Pakistan and Nigeria have exposures above the WHO's highest interim target guideline of 35 $\mu g/m^3$. Among the ten largest countries by population, population-weighted ambient $PM_{2.5}$ in 2017 varied by more than 12-fold; from 7 $\mu g/m^3$ in the United States to 91 $\mu g/m^3$ in India. For NO_2, global population-weighted mean concentrations were estimated to be 1.6 ppb during 1996–2012, and were observed to have increased by 0.9% (95% confidence interval (CI) 0.6–1.1) per year during that time.[11] Areas with the highest population-weighted mean concentrations were high-income Asia Pacific (4.9 ppb), Western Europe (4.1 ppb), and high income North America (3.7 ppb), though there was a decreasing trend ranging from 2.1 to 4.7% per year. Population-weighted mean concentrations in East Asia were 2.9 ppm and increasing at the highest rate of 6.7% per year. In contrast, population-weighted mean concentrations in areas of South and Southeast Asia, Africa, and the Caribbean were ≤ 0.5 ppb. The global population-weighted mean O_3 concentration worldwide was 57 ppb in 2017, unchanged from 1990.[10]

An overview of the epidemiological evidence linking outdoor ambient air pollution with lung cancer incidence and mortality is provided below, followed by studies of other types of

cancers in adults and children. Studies were identified through literature searches of Medline through June 2020, reference lists of identified studies and authoritative reports, as well as via personal correspondence. Although numerous epidemiological studies have evaluated some aspect of the association of outdoor air pollution and cancer, here we sought to highlight key contributions including meta-analyses and large-scale original studies, with a focus on the most recent and informative published literature. Methodological considerations and research needs are also discussed.

Epidemiological Studies of Outdoor Air Pollution and Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide and is the leading cause of cancer death, with an estimated 2.1 million new cases and 1.8 million deaths occurring in 2018, representing 11.6% of all new cancer diagnoses and 18.4% of all cancer deaths.[12] In the United States, approximately 234,030 new lung cancer cases occurred and 154,050 deaths were estimated in the same year.[13] Lung cancer is highly fatal, with an overall 5-year survival rate of only 18%.[13] Rates of lung cancer incidence and mortality vary substantially within and between countries, depending largely on historical patterns of cigarette smoking, [12] with long latency periods of up to approximately 30 years between the start of the smoking epidemic and the rise of lung cancer incidence. The highest incidence rates for lung cancer among men are currently observed in Micronesia/Polynesia, Eastern Asia, and Eastern Europe, and for women in North America, Northern and Western Europe, and Australia/New Zealand.[12] In several European countries, lung cancer incidence rates are beginning to converge in men and women as increasing rates in women are approaching declining rates in men.[12]

Although cigarette smoking accounts for more than 80% of lung cancers, substantial numbers of lung cancer cases are observed among never smokers. Outdoor ambient air pollution and exposure to other inhalable agents, such as household burning of solid fuels, residential radon, second hand tobacco smoke, asbestos, certain metals and organic chemicals, and work in rubber manufacturing, paving, roofing, painting, or chimney sweeping, and other occupational exposures have also been associated with lung cancer risk.[12–14]

Based on sufficient evidence in studies of humans and experimental animals, as well as strong mechanistic evidence, the International Agency for Research on Cancer (IARC) in 2013 classified both outdoor air pollution and PM in outdoor air pollution as Group 1 human carcinogens for lung cancer.[15] The IARC evaluation noted that general population cohort studies with quantitative data on long-term estimates of outdoor air pollution exposure, including the large-scale American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II) and the European Study of Cohorts for Air Pollution Effects (ESCAPE), were particularly informative in their evaluation with a broad range of exposures considered and detailed information on potential confounders, notably cigarette smoking.[16–18] Because the possibility of residual confounding by cigarette smoking of reported air pollution effects had remained a concern, the analysis of thousands of never-smokers in the ACS CPS-II study, which observed increased lung cancer mortality associated with long-term $PM_{2.5}$ exposure, was particularly influential.[17] Interestingly, the IARC conclusion of a causal link between

outdoor air pollution and PM in outdoor air with increased lung cancer risk was long ago foreshadowed, given the presence of carcinogens in ambient air. Indeed, in the introduction to their landmark report on the preliminary findings of their case-control study of lung cancer in London, Doll and Hill[19] commented: "Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco." In the ensuing 70 years, the dominance of tobacco smoking as a cause of lung cancer perhaps distracted attention away from the role of outdoor air pollution as another avoidable cause.

IARC has also classified household burning of coal as a Group 1 human carcinogen and household burning of biomass fuel as a Group 2A (probably carcinogenic) for lung cancer.[20,21] Household burning of solid fuels, both coal and biomass, contribute significantly to high levels of outdoor air pollution and hence burden of disease in low- and middle-income countries.[22–25]

Meta-analysis of findings from 14 studies of outdoor air pollution conducted largely in North America and Europe reported a statistically significant 9% (95% CI 4–14%) increase in risk for lung cancer incidence or mortality per each 10 μg/m^3 increase in $PM_{2.5}$ concentrations and in 9 studies of PM_{10}, an 8% (95% CI 0–17%) increase in risk per 10 μg/m^3.[26] Lung cancer incidence and mortality were considered together here, since due to the highly fatal nature of the disease, mortality is considered a valid indicator of incidence. Although significant heterogeneity in findings by continent was not observed, there were few studies conducted in Asia or other regions of the world. Findings were also generally similar by exposure assessment method, among studies using either fixed site monitoring or model-based indicators of outdoor air pollution exposure, as well as by covariate adjustment for cigarette smoking or other sociodemographic variables. In an even more recent updated meta-analysis of findings from 20 cohort studies, a somewhat larger increase in lung cancer incidence or mortality (i.e., 14%, 95% CI 8–21% per 10 μg/m^3 $PM_{2.5}$) was observed with similar findings again in studies from different regions (Figure 2).[27] When extrapolated to the global population-weighted mean annual average $PM_{2.5}$ concentration (46 μg/m^3) relative to the WHO's health-based world air quality guideline (10 μg/m^3), this represents an approximately 60% excess risk of lung cancer mortality.

There were also significant adverse associations in meta-analyses of studies of NO_2 exposure, a marker of traffic-related air pollution, for lung cancer mortality (relative risks (RRs) of 1.04 to 1.05 per 10 μg/m^3), although results were attenuated somewhat in studies that adjusted for individual-level cigarette smoking status and were no longer significant.[28,29] Additional research in Asia and in other understudied and more highly polluted regions is needed,[27] as well as with improved data on individual and lifetime outdoor air pollution exposures, including time-varying estimates of outdoor air pollution exposures over long time periods and consideration of individual and residential mobility over time.

Results from several recent large-scale epidemiological studies also showed adverse findings. There was a significant adverse association of ambient $PM_{2.5}$ and lung cancer mortality among 635,539 United States National Health Interview Survey (NHIS)

participants (hazard ratio (HR) per 10 μg/m^3 = 1.13, 95% CI 1.00–1.26, n = 7,420 lung cancer deaths).[30] There were suggestive adverse associations of both $PM_{2.5}$ and PM_{10} with lung cancer mortality in analysis of 49,564 participants in the Danish Diet, Cancer and Health Cohort but no associations with black carbon, NO_2, or O_3.[31] However, there was no clear association of $PM_{2.5}$, PM_{10}, or NO_2 and lung cancer mortality among Dutch national health survey participants (n = 339,633), possibly due to the short follow-up or other methodological characteristics of this study.[32] Among studies without individual-level information on cigarette smoking history, in analysis of ~4.9 million individuals in the Ontario Population Health and Environment Cohort (ONPHEC), there were significant adverse associations of both ambient $PM_{2.5}$ (HR per 5.3 μg/m^3 = 1.02, 95% CI 1.01–1.05) and NO_2 (HR per 14 ppb = 1.05, 95% CI 1.03–1.07) but not O_3 or O_x (combined oxidant capacity of NO_2 and O_3) and incident lung cancer.[33] In analysis of 18.9 million United States Medicare beneficiaries, there were significant adverse associations particularly with longer-term moving average $PM_{2.5}$ exposure and lung cancer mortality (HR per 10 μg/m^3 60 month moving average = 1.33, 95% CI 1.24–1.40).[34] There were also some significant adverse associations with O_3 and NO_2.[35,36] Although analysis extended to 53 million Medicare beneficiaries reported no association of $PM_{2.5}$ and lung cancer mortality, there may be confounding by cigarette smoking status in rural populations included here.[37]

Worldwide, ambient $PM_{2.5}$ air pollution was estimated to have contributed to 265,267 lung cancer deaths (95% uncertainty interval (UI) 182,903–350,835) in 2017, or 14.1% (UI 9.8–18.7) of all lung cancer deaths.[1] The global proportion of lung cancer deaths attributable to ambient $PM_{2.5}$ was second only to tobacco smoking (14.1% vs. 63.2%)[1].

Mortality attributable to $PM_{2.5}$ depends not only on patterns in ambient pollutant levels, but also on other factors including underlying population dynamics, ageing, mortality rates, access to health care and other racial and socioeconomic disparities[38] and as such, the number of estimated attributable lung cancer deaths has increased by nearly 30% since 2007. These factors may also explain, at least in part, the wide variation in country-specific estimates. Age-standardized $PM_{2.5}$-attributable lung cancer mortality rates and population-attributable fractions in the United States for example were 1.6/100,000 (UI 0.65–2.91) and 4.7% (UI 1.9–8.5) compared to 7.4/100,000 (UI 5.4–9.5) and 20.5% (UI 14.8–25.9) in China (Figure 3).

Despite such major advances in knowledge surrounding associations of outdoor air pollution and lung cancer, additional questions remain. For example, less is known regarding associations for specific histologic types of lung cancer, of relevance to treatment and prognosis, an area of active investigation with regard to tobacco smoking. The increasing risk of adenocarcinoma over the last four decades is considered as reflecting changes in cigarettes and the delivery of carcinogens.[39] A mechanistic basis for a link of air pollution to particular histological types is uncertain though some studies have suggested stronger findings with adenocarcinoma. In the meta-analysis of Hamra et al.[26] results for both $PM_{2.5}$ and PM_{10} were somewhat stronger for adenocarcinoma (RRs per 10 μg/m^3 = 1.40, 95% CI 1.07–1.83 and 1.29, 95% CI 1.02–1.63 respectively), though there were few studies. Among more recent work, in an analysis of 89,234 women in the Canadian National Breast Screening Study, there was a significant adverse association of $PM_{2.5}$ and incident lung

cancer overall (HR per 10 μg/m^3 = 1.34, 95% CI 1.10–1.65), which strengthened somewhat for both small cell carcinoma (HR = 1.53, 95% CI 0.93–2.53) and adenocarcinoma (HR = 1.44, 95% CI 1.06–1.97).[40] In analysis of 80,285 participants in the Adventist Health and Smog Study-2, there was a significant adverse association of $PM_{2.5}$ and total lung cancer incidence (HR per 10 ug/m^3 = 1.43, 95% CI 1.11–1.84).[41] There was also an adverse association with adenocarcinoma (HR = 1.31, 95% CI 0.87–1.97) which strengthened in participants reporting spending >1h/day outdoors.[42] There was also an adverse association of ambient PM_{10} concentrations and total lung cancer incidence in the EAGLE study, consisting of 2,099 cases and 2,120 controls in the Lombardy Region of Italy (odds ratio (OR) per 10 μg/m^3 = 1.28, 95% CI 0.95–1.72) with somewhat stronger findings for squamous cell carcinoma (OR = 1.44, 95% CI 0.90–2.29).[43] In a large-scale South Korean study, including 6,567,909 participants from a National Health Insurance database, there was no overall association of either PM_{10} or NO_2 concentrations and incident lung cancer but an adverse association of PM_{10} and adenocarcinoma in male smokers (HR > 60.9 vs < 50.40 μg/m^3 = 1.14; 95% CI 1.03–1.25).[44] Further research on air pollution and lung cancer by histological type is needed.

Knowledge regarding effects of differing PM components for lung cancer is also limited.[26,45] In analysis of 669,046 ACS CPS-II participants, there was a significant adverse association of total $PM_{2.5}$ and lung cancer mortality (HR per 10 ug/m^3 = 1.09, 95% CI 1.03–1.16), as well as with both near source (largely traffic-related) and regional $PM_{2.5}$ components.[46] There were also stronger lung cancer mortality associations in the ACS CPS-II with coal combustion-related $PM_{2.5}$ as well as with Se, a coal combustion tracer, and S elemental components specifically.[47] In an analysis of 193,300 participants in the Canadian Census Health and Environment Cohort (CanCHEC) there were significant adverse associations of glutathione- but not ascorbate-related $PM_{2.5}$ oxidative burden (the product of $PM_{2.5}$ mass and oxidative potential (the ability of regional filter extracts to deplete antioxidants glutathione or ascorbate in a synthetic respiratory tract lining fluid)) and lung cancer mortality.[48] In an analysis of 2.6 million CanCHEC participants, associations of total $PM_{2.5}$ and lung cancer mortality were similar by spatial climatic zone.[49] The ESCAPE study of 245,782 participants from 14 cohorts reported elevated RRs for incident lung cancer risk associated with various $PM_{2.5}$ or PM_{10} components, particularly for S (long-range transport, secondary combustion-related components) and nickel (Ni) (oil-burning, industry).[50] IARC also concluded that there is sufficient evidence in humans for the carcinogenicity of diesel engine exhaust, as well as some PM constituents (e.g., Ni, chromium (Cr), Cd, silica dust) for lung cancer.[51,52] There was also sufficient evidence in experimental animals for the carcinogenicity of condensates of gasoline engine exhaust.[51] Therefore while limited, the strongest evidence to date implicates fine PM of fossil fuel combustion origins.

There is also limited information regarding modification of outdoor air pollution associations by other individual or lifestyle factors. Hamra et al.[26] reported that associations with $PM_{2.5}$ were somewhat stronger among former smokers (RR = 1.44, 95% CI 1.04–2.01) and never smokers (RR = 1.18, 95% CI 1.00–1.39) than in current smokers (RR = 1.06, 95% CI 0.97–1.15). However, few studies have examined possible joint effects of air pollution and cigarette smoking on an additive scale, which may be most relevant for public health. In analysis in the ACS CPS-II, there was some evidence for an interaction between ambient

$PM_{2.5}$ and cigarette smoking for lung cancer mortality, with risk among those with both exposures greater than what was expected from the sum of the effects of both exposures alone.[53] It was estimated that 14% (95% CI 0–25%) of lung cancer deaths in that study were attributable to the interaction between these two factors. The ESCAPE lung cancer study reported no interaction between ambient $PM_{2.5}$ or PM_{10} concentrations and fruit consumption.[18] Future studies with individual-level information on potential confounding and modifying factors, including cigarette smoking and diet, captured over time are needed.

Finally, ambient $PM_{2.5}$, PM_{10} and NO_2 were associated with poorer lung cancer survival, particularly early-stage non-small cell cancers, among 352,053 California lung cancer patients.[54] There was also an adverse association of long-term exposure to $PM_{2.5}$ and first hospital admission for lung cancer in a cohort of 11 million Medicare beneficiaries in the South-Eastern United States, indicating a potential association with exacerbation of disease.[55] Further research is needed to better understand the impact of outdoor air pollution on patterns of morbidity and mortality following lung cancer diagnosis.

Epidemiological Studies of Outdoor Air Pollution and Other Types of Cancer

Epidemiological evidence for associations of outdoor air pollution with other types of cancer than lung is more limited, although adverse associations have been reported in an increasing number of studies. Previous studies are typically limited by small numbers of cancer cases, the use of fatal rather than incident disease endpoints (particularly relevant for cancers with more favorable prognoses), the use of recent as opposed to historical estimates of long-term outdoor air pollution concentrations, as well as some conflicting findings. Outdoor air pollution might cause cancer at sites other than the lung through absorption, metabolism, and distribution of inhaled carcinogens.

Following lung cancer, the subsequent leading causes of cancer diagnoses worldwide include female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%).[12] For mortality, cancer of the colorectum (9.2%), stomach (8.2%), and liver (8.2%) account for the next greatest numbers of cancer deaths.[12] In addition to lung cancer, cigarette smoking is also considered an IARC Group 1 carcinogen for cancers of the oral cavity, nasal cavity, pharynx, nasopharynx, larynx, esophagus, stomach, colorectum, pancreas, liver/bile duct, kidney, renal pelvis/ureter, bladder, ovary, cervix, and myeloid leukemia with limited evidence for other types of cancer, such as breast cancer.[21] Second hand tobacco smoke has also been suggestively associated with many of these types of cancer.[39]

Other inhalable pollutants have also been associated with multiple types of cancer. A meta-analysis of household air pollution from burning of solid fuels also noted adverse associations with oral, cervical, and esophageal cancer.[56] Occupational exposure to various agents have also been associated with cancer at different sites, including for example diesel and gasoline exhaust, polyaromatic hydrocarbons (PAHs), inhalable dusts (metals, silica), or work in trucking, mining, foundries, carbon black production, or work with asphalt.[14,51,57–60]

The IARC evaluation noted that beyond lung cancer, some adverse associations with outdoor air pollution were observed for bladder cancer in studies using different metrics of exposure to outdoor air pollution, traffic, or occupation as a surrogate indicator of exposure.[15] Bladder cancer shares several risk factors with lung cancer. However, results from more recent studies are mixed. In analysis of 623,048 ACS CPS-II participants, there was a significant adverse association of $PM_{2.5}$ and bladder cancer mortality (HR per 4.4 μg/m^3 = 1.13, 95% CI 1.03–1.23, n = 1,324) but no association with NO_2 or O_3.[61] There was also a significant adverse association of $PM_{2.5}$ and bladder cancer mortality in the NHIS (HR per 10 μg/m^3 = 1.48, 95% CI 1.00–2.20, n = 589).[30] Although an early hospital-based study of 1,219 incident bladder cancer cases and 1,271 controls in Spain reported an adverse association of living more than 40 years in a city of > 100,000 inhabitants and bladder cancer risk (OR = 1.30, 95% CI 1.04–1.63),[62] an updated analysis including estimates of ambient $PM_{2.5}$ and NO_2 at the participant residence based on European land-use regression models, showed no clear association.[63] There was also no association of ambient PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2, NO_x, other elemental PM components, organic carbon, or traffic density with bladder cancer incidence in the ESCAPE study.[64]

Previous studies have suggested some adverse associations of both NO_2 and NO_x and breast cancer, with fewer clear associations with PM.[65] Among most recent studies, in analysis of 47,433 women in the United States Sister Study there were adverse associations of both NO2 (HR per 5.8 ppb = 1.06, 95% CI 1.02–1.11) and $PM_{2.5}$ (HR per 3.6 μg/m^3 = 1.05, 95% CI 0.99–1.11) and breast cancer incidence overall (n = 2,848).[66] There were also adverse associations of $PM_{2.5}$ concentrations characterized by low S and high sodium (Na) and NO_3-fractions and invasive breast cancer incidence in California participants, and of $PM_{2.5}$ characterized by high fractions of silicon (Si), calcium (Ca), potassium (K), and aluminium (Al) among participants in the Western United States. There were also adverse associations of several non-metallic air toxics, including methylene chloride and breast cancer incidence observed.[67] In analysis of 57,589 women in the Multiethnic Cohort, significant adverse associations of NO_x, NO_2, $PM_{2.5}$, and PM_{10} with breast cancer incidence were observed among those living within 500 m of major roads, with stronger associations for NO_x and NO_2 among African American and Japanese American women overall.[68] In the Canadian National Breast Screening Study (n=89,247) there were adverse associations of both $PM_{2.5}$ (HR per 10 μg/m^3 = 1.26, 95% CI 0.99–1.61) and NO_2 (HRs per 9.7 ppb ranging from 1.13–1.17) and risk of incident premenopausal but not postmenopausal disease.[69,70] However, results from other recent studies have reported no clear associations with incident breast cancer risk.[33,71,72] Further, in one case-control study of 4,059 breast cancer cases and 4,059 matched controls nested in the French E3N cohort, there were significant inverse associations of ambient Cd and risk of both incident estrogen receptor (ER) - and ER-/progesterone receptor (PR)- disease.[73] In the Nurses Health studies, there was an adverse association of PM and all-cause mortality among women diagnosed with breast cancer, as well as greater breast cancer specific mortality among women with stage 1 disease.[74] Results of studies of mammographic density, a breast cancer risk factor, are also mixed.[75–77]

For other types of cancer, there are fewer studies and results are also inconsistent. Although there was an adverse association of NO_x and brain tumour incidence in analysis of 54,304 participants in the Danish Diet Cancer and Health cohort (incidence rate ratio (IRR) per 100

μg/m^3 = 2.28, 95% CI 1.25–4.19, n = 95),[78] findings were not replicated in subsequent studies.[79,80] There was an adverse, but non-significant association of $PM_{2.5}$ absorbance and malignant (HR per $10^{-5}/m^3$ = 1.67, 95% CI 0.89–3.14; n=466) but not non-malignant (n=366) brain tumour incidence in ESCAPE, though there were no data on brain tumour histology or morphology.[81] Analysis of 103,308 Multiethnic Cohort participants reported significant adverse associations of both outdoor benzene and PM_{10} exposure and malignant brain tumor risk in men (n = 94), particularly among Latino men, but not in women.[82] There was also a significant adverse association of O_3 and meningioma risk among men (n = 130). There was a significant adverse association of within-city ambient UFP concentration and malignant brain tumour incidence in analysis of 1.9 million CanCHEC participants in Montreal and Toronto (HR per 10,000/cm^3 = 1.11, 95% CI 1.04–1.19, n = 1,400).[83]

Among other cancers of the digestive organs and urinary tract, in the ACS CPS-II cohort, there were significant adverse associations of $PM_{2.5}$ with kidney cancer mortality (HR per 4.4 μg/m^3 = 1.14, 95% CI 1.03–1.27, n = 927) and of NO_2 with colorectal cancer mortality (HR per 6.5 ppb = 1.06, 95% CI 1.02–1.10, n = 6,475).[61] The NHIS study reported significant adverse associations of $PM_{2.5}$ and stomach (HR per 10 μg/m^3 = 1.87, 95% CI 1.20–2.92, n = 525) and colorectal (HR per 10 μg/m^3 = 1.29, 95% CI 1.05–1.59, n = 2,572) cancer mortality.[30] There were also some suggestive adverse associations in analysis of both kidney (n=697) and liver (n= 279) cancer incidence in ESCAPE, though there were small numbers of cancer cases.[84,85] Total $PM_{2.5}$ and $PM_{2.5}$ S were also associated with incident gastric cancer risk.[86,87] A Hong Kong cohort of 66,820 participants reported significant adverse associations of $PM_{2.5}$ with both upper digestive tract (HR per 10 μg/m^3 = 1.42, 95% CI 1.06–1.89, n = 323) and accessory organ (HR = 1.35, 95% CI 1.06–1.71, n = 676) cancer mortality.[88] A Taiwan cohort including 23,820 participants and 464 incident hepatocellular carcinoma (HCC) cases, accounting for 85–90% of primary liver cancer cases, reported adverse associations with $PM_{2.5}$ mediated by alanine transaminase levels, an indicator of chronic liver inflammation.[89] In a study including 56,245 HCC cases in the United States Surveillance, Epidemiology, and End Results (SEER) database, there was a significant adverse association with $PM_{2.5}$ (IRR per 10 μg/m^3 = 1.26, 95% CI 1.08–1.47).[90] $PM_{2.5}$ was also related with reduced HCC survival.[91]

Results of studies of hematopoietic cancers, leukemias and lymphomas, are also limited and mixed, with few studies having power to consider specific hematopoietic cancer subtypes. In the ACS CPS-II, there were no clear associations of ambient air pollutant exposure and non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), multiple myeloma, or leukemia mortality.[61] However, in a more recent analysis among 115,996 ACS CPS-II Nutrition cohort participants including 2,595 incident hematologic cancer cases, there were significant adverse associations of outdoor benzene exposure and incident myelodysplastic syndromes and T-cell lymphoma overall, and follicular lymphoma among men.[92] The NHIS study reported significant adverse $PM_{2.5}$ associations with HL (HR per 10 μg/m^3 = 4.18, 95% CI 1.02–14.60, n = 59), NHL (HR = 1.48, 95% CI 1.10–1.98, n = 1,016), and leukemia (HR = 1.43, 95% CI 1.05–1.97, n = 970) mortality.[30] A case-control study including 1,064 total incident leukemia cases and 5,039 controls across Canada observed no clear association with $PM_{2.5}$ overall or when examining chronic lymphocytic leukemia specifically.[93] Studies in Denmark have reported no clear associations of ambient air pollutant exposure and incident

NHL,[78,94] though in one study significant adverse associations of primary carbonaceous and secondary organic aerosols were observed.[95] A Danish case-control study of 1,967 incident leukemia cases and 3,381 controls reported significant adverse associations of ambient NO_2 (OR per 10 μg/m^3 = 1.31, 95% CI 1.02–1.68) and NO_x (OR per 20 μg/m^3 = 1.20, 95% CI 1.04–1.38) and incident acute myeloid leukemia (AML).[96]

Epidemiological Studies of Outdoor Air Pollution and Childhood Cancer

The incidence of childhood cancers is increasing, based on a recent report of data from 68 countries and over 100 population-based registries.[97] An average of 215,000 children aged younger than 15 years, and 85,000 children aged 15–19 years were diagnosed with cancer each year from 1990–2017, which is likely an underestimate due to a lack of data in low income countries. In children, leukemia and lymphoma account for almost half of all cancers, followed by central nervous system (CNS) tumors and tumors originating in embryonic tissues, such as neuroblastoma, retinoblastoma and nephroblastoma.

The literature on outdoor air pollution and childhood cancers is limited. Most studies have examined leukemias, CNS tumors, or all childhood cancers combined, and few had sufficient sample sizes to stratify by more specific cancer subtypes. Most studies considered outdoor ambient air pollution exposure at birth or during childhood, while fewer examined prenatal exposure. Most early studies relied on metrics of traffic density, and were unable to examine concentrations of specific air pollutants. For example, a nationwide cohort in Switzerland observed that the risk of leukemia in children who lived < 100 m from a highway was 1.43 (95% CI 0.79–2.61) times greater than that of children who lived ≥ 500 m away, particularly for children aged younger than 5 years.[98]

Despite these limitations, there is some suggestive evidence for an adverse association of traffic-related air pollution and acute childhood leukemia.[15,99–103] IARC noted that a weak adverse association with childhood leukemia, particularly acute lymphoblastic leukemia (ALL), could not be ruled out, but noted that results were inconsistent with evidence of potential publication bias.[15] In a meta-analysis of 12 studies of traffic-related benzene exposure there was a nearly 1.5-fold higher risk of ALL and a 2-fold higher risk of AML.[100] In an even more recent meta-analysis of 29 studies, benzene exposure was adversely and linearly associated with risk of childhood leukemia, particularly AML, and most consistently among children < 6 years.[102] There was also no association observed of NO_2 and leukemia risk, except at the highest exposure levels, as well as no association with traffic density or $PM_{2.5}$, though there were some possible associations with ALL.

Few studies have examined the relationship between air pollution and childhood CNS tumors.[104–107] One difficulty is the potential for etiologic heterogeneity among phenotypes (e.g., astrocytomas and medulloblastomas), as few studies have data to examine these rare CNS subtypes. Danysh et al.[104] in a study of 1,949 children diagnosed with a CNS tumor in Texas, reported significant adverse associations of both medium and medium-high 1,3-butadiene concentrations and medium diesel particulate matter (DPM) concentrations with astrocytomas (IRRs = 1.46; 95% CI 1.05–2.01; 1.69; 95% CI 1.22–2.33; and 1.42; 95% CI 1.05–1.94 respectively), as well as of medium DPM concentrations and medulloblastoma

(IRR = 1.46; 95% CI 1.01–2.12) compared to low concentrations. Other studies reported no clear associations of traffic-related air pollution and childhood CNS tumors.[105–107]

Among studies of prenatal outdoor air pollution exposure, studies of child cancer in California have observed significant adverse associations of exposure to traffic pollution during gestation and risk of ALL, germ-cell tumors and retinoblastoma.[106] In another California study, each 25 ppb increase in average maternal exposure to NO, NO_2, and NO_x during pregnancy increased the risk of ALL in offspring by 9, 23, and 8% respectively.[105] Bilateral retinoblastoma was also associated with second and third trimesters exposures. Prenatal exposure to acetaldehyde, 1,3-butadiene, benzene, and toluene were adversely associated with central nervous system primitive neuroectodermal tumor (PNET) and PAHs with medulloblastoma.[108] A Texas study reported an adverse association of embryonal tumors in children whose mothers lived < 500 m from a major road during pregnancy compared with 500 m or more (OR = 1.24; 95% CI 1.00–1.54), with the strongest findings observed for unilateral retinoblastoma (OR = 1.67; 95% CI 0.96–2.93).[109] In a study of more than two million Canadian children followed-up from birth to 4 years, $PM_{2.5}$ exposure during the first trimester was associated with a significant adverse association of astrocytoma (HR per 4.0 $\mu g/m^3$ = 1.40; 95% CI 1.05–1.86, n = 94) and first trimester NO_2 with ALL (HR per 13.3 ppb =1.20; 95% CI 1.02–1.41, n = 302).[110]

Lastly, a Utah study reported significant adverse $PM_{2.5}$ - cancer mortality associations among pediatric patients with lymphoma and CNS tumors as well as among adolescent and young adult patients with CNS tumors, carcinomas, melanomas, breast, and colorectal cancers.[111] Further research of mortality in childhood cancer patients is needed.

Biological Mechanisms of Air Pollution-Derived Carcinogenesis

The biological mechanisms behind air pollution-related carcinogenesis remain to be elucidated. Still, extensive evidence from indirect models show how outdoor air pollution contributes to abnormal cell proliferation and cancer.[112] Post-inhalation, air pollutants may generate effects along the respiratory tract, in locations such as the extra-thoracic, tracheobronchial, or alveolar airways. Retained particles and gas can have significant consequences on both the local and systemic level, generating low-grade and long-term inflammation and oxidative stress.[113] Air pollution contains several mutagens and carcinogens, including PAHs (e.g., benzo(a)pyrene and polar compounds),[114] dioxins,[115] sulfur-containing compounds (SO_3, H_2SO_4),[116] and 3-nitrobenzanthrone.[117] PAHs are a class of compounds associated with human cancer risk due to their ability to generate DNA adducts.[118] One meta-analysis has confirmed the nonlinear dose-response relationship between air pollution PAH and DNA adducts,[119] and several studies have indicated that carcinogen-DNA adducts are closely associated with cancer risk.[120–122] However, an individual's repair capacity may determine if DNA adducts are eliminated by the repair machinery, potentially inducing DNA mutations.[123]

Gene mutations and gene silencing are particularly relevant during carcinogenic processes when they can affect tumor suppressor genes (TSGs).[124] Several studies have shown that there are fractions of outdoor air that contain mutagenic particulate and volatile matter.[125]

Also, mice exposed to industrial ambient air pollution showed higher heritable mutation at tandem-repeat DNA loci.[126] *TP53* is a TSG involved in cell proliferation, apoptosis, and damage repair, and its mutation/inactivation contributes to the pathogenesis of lung cancer.[127] Studies have shown that low-dose $PM_{2.5}$ may induce epigenetic silencing of *TP53* in human alveolar epithelial cells.[128] Remarkably, studies from Yu et al.[129] showed that the number of mutations was three times higher in air pollution-related lung cancers than in lung cancers from low-exposed regions. These mutations were seen across hundreds of genes, including *TP53*.

Outdoor air pollution has also been linked to several epigenetic modifications,[130] including changes to post-translational modifications of histones,[131] 5-hydroxymethylation,[130] and most notably DNA methylation (DNAm). DNAm is a biochemical change that occurs in cytosines, particularly at the CpG context, and modifies gene expression as well as several other functions. As mentioned for *TP53*, hypermethylation contributes to gene silencing,[132] but DNA hypomethylation contributes to chromosome instability[133] and activation of retrotransposon sequences and repetitive elements such as LINE-1[134] and Alu.[135] DNA hypomethylation also affects critical chromosome regions such as the subtelomeric and pericentromeric regions.[136] Exposure to ambient air pollution, whether short-term or long-term, is associated with abnormal DNA methylation.[137–139] Other studies have also shown that human epithelial cells exposed to $PM_{2.5}$ are more susceptible to hypomethylation and transcriptional activation of several genes and also microRNAs (miRNAs), modifying cancer-related signaling pathways.[140] $PM_{2.5}$ is also able to induce changes in long non-coding RNAs (lncRNA) such as loc146880 via reactive oxygen species (ROS), promoting autophagy and malignancy of lung cells.[141]

Transcriptional changes in miRNAs have also been described in human bronchial cells exposed to ambient $PM_{2.5}$, including downregulation of miR-182 and miR-185, potentially deregulating oncogenes (*SLC30A1*, *SERPINB2,* and *AKR1C1*) and facilitating neoplastic transformation.[142] Other studies have found that dysregulation of actin cytoskeleton and down-regulation of miR-802 expression is present in the A549 cell line after particulate matter exposure.[143] Human bronchial epithelial cells exposed to various concentrations of $PM_{2.5}$ also show transcription changes in hundreds of genes, affecting some involved in inflammatory and immune response, oxidative stress, and DNA damage, as well as decreased cell viability in a dose-dependent manner.[144] Several other studies have found that air pollution compounds induce the release of pro-inflammatory cytokines, including IL-6, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF), resulting in low-grade, chronic inflammation in the airway and throughout the body.[145–147] Another critical driver of carcinogenesis associated with air pollution is oxidative stress (OS).[148] OS is characterized by the increase in free radicals (reactive oxygen species [ROS] and reactive nitrogen species [RNS]). The most-studied air pollutants concerning the intracellular formation of free radicals are ozone (O_3),[149] nitrogen oxides (NO and NO_2), and metals.[150] Early studies demonstrated that mouse fibroblasts exposed to ROS could lead to carcinogenic transformation of cells.[151] ROS are considered pro-neoplastic factors, they stimulate cell proliferation, invasiveness, angiogenesis, and metastasis, and inhibit apoptosis.[152]

Air pollution-related carcinogenesis is expected to follow a multi-step process that includes initiation, promotion, and progression (Figure 4).[153] Although not completely understood, individual and time-dependent dose influences the mechanisms by which environmental air pollutants result in cancer cell transformation. The impact of air pollution particular carcinogens and their mixtures disrupt several molecular processes via direct or indirect (inflammation and OS) damage, inducing TSG inactivation and the activation of oncogenes,[154] cell cycle alterations dependent on *TP53* activation,[155] activation of energetic dysregulation,[156] chromosome instability,[157–158] the inhibition of apoptosis,[159] and the induction of cell proliferation in somatic cells.[160] Further research will clarify which mechanisms are most relevant and can be used as early biomarkers of air pollution-related cancer.

Public Health/Policy Recommendations

Few cancers have been as well characterized as lung cancer from the perspective of etiology, leading to the well-documented predominant role of environmental factors in causing this highly fatal malignancy. As mentioned above, outdoor air pollution and specifically PM was classified by IARC as a causal agent (Group 1 carcinogen) for lung cancer.[15] Despite this, the United States Environmental Protection Agency (EPA) in its most recent review of the evidence on PM, the Integrated Science Assessment, found the weight-of-evidence to indicate that $PM_{2.5}$ is only "likely to be causal".[161] Nonetheless, when the IARC conclusion was published,[162] its policy implications figured prominently in media reports.

From a public health policy perspective, the addition of outdoor air pollution to the list of causes of lung cancer, and potentially also to a growing list of cancers at other sites, offers another imperative for air quality management. Given widespread recognition that lung cancer is highly fatal, the IARC conclusion may prove a more powerful motivator than other less well understood, adverse effects of air pollution.

Implementing measures to reduce cancer due to outdoor air pollution is challenging, as there are typically numerous combustion sources with emissions including both specific carcinogens and other agents that may increase cancer risk. Based on understanding of carcinogenesis and considering the agents known to be in air pollution, a linear non-threshold relationship between exposure and risk can be reasonably assumed.[26,163,164] From a regulatory perspective, this implies that any exposure conveys some risk and that lowering exposure to the maximum extent feasible should be the goal.

The definition of "acceptable risk" by Lowrance[165] is a useful starting point for considering management of cancer risk caused by air pollution: "A thing is safe if its risks are judged to be acceptable." For lung cancer, using PM as the indicator of exposure, risks have been quantified with sufficient certainty for carrying out a risk assessment, but any consensus societal judgment as to the acceptability of lung cancer risk from air pollution is lacking. Estimates of the burden of lung cancer attributable to air pollution have been made at the population level (above). The global proportion of lung cancer deaths attributable to ambient $PM_{2.5}$ is second only to tobacco smoking.

Interventions to reduce air pollution exposure may be considered at various scales including the individual, community, industrial, and broader regional scales.[166] In the United States, the Clean Air Act calls on the Administrator of the EPA to set National Ambient Air Quality Standards (NAAQS) that protect public health "with an adequate margin of safety." For PM, that goal cannot be absolutely achieved as adverse effects of air pollution have been demonstrated at levels well below current NAAQS and for some adverse effects, including lung cancer, non-threshold risk relationships are biologically plausible. Acknowledging that risk cannot be fully avoided through regulatory action, the EPA uses risk assessment methods and scenarios of exposure reduction under different changes to the NAAQS. The adverse health effects considered have been those for which the agency has found the relationship to be causal. Thus, in the current revision of the PM NAAQS, lung cancer will likely not be an element of the risk assessment considered. Nonetheless, the many organizations concerned with lung cancer, should use the mounting evidence and IARC finding to advocate for accurate air pollution monitoring and tighter air quality management and for specific consideration of sources that most prominently contribute to the dose of inhaled carcinogens, including controlling fine PM from combustion, especially from fossil fuel sources.

Multiple interventions occurring over long time scales have led to improvements in outdoor air quality in many higher-income and some middle-income countries and improvements in health.[23,24,167–170] Further research to evaluate the effectiveness of specific interventions in low- and middle- income countries, where air quality continues to worsen, is needed.[167] Reductions in biomass burning, which can contribute to high levels of air pollution outdoors, as well as improvements in cooking stoves and indoor ventilation are important air quality improvement strategies worldwide.[171,172] Impacts in terms of reduction of lung cancer incidence, as noted above, requires long-term and sustained intervention over multiple years and decades. Although potential impacts on cancer survival post-diagnosis have also been suggested, further research is required to evaluate impacts of reducing patient-level outdoor air pollution exposure on survival.[54]

Available research regarding interventions to reduce outdoor air pollution levels has resulted in subsequent calls for cities to pursue more compact and mixed-use urban designs with a transport modal shift from private vehicles to active transport.[173] Specific interventions may relate to destination accessibility, employment distribution, residential density, availability and cost of parking, and enhancement of active travel networks.[174] Interventions related with road-traffic emissions have also included planning and development management, car-free policies, clean air zones, vehicle technologies and reducing emissions from public sector transport services, smooth driving and speed reduction, public transportation provision, and raising public awareness of the adverse human health impacts of outdoor air pollution.[169,175] The key role of the medical and healthcare community in raising public and patient awareness, including of monitoring of local air quality indices and guidelines,[172] motivating action on air quality management, and involvement in the policy process has been described.[171,173,175,176] The support of the medical and healthcare community in the further conduct of relevant etiological and innovative intervention studies is also needed.[173] There is also increasing interest in the use of green spaces and green infrastructure in air pollution mitigation, though further research in terms of specific infrastructure deployment

is needed to optimize health benefits, reduce unintended consequences, and develop evidence-based guidelines for implementation.[177]

Individual-level interventions have also been described including the use of personal respirators, though impacts on exposure and health are difficult to evaluate in the general population.[171,178] Reductions in exposure to $PM_{2.5}$ and other particle pollutants have been reported in some studies,[179] though the overall evidence remains inadequate.[178] The use of personal respirators in combination with avoidance behaviour, such as route selection for example, has been recommended.[178] Reductions in indoor levels of $PM_{2.5}$ have been observed with the use of some household filtration systems.[180,181] In terms of commuting mode, in a review of studies of travel microenvironments in Europe, pedestrians experienced the lowest exposure to air pollution and car users the highest, though results may not be applicable to other areas.[182] Personal mobile monitoring technologies, including mobile phones, may support avoidance behaviours in the future.[183]

Lastly, the suggestion of possible greater-than-additive joint effects of cigarette smoking and $PM_{2.5}$ concentrations for lung cancer mortality may also imply that public health efforts in tobacco control and air quality management may result in greater than expected reductions in lung cancer rates due to the reduction of cases attributable to the interaction of both factors.[53]

Conclusion

In conclusion, there is clear and substantial evidence of a link between outdoor ambient air pollution, and particularly PM in outdoor air, with lung cancer incidence and mortality causing hundreds of thousands of lung cancer deaths annually worldwide. This burden represents an urgent worldwide public health challenge requiring multiple multi-level public health and policy interventions for cancer prevention. Epidemiological evidence on outdoor air pollution and other types of cancer is more limited. Further research on cancer incidence and survival at other cancer sites is needed, as well as on the effectiveness of specific interventions for cancer prevention, particularly in low- and middle- income countries.

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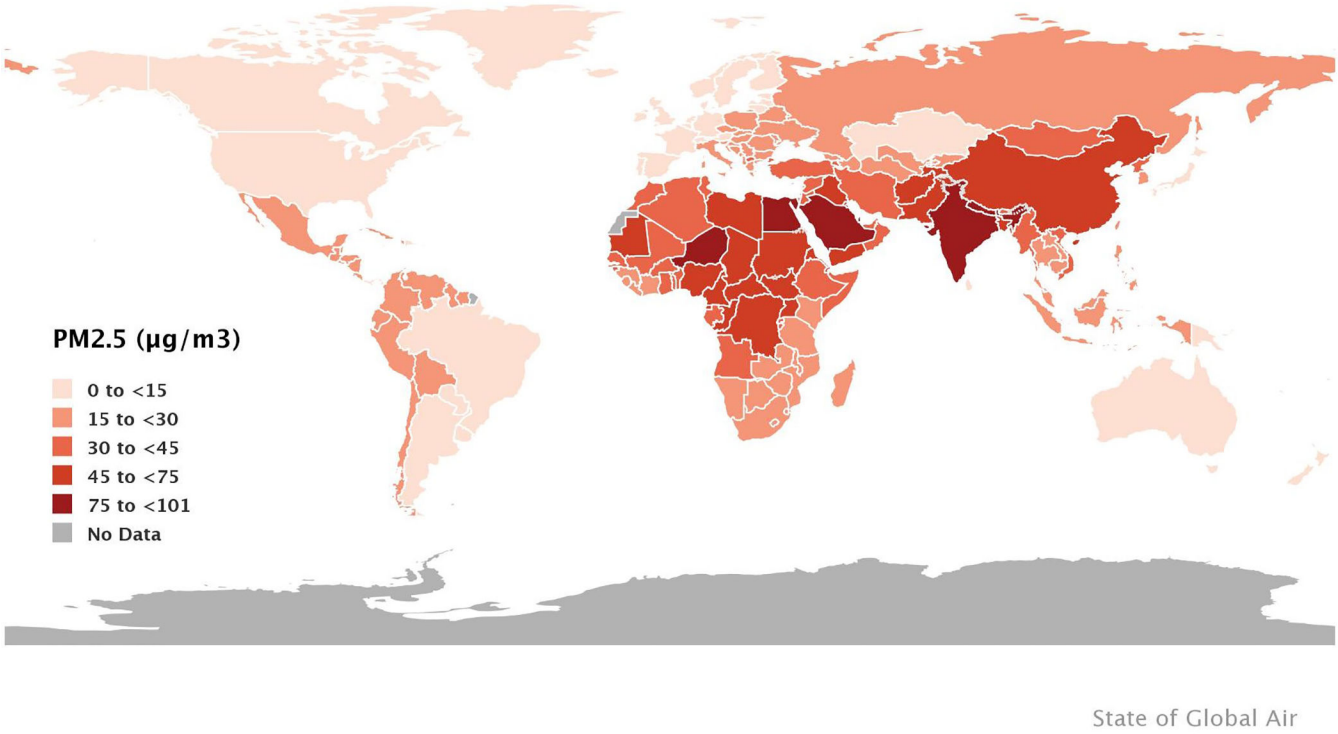

Figure 1.

Average annual population-weighted $PM_{2.5}$ concentrations in 2017. Source: Health Effects Institute. 2019. State of Global Air 2019. Data source: Global Burden of Disease Study 2017. IHME, 2018.

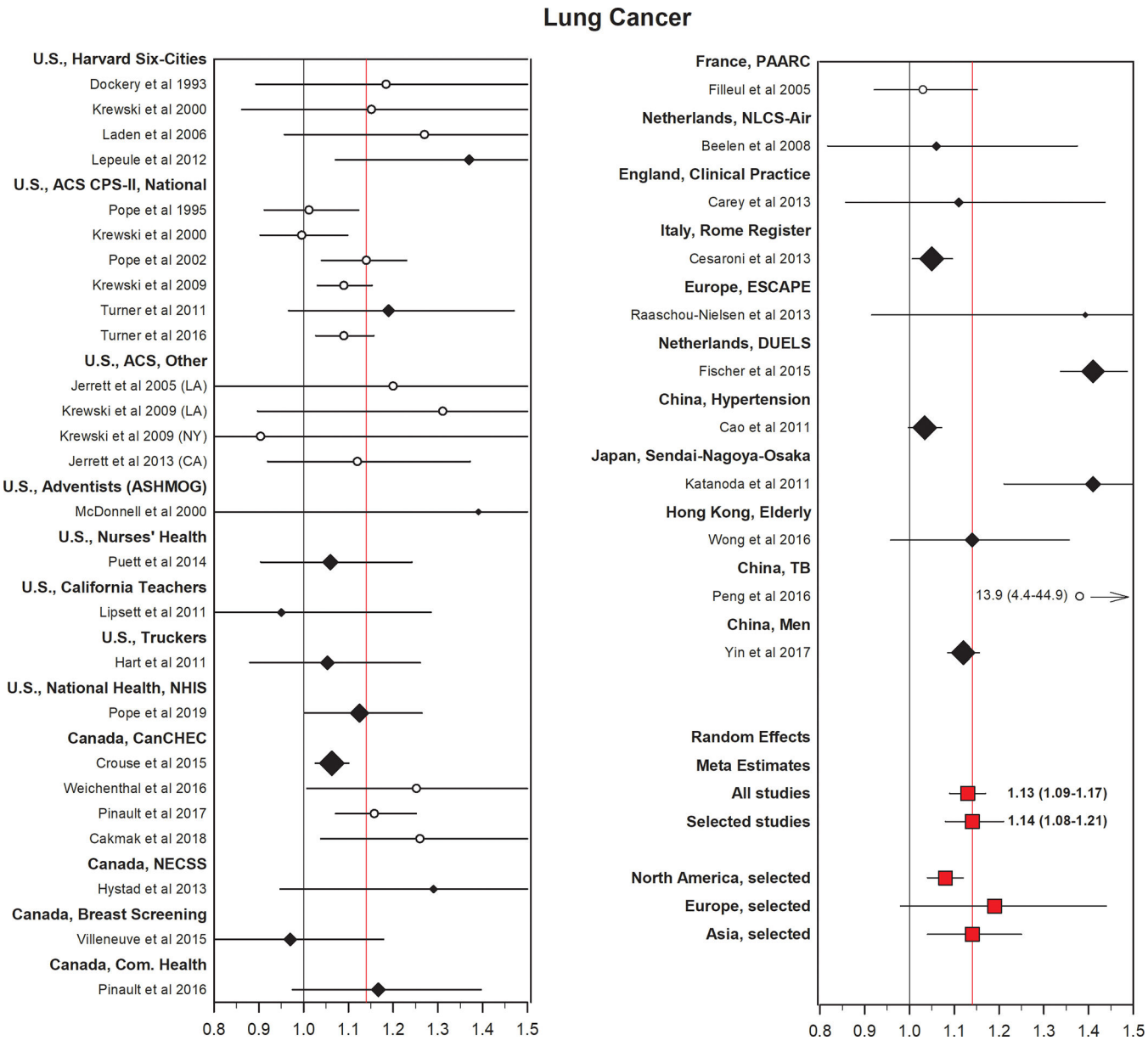

Figure 2.

Estimated adjusted HRs (and 95% CIs) for lung cancer mortality per 10 μg/m^3 elevation in $PM_{2.5}$ from multiple cohort studies. Black diamonds represent selected studies with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The red squares represent random effects meta-estimates. The black line is a reference line at HR = 1. The red line is a reference line at HR equals the random effects meta-estimate using the selected studies. Source: modified and updated figure from, Pope CA III, Coleman N, Pond ZA, Burnett RT. Fine particulate air pollution and human mortality: 25+ years of cohort studies. Environ Res. 2020;183:108924. Reprinted under a CC BY-NC-ND 4.0 creative commons license.

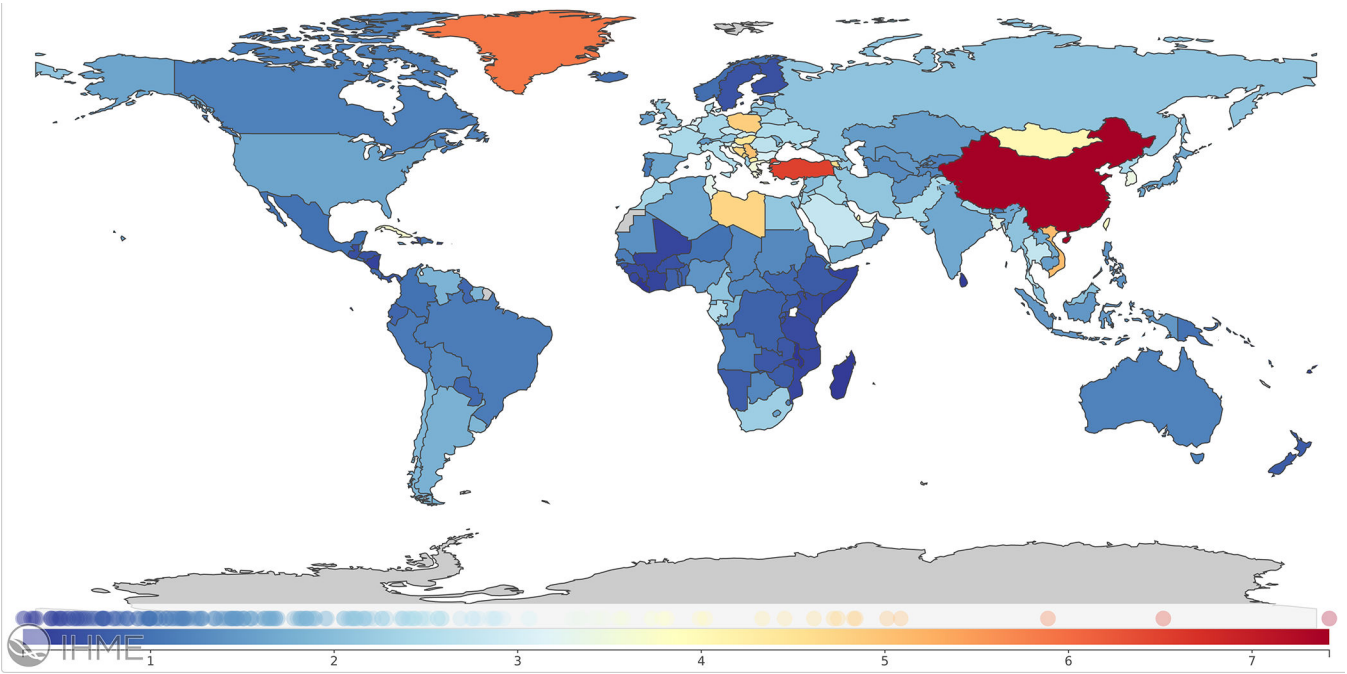

Figure 3.

Global age-standardized $PM_{2.5}$-attributable trachea, bronchus, and lung cancer mortality rates per 100,000 in 2017. Source: https://vizhub.healthdata.org/gbd-compare/; accessed April 29, 2020.

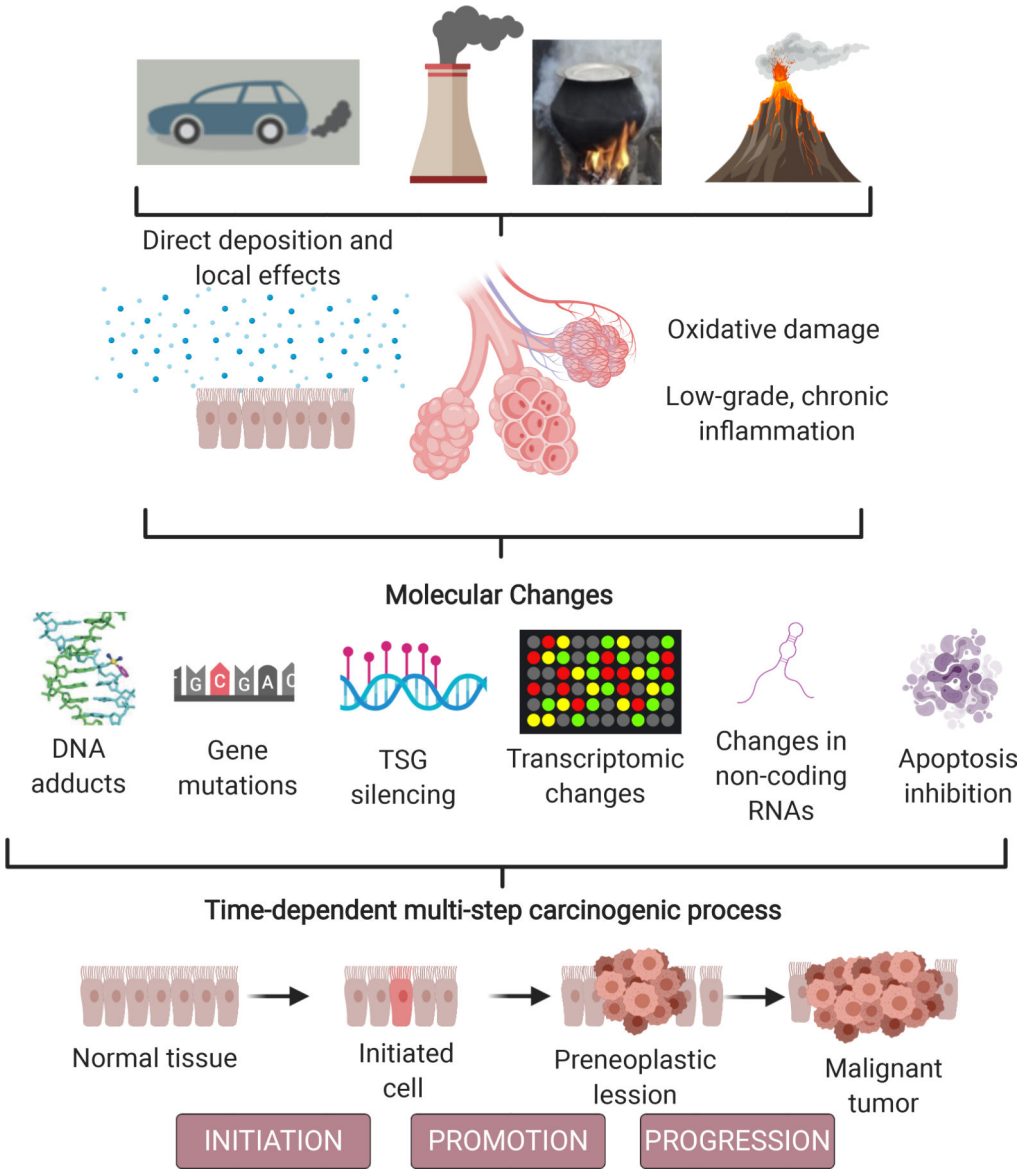

Figure 4.

Air pollution-related cancer: Potential pathways and mechanisms. TSG: Tumor suppressor genes.

Table 1.

Common health impacting air pollutants, grouped by origin

Air Pollutant	Typical Sources
1: Predominantly Outdoor Air Pollutants	
Sulfur dioxide (SO_2)	Fuel combustion, smelters
Ozone (O_3)	Generated via photochemical reactions in the atmosphere from nitrogen oxides (NO_x) and volatile organic compounds (VOCs), as well as natural processes (e.g., stratosphere)
Arsenic (As), Chromium (Cr)	Coal combustion fine particulate matter ($PM_{2.5}$)
Nickel (Ni), Vanadium (V)	Residual oil combustion fine particulate matter ($PM_{2.5}$)
2. Predominantly Indoor Air Pollutants	
Radon	Building materials (concrete, stone), ground water
Asbestos, mineral, synthetic fibers	Fire-retardant, acoustic, thermal, or electrical insulation
Biological contaminant	Infections, dust mites, animal dander, allergens
3: Both Outdoor and Indoor Air Pollutants	
Suspended particulate matter (PM)	
Fine PM ($PM_{2.5}$)	Outdoor: Fossil fuel combustion, gas-to-particle conversion, biomass burning Indoor: Biomass fuel combustion, tobacco smoking
Coarse PM ($PM_{2.5–10}$)	Outdoor: Dust storms, windblown soil, pollens Indoor: Mold spores, re-suspended dust
Nitrogen dioxide (NO_2)	Outdoor: Fossil fuel combustion (e.g., diesel vehicle emissions) Indoor: Tobacco smoking, gas cooking stoves
Volatile organic compounds (VOCs)	Outdoor: Petrochemical solvents, evaporated fuels, biogenics Indoor: Fuel and paint vapors, combustion, adhesives, cosmetics, solvents, particleboard (formaldehyde), insulation, furnishings, tobacco smoke
Carbon monoxide (CO)	Outdoor: Fossil fuel combustion, biomass burning, wildfires Indoor: Tobacco smoke, unvented gas heaters
Lead (Pb)	Outdoor: Industrial emissions, leaded fuel combustion, lead processing Indoor: Leaded paint wear
Mercury (Hg)	Outdoor: Coal combustion, ore refining Indoor: Fungicides in paints, thermometer breakage, ritual use
Pesticides	Outdoor: Agricultural Indoors: Home applications of herbicides, insecticides, fungicides, etc.
Ammonia	Outdoor: Livestock yards Indoor: Metabolic activity, cleaning products
Hazardous air pollutants (HAPs) (e.g., benzene, 1,3-butadiene, formaldehyde, acids)	Outdoor: Incomplete combustion, chemical processing Indoor: Solvent use

Adapted from: World Health Organization (WHO). Estimating Human Exposures to Air Pollutants. Offset Pub. No. 69. Geneva: World Health Organization; 1982 and International Agency for Research on Cancer (IARC). Outdoor Air Pollution. Volume 109. Lyon: International Agency for Research on Cancer; 2013.