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, because of 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, 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 the 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, although 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 multilevel interventions aimed at individual, community, and regional scales. Specific roles for medical and health care communities with regard to prevention and advocacy and recommendations for further research are also described. CA Cancer J Clin 2020;70:460-479. © 2020 American Cancer Society.

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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, because of 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 multilevel interventions aimed at the individual, community, and regional scales. The specific role for the medical and health care 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. 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 [SO₂], nitrogen dioxide [NO₂], carbon monoxide [CO], and volatile organic compounds [VOCs]) and particulate matter (PM) (including carbonaceous aerosol particles, such as black soot). Although CO levels are often low outdoors in the developed world today (because of the use of emission controls such as catalytic converters on automobiles), high levels can be experienced near biomass burning sources, including wildfires. In addition, secondary air pollutants are formed in the atmosphere from primary pollutants and include gaseous ozone (O₃), a major component of photochemical smog, formed in the atmosphere when nitrogen oxides (NOₓ) and hydrocarbons such as VOCs react in the presence of sunlight. Similarly, particulate sulfate (eg, sulfuric acid [H₂SO₄]) and nitrate (eg, ammonium nitrate [NH₄NO₃]) aerosols are commonly created in the atmosphere from SO₂ and NOₓ, respectively. Primary combustion particles and secondary particles are small in diameter and are often referred to as fine particulate matter, or PM₂.₅ (particles ≤ 2.₅ µm in aerodynamic diameter). Submicron combustion-related PM₂.₅ is of particular health concern because it contains numerous toxic compounds (eg, acids and heavy metals), and can penetrate deeper into the lung than the larger PM generated by natural processes, such as windblown soil particle mass.

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 3 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: PM₂.₅, SO₂, NO₂, O₃, 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 2 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 SO₂ and NOₓ gases (discussed above). Other primary sources include nonexhaust 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.

PM is commonly characterized according to the following size fractions:

- **PM₁₀** (PM ≤ 10 µm in aerodynamic diameter) includes the largest inhalable particles. Particles >10 µm are generally not inhaled past the trachea, are caught in the nose and throat, and are not deposited in the lung. PM₁₀ also includes all the fractions described below:
  - **PM₂.₅-₁₀**, also known as coarse fraction particles (PM with an aerodynamic diameter >2.₅ µm but ≤ 10 µm);
  - **PM₂.₅**, also known as fine particulate matter (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, PM₂.₅ has increasingly become a major research focus of adverse human health impacts of outdoor air pollution exposure over recent decades; and
  - The smallest fraction of PM₂.₅ contains nanoparticles, also known as ultrafine particles (UFPs), generally defined as particles ≤ 0.1 µm in aerodynamic diameter.

The mass concentration (as µg/m³) is the common metric used to evaluate and regulate PM pollution, although some constituents, such as lead (Pb) concentration, have been separately regulated. Whereas UFPs usually make up only a small fraction of PM₂.₅ mass, they commonly account for a majority of the number concentration of particles in PM₂.₅. It has been hypothesized, based on toxicological studies, that UFPs may be an especially toxic component of PM₂.₅ because of their small size, large numbers, and large surface area-to-mass ratio, but epidemiological evidence is currently sparse.

PM₂.₅ is directly emitted from combustion sources, and is also formed from gaseous precursors, such as SO₂ and NOₓ, or organic compounds (discussed above). In some areas and under some conditions, these secondary particles make up a substantial proportion of the PM₂.₅ 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). Indeed, coal combustion has been found to account for approximately one-quarter of the world’s emissions of both As and mercury (Hg). PM$_{2.5}$ can remain in the atmosphere for days to weeks and travel through the atmosphere hundreds to thousands of kilometers; 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 µg/m$^3$ in 2017, which is 4-fold greater than the WHO’s health-based world air-quality guideline of 10 µg/m$^3$ (Fig. 1). Ninety-two percent of the global population worldwide lives in areas where ambient PM$_{2.5}$ concentrations exceed the WHO

| 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 (eg, stratosphere) |
| Arsenic (As), chromium (Cr) | Coal combustion fine particulate matter (PM$_{2.5}$) |
| Nickel (Ni), vanadium (V) | Residual oil combustion fine PM (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 | |
| Fine PM (PM$_{2.5}$) | Outdoor: Fossil fuel combustion, gas-to-particle conversion, biomass burning |
| Coarse PM (PM$_{2.5-10.0}$) | Outdoor: Dust storms, windblown soil, pollens |
| Nitrogen dioxide (NO$_2$) | Outdoor: Fossil fuel combustion (eg, diesel vehicle emissions) |
| Volatile organic compounds (VOCs) | Outdoor: Petrochemical solvents, evaporated fuels, biogenics |
| Carbon monoxide (CO) | Outdoor: Fossil fuel combustion, biomass burning, wildfires |
| Lead (Pb) | Outdoor: Industrial emissions, leaded fuel combustion, lead processing |
| Mercury (Hg) | Outdoor: Coal combustion, ore refining |
| Pesticides | Outdoor: Agricultural |
| Ammonia | Outdoor: Livestock yards |
| Hazardous air pollutants (HAPs) (eg, benzene, 1,3-butadiene, formaldehyde, acids) | Outdoor:Incomplete combustion, chemical processing |

Adapted from: World Health Organization (WHO) & Global Environment Monitoring System. Estimating Human Exposures to Air Pollutants. WHO Offset Publication No. 69. WHO; 1982; and International Agency for Research on Cancer (IARC). Outdoor Air Pollution. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 109. IARC; 2013.
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 µg/m³. Among the 10 largest countries by population, population-weighted ambient PM 2.5 in 2017 varied by >12-fold, from 7 µg/m³ in the United States to 91 µg/m³ in India. For NO2, global population-weighted mean concentrations were estimated to be 1.6 parts per billion (ppb) during 1996 through 2012 and were observed to have increased by 0.9% (95% CI, 0.6%-1.1%) per year during that time. 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), although 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 were 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 O3 concentration worldwide was 57 ppb in 2017, which was unchanged from 1990.

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, from reference lists of identified studies and authoritative reports, and through 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. In the United States, approximately 234,030 new lung cancer cases, and 154,050 deaths were estimated in the same year. Lung cancer is highly fatal, with an overall 5-year survival rate of only 18%. Rates of lung cancer incidence and mortality vary substantially within and between countries, depending
largely on historical patterns of cigarette smoking,\textsuperscript{15} 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/Palau, Eastern Asia, and Eastern Europe and, among women, in North America, Northern and Western Europe, and Australia/New Zealand.\textsuperscript{15} 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.\textsuperscript{15}

Although cigarette smoking accounts for the majority 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.\textsuperscript{15-17}

On the basis of 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.\textsuperscript{6} 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.\textsuperscript{18-20} 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\textsubscript{2.5} exposure, was particularly influential.\textsuperscript{19} 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\textsuperscript{21} commented in 1950 that 2 main causes had been put forward: 1) general atmospheric pollution from automobile exhaust and surface dust from tarred roads and from gas works, industrial plants, and coal fires; and 2) smoking 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.

The IARC has also classified household burning of coal as a Group 1 human carcinogen and household burning of biomass fuel as Group 2A (probably carcinogenic) for lung cancer.\textsuperscript{22,23} Household burning of solid fuels, both coal and biomass, contribute significantly to high levels of outdoor air pollution, and thus to the burden of disease, in low-income and middle-income countries.\textsuperscript{24-27}

A 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\textsuperscript{3} increase in PM\textsubscript{2.5} concentrations and, in 9 studies of PM\textsubscript{10} an 8% (95% CI, 0%-17%) increase in risk per 10 µg/m\textsuperscript{3}.\textsuperscript{28} Lung cancer incidence and mortality were considered together here because, 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 (ie, 14%; 95% CI, 8%-21% per 10 µg/m\textsuperscript{3} PM\textsubscript{2.5}) was observed with similar findings again in studies from different regions (Fig. 2).\textsuperscript{18-20,29-60} When extrapolated to the global population-weighted mean annual average PM\textsubscript{2.5} concentration (46 µg/m\textsuperscript{3}) relative to the WHO health-based world air-quality guideline (10 µg/m\textsuperscript{3}), this represents an approximately 60% excess risk of lung cancer mortality.

There were also significant adverse associations reported in meta-analyses of studies on NO\textsubscript{2} exposure, a marker of traffic-related air pollution, for lung cancer mortality (relative risks [RRs], 1.04-1.05 per 10 µg/m\textsuperscript{3}), although results were attenuated somewhat in studies that adjusted for individual-level cigarette smoking status and were no longer significant.\textsuperscript{61,62} Additional research in Asia and in other understudied and more highly polluted regions is needed,\textsuperscript{60} as well as studies 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\textsubscript{2.5} and lung cancer mortality among 635,539 US National Health Interview Survey (NHIS) participants (hazard ratio [HR] per 10 µg/m\textsuperscript{3}, 1.13; 95% CI, 1.00-1.26; n = 7420 lung
There were suggestive adverse associations of both PM$_{2.5}$ and PM$_{10}$ with lung cancer mortality in an analysis of 49,564 participants in the Danish Diet, Cancer, and Health Cohort, but no associations with black carbon, NO$_2$, or O$_3$. 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 because of the short follow-up or other methodological characteristics of that study.

Among studies without individual-level information on cigarette smoking history, in an analysis of approximately 4.9 million individuals in the Ontario Population Health and Environment Cohort, 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. In an analysis of 18.9 million US Medicare beneficiaries, there were significant adverse associations particularly with longer term moving average PM$_{2.5}$ exposure and lung cancer...
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mortality (HR per 10 µg/m³ [60-month moving average], 1.33; 95% CI, 1.24-1.40). There were also some significant adverse associations with O₃ and NO₂. Although an analysis extended to 53 million Medicare beneficiaries reported no association of PM₂.₅ and lung cancer mortality, there may have been confounding by cigarette smoking status in rural populations that were included.

Worldwide, ambient PM₂.₅ air pollution was estimated to have contributed to 265,267 lung cancer deaths (95% uncertainty interval [UI], 182,903-350,835 lung cancer deaths) in 2017, or 14.1% (95% UI, 9.8%-18.7%) of all lung cancer deaths. The global proportion of lung cancer deaths attributable to ambient PM₂.₅ was second only to tobacco smoking (14.1% vs 63.2%).

Mortality attributable to PM₂.₅ 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, 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 PM₂.₅-attributable lung cancer mortality rates and population-attributable fractions in the United States, for example, were 1.6 per 100,000 (95% UI, 0.65-2.91 per 100,000) and 4.7% (95% UI, 1.9%-8.5%) compared with 7.4 per 100,000 (95% UI, 5.4-9.5 per 100,000) and 20.5% (95% UI, 14.8%-25.9%) in China (Fig. 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 4 decades is considered as reflecting changes in cigarettes and the delivery of carcinogens. A mechanistic basis for a link of air pollution to particular histologic types is uncertain, although some studies have suggested stronger findings with adenocarcinoma. In the meta-analysis by Hamra et al, results for both PM₂.₅ and PM₁₀ were somewhat stronger for adenocarcinoma (RR per 10 µg/m³, 1.40 [95% CI, 1.07-1.83] and 1.29 [95% CI, 1.02-1.63], respectively), although 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 PM₂.₅ and incident lung cancer overall (HR per 10 µg/m³, 1.34; 95% CI, 1.10-1.65), which strengthened somewhat for both small cell carcinoma (HR per 10 µg/m³, 1.53; 95% CI, 0.93-2.53) and adenocarcinoma (HR per 10 µg/m³, 1.44; 95% CI, 1.06-1.97). In analysis of 80,285 participants in the Adventist Health and Smog Study-2, there was a significant adverse association of PM₂.₅ and total lung cancer incidence (HR per 10 µg/m³, 1.43; 95% CI, 1.11-1.84). There was also an adverse association with adenocarcinoma (HR per 10 µg/m³, 1.31; 95% CI, 0.87-1.97), which strengthened in participants who reported spending >1 hour per day outdoors. There was also an adverse association of ambient PM₁₀ concentrations and total lung cancer incidence in
the EAGLE study (Environment and Genetics in Lung Cancer Etiology), consisting of 2099 cases and 2120 controls in the Lombardy Region of Italy (odds ratio [OR] per 10 µg/m³, 1.28; 95% CI, 0.95-1.72), with somewhat stronger findings for squamous cell carcinoma (OR per 10 µg/m³, 1.44; 95% CI, 0.90-2.29).\(^\text{77}\) In a large-scale South Korean study that included 6.5 million 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 there was an adverse association of PM\(_{10}\) and adenocarcinoma in male smokers (HR per >60.9 vs <50.40 µg/m³, 1.14; 95% CI, 1.03-1.25).\(^\text{78}\) Further research on air pollution and lung cancer by histologic type is needed.

Knowledge regarding the effects of differing PM components for lung cancer is also limited.\(^\text{28,79}\) In an 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 µg/m³, 1.09; 95% CI, 1.03-1.16), as well as with both near source (largely traffic-related) and regional PM\(_{2.5}\) components.\(^\text{35}\) There were also stronger lung cancer mortality associations in ACS CPS-II with coal combustion-related PM\(_{2.5}\) as well as with Se, a coal combustion tracer, and specifically with S elemental components.\(^\text{80}\) In an analysis of 193,300 participants in the Canadian Census Health and Environment Cohort (CanCHEC), there were significant adverse associations of glutathione-related, 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.\(^\text{74}\) 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.\(^\text{46}\) 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 components (long-range transport, secondary combustion-related components) and nickel (oil-burning, industry).\(^\text{81}\) The IARC also concluded that there is sufficient evidence in humans for the carcinogenicity of diesel engine exhaust as well as some PM constituents (eg, nickel, chromium, Cd, silica dust) for lung cancer.\(^\text{82,83}\) There was also sufficient evidence in experimental animals for the carcinogenicity of condensates of gasoline engine exhaust.\(^\text{82}\) Therefore, although limited, the strongest evidence to date implicates fine PM of fossil fuel combustion origins.

There is also limited information regarding the modification of outdoor air pollution associations by other individual or lifestyle factors. Hamra et al\(^\text{28}\) reported that associations with PM\(_{2.5}\) were somewhat stronger in 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 the possible joint effects of air pollution and cigarette smoking on an additive scale, which may be most relevant for public health. In an analysis of 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 either exposure alone.\(^\text{74}\) It was estimated that 14% (95% CI, 0%-25%) of lung cancer deaths in that study were attributable to the interaction between these 2 factors. The ESCAPE lung cancer study reported no interaction between ambient PM\(_{2.5}\) or PM\(_{10}\) concentrations and fruit consumption.\(^\text{80}\) 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 nonsmall cell cancers, among 352,053 California patients with lung cancer.\(^\text{85}\) 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.\(^\text{86}\) Further research is needed to better understand the impact of outdoor air pollution on patterns of morbidity and mortality after lung cancer diagnosis.

### Epidemiological Studies of Outdoor Air Pollution and Other Types of Cancer

Epidemiological evidence for associations of outdoor air pollution with types of cancer other than lung cancer 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.

After 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%).\(^\text{15}\) For mortality, cancers of the colorectum (9.2%), stomach (8.2%), and liver (8.2%) account for the next greatest numbers of cancer deaths.\(^\text{15}\) 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. Second-hand tobacco smoke has also been suggestively associated with many of these types of cancer.

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. 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), work in trucking, mining, foundries, or carbon black production, and work with asphalt.

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. Bladder cancer shares several risk factors with lung cancer. However, results from more recent studies are mixed. In an analysis of 623,048 ACS CPS-II participants, there was a significant adverse association of PM2.5 and bladder cancer mortality (HR per 4.4 μg/m3, 1.13; 95% CI, 1.03–1.23; n = 1324) but no association with NO2 or O₃. There was also a significant adverse association of PM2.5 and bladder cancer mortality in the NHIS (HR per 10 μg/m3, 1.48; 95% CI, 1.00–2.20; n = 589). Although an early hospital-based study of 1219 incident bladder cancer cases and 1271 controls in Spain reported an adverse association of living for >40 years in a city of >100,000 inhabitants and bladder cancer risk (OR, 1.30; 95% CI, 1.04–1.63), an updated analysis, including estimates of ambient PM2.5 and NO2 at the participant residence based on European land-use regression models, showed no clear association. There was also no association of ambient PM10, PM2.5, PM2.5 absorbance, NO2, NO3, other elemental PM components, organic carbon, or traffic density with bladder cancer incidence in the ESCAPE study.

Previous studies have suggested some adverse associations of both NO2 and NO3 and breast cancer, with fewer clear associations with PM. Among most recent studies, in an analysis of 47,433 women in the US Sister Study, there were adverse associations of both NO2 (HR per 5.8 ppb, 1.06; 95% CI, 1.02–1.11) and PM2.5 (HR per 3.6 μg/m3, 1.05; 95% CI, 0.99–1.11) and breast cancer incidence overall (n = 2848). There were also adverse associations of PM2.5 concentrations characterized by low S component fractions and high sodium (Na) and NO3 fractions and invasive breast cancer incidence in California participants, and of PM2.5 characterized by high fractions of silicon (Si), calcium (Ca), potassium (K), and aluminum (Al) among participants in the Western United States. There were also adverse associations of several nonmetallic air toxics, including methylene chloride, and breast cancer incidence observed. In an analysis of 57,589 women in the Multiethnic Cohort, significant adverse associations of NO3, NO2, PM2.5, and PM10 with breast cancer incidence were observed among those living within 500 meters of major roads, with stronger associations for NO3 and NO2 among African American and Japanese American women overall. In the Canadian National Breast Screening Study (n = 89,247), there were adverse associations of both PM2.5 (HR per 10 μg/m3, 1.26; 95% CI, 0.99–1.61) and NO2 (HRs per 9.7 ppb, range 1.13–1.17) and the risk of incident premenopausal, but not postmenopausal, disease. However, results from other recent studies have reported no clear associations with incident breast cancer risk.

Furthermore, in one case-control study of 4059 breast cancer cases and 4059 matched controls nested in the French E3N cohort, there were significant inverse associations of ambient Cd and the risk of both incident estrogen receptor-negative and estrogen receptor-negative/progesterone receptor-negative disease. 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 I disease. Results of studies of mammographic density, a breast cancer risk factor, are also mixed.

For other types of cancer, there are fewer studies and the results are also inconsistent. Although there was an adverse association of NOx and brain tumor incidence in an analysis of 54,304 participants in the Danish Diet Cancer and Health cohort (incidence rate ratio [IRR] per 100 μg/m3, 2.28; 95% CI, 1.25–4.19; n = 95), the findings were not replicated in subsequent studies. There was an adverse, but nonsignificant, association of PM2.5 absorbance and malignant (HR per 10⁻⁵/m³, 1.67; 95% CI, 0.89–3.14; n = 466), but not nonmalignant (n = 366), brain tumor incidence in the ESCAPE study, although there were no data on brain tumor histology or morphology. An analysis of 103,308 Multiethnic Cohort participants reported significant adverse associations of both outdoor benzene and PM10 exposure and malignant brain tumor risk in men (n = 94), particularly among Latino men, but not in women. There was also a significant adverse association of O3 and meningioma risk among men (n = 130). There was a significant adverse association of within-city ambient UFP concentration and malignant brain tumor incidence in an analysis of 1.9 million CanCHEC participants in Montreal and Toronto (HR per 10,000/cm³, 1.11; 95% CI, 1.04–1.19; n = 1400).
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 = 6475). 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, 1.05–1.58; n = 2572) cancer mortality. There were also some suggestive adverse associations in an analysis of both kidney (n = 697) and liver (n = 279) cancer incidence in ESCAPE, although there were small numbers of cancer cases. Total PM$_{2.5}$ and PM$_{2.5}$ S components were also associated with incident gastric cancer risk. 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. A Taiwan cohort that included 23,820 participants and 464 incident cases of hepatocellular carcinoma (HCC), accounting for 85% to 90% of primary liver cancer cases, reported adverse associations with PM$_{2.5}$ mediated by alanine transaminase levels, an indicator of chronic liver inflammation. In a study that included 56,245 HCC cases in the US Surveillance, Epidemiology, and End Results 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). PM$_{2.5}$ was also related to reduced HCC survival.

Results from studies of hematopoietic cancers, leukemias, and lymphomas are also limited and mixed, with few studies having power to consider specific hematopoietic cancer subtypes. In ACS CPS-II, there were no clear associations of ambient air pollutant exposure and non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, multiple myeloma, or leukemia mortality. However, in a more recent analysis among 115,996 ACS CPS-II Nutrition Cohort participants, including 2595 with incident hematologic cancer, there were significant adverse associations of outdoor benzene exposure with incident myelodysplastic syndromes and T-cell lymphoma overall and with follicular lymphoma among men. The NHIS study reported significant adverse PM$_{2.5}$ associations with Hodgkin lymphoma (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 = 1016), and leukemia (HR, 1.43; 95% CI, 1.05–1.97; n = 970) mortality. A case-control study that included 1064 total incident leukemia cases and 5039 controls across Canada observed no clear association with PM$_{2.5}$ overall or when examining chronic lymphocytic leukemia specifically. Studies in Denmark have reported no clear associations of ambient air pollutant exposure and incident NHL, although, in one study, significant adverse associations of primary carbonaceous and secondary organic aerosols were observed. A Danish case-control study of 1967 incident leukemia cases and 3381 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).

Epidemiological Studies of Outdoor Air Pollution and Childhood Cancer

The incidence of childhood cancers is increasing, based on a recent report of data from 62 countries and >100 population-based registries. A total of 284,649 children aged <15 years and 100,860 aged 15–19 years were diagnosed with cancer from 2001–2010, which is an underestimate because of a lack of data in low-income countries. In children, leukemia and lymphoma account for almost one-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, whereas 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, in a nationwide cohort in Switzerland, it was observed that the risk of leukemia in children who lived <100 meters from a highway was 1.43 times greater (95% CI, 0.79–2.61 times greater) than that of children who lived ≥500 meters away, particularly for children aged <5 years.

Despite these limitations, there is some suggestive evidence for an adverse association of traffic-related air pollution and acute childhood leukemia. The IARC noted that a weak adverse association with childhood leukemia, particularly acute lymphoblastic leukemia (ALL), could not be ruled out but that the results were inconsistent with evidence of potential publication bias. 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. In an even more recent meta-analysis of 29 studies, benzene exposure was adversely and linearly associated with the risk of childhood leukemia, particularly AML and most consistently among children aged <6 years. 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$_{2.5}$, although there were some possible associations with ALL.

Few studies have examined the relationship between air pollution and childhood CNS tumors.\textsuperscript{134-137} One difficulty is the potential for etiologic heterogeneity among phenotypes (eg, astrocytomas and medulloblastomas), as few studies have data to examine these rare CNS subtypes. Danysh et al.\textsuperscript{134} in a study of 1949 children diagnosed with CNS tumors in Texas, reported significant adverse associations for both medium and medium-high 1,3-butadiene concentrations and medium diesel PM concentrations with astrocytomas (IRR, 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 medium diesel PM concentrations and medulloblastoma (IRR, 1.46; 95% CI, 1.01-2.12), compared with low concentrations. Other studies reported no clear associations of traffic-related air pollution and childhood CNS tumors.\textsuperscript{135-137}

Among studies of prenatal outdoor air pollution exposure, studies of childhood cancer in California have observed significant adverse associations of exposure to traffic pollution during gestation and the risk of ALL, germ-cell tumors, and retinoblastoma.\textsuperscript{136} 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.\textsuperscript{135} Bilateral retinoblastoma was also associated with second-trimester and third-trimester exposures. Prenatal exposure to acetaldehyde, 1,3-butadiene, benzene, and toluene were adversely associated with CNS primitive neuroectodermal tumor, and PAHs were adversely associated with medulloblastoma.\textsuperscript{138} A Texas study reported an adverse association of embryonal tumors in children whose mothers lived <500 meters from a major road during pregnancy compared with ≥500 meters (OR, 1.24; 95% CI, 1.00-1.54), with the strongest findings observed for unilateral retinoblastoma (OR, 1.68; 95% CI, 0.96-2.93).\textsuperscript{139} In a study of more than 2 million Canadian children who were followed from birth to 4 years, PM$_{2.5}$ exposure during the first trimester had a significant adverse association with astrocytoma (HR per 4.0 μg/m$^3$, 1.40; 95% CI, 1.05-1.86, n = 94), and first-trimester NO$_2$ had a significant adverse association with ALL (HR per 13.3 ppb,1.20; 95% CI, 1.02-1.41; n = 302).\textsuperscript{140}

Finally, 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 cancers, and colorectal cancers.\textsuperscript{141} Further research of mortality among patients with childhood cancer 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 shows how outdoor air pollution contributes to abnormal cell proliferation and cancer.\textsuperscript{142} Postinhalation, air pollutants may generate effects along the respiratory tract, in locations such as the extrathoracic, tracheobronchial, or alveolar airways. Retained particles and gas can have significant consequences on both the local and systemic levels, generating low-grade and long-term inflammation and oxidative stress.\textsuperscript{143} Air pollution contains several mutagens and carcinogens, including PAHs (eg, benzo[a]pyrene and polar compounds),\textsuperscript{144} dioxins,\textsuperscript{145} sulfur-containing compounds (SO$_3$, H$_2$SO$_4$),\textsuperscript{146} and 3-nitrobenzanthrone.\textsuperscript{147} PAHs are a class of compounds associated with human cancer risk because of their ability to generate DNA adducts.\textsuperscript{148} One meta-analysis has confirmed the nonlinear dose-response relationship between air pollution PAH and DNA adducts,\textsuperscript{149} and several studies have indicated that carcinogen-DNA adducts are closely associated with cancer risk.\textsuperscript{150-152} However, an individual’s repair capacity may determine whether DNA adducts are eliminated by the repair machinery, potentially inducing DNA mutations.\textsuperscript{153}

Gene mutations and gene silencing are particularly relevant during carcinogenic processes, when they can affect tumor suppressor genes (TSGs).\textsuperscript{154} Several studies have shown that there are fractions of outdoor air that contain mutagenic particulate and volatile matter.\textsuperscript{155} Also, mice exposed to industrial ambient air pollution showed higher heritable mutations at tandem-repeat DNA loci.\textsuperscript{156} TP53 is a TSG involved in cell proliferation, apoptosis, and damage repair, and its mutation/inactivation contributes to the pathogenesis of lung cancer.\textsuperscript{157} Studies have shown that low-dose PM$_{2.5}$ may induce epigenetic silencing of TP53 in human alveolar epithelial cells.\textsuperscript{158} Remarkably, studies from Yu et al\textsuperscript{159} showed that the number of mutations was 3 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,\textsuperscript{160} including changes to posttranslational modifications of histones,\textsuperscript{161} 5-hydroxymethylation,\textsuperscript{162} and, most notably, DNA methylation, which 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,\textsuperscript{162} but DNA hypomethylation contributes to chromosome instability\textsuperscript{163} and activation of retrotransposon sequences and repetitive elements such as LINE-1\textsuperscript{164} and Alu.\textsuperscript{165} DNA hypomethylation also affects
critical chromosome regions, such as the subtelomeric and pericentromeric regions. Exposure to ambient air pollution, whether short-term or long-term, is associated with abnormal DNA methylation. Other studies have also shown that human epithelial cells exposed to PM\textsubscript{2.5} are more susceptible to hypomethylation and transcriptional activation of several genes and microRNAs (miRs), modifying cancer-related signaling pathways. PM\textsubscript{2.5} is also able to induce changes in long-noncoding RNAs, such as loc146880, through reactive oxygen species (ROS), promoting autophagy and malignancy of lung cells.

Transcriptional changes in miRs have also been described in human bronchial cells exposed to ambient PM\textsubscript{2.5}, including the downregulation of miR-182 and miR-185, potentially deregulating oncogenes (SLC30A1, SERPINB2, and AKR1C1) and facilitating neoplastic transformation. Other studies have found that dysregulation of actin cytoskeleton and down-regulation of miR-802 expression is present in the A549 cell line after PM exposure. Human bronchial epithelial cells exposed to various concentrations of PM\textsubscript{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. Several other studies have found that air pollution compounds induce the release of proinflammatory cytokines, including IL-6, TNF-\(\alpha\), and granulocyte-macrophage colony-stimulating factor, resulting in low-grade, chronic inflammation in the airway and throughout the body.

Another critical driver of carcinogenesis associated with air pollution is oxidative stress, which is characterized by an increase in free radicals (ROS and reactive nitrogen species). The most studied air pollutants concerning the intracellular formation of free radicals are O\textsubscript{3}, nitrogen oxides (NO and NO\(_2\)), and metals. Early studies demonstrated that mouse fibroblasts exposed to ROS could lead to carcinogenic transformation of cells. ROS are considered proneoplastic factors: they stimulate cell proliferation, invasiveness, angiogenesis, and metastasis, and they inhibit apoptosis.

Air pollution-related carcinogenesis is expected to follow a multistep process that includes initiation, promotion, and progression (Fig. 4). Although not completely
understood, individual and time-dependent doses influence 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 through direct or indirect (inflammation and oxidative stress) damage, inducing TSG inactivation and the activation of oncoproteins, cell cycle alterations dependent on TP53 activation, activation of energetic dysregulation, chromosome instability, the inhibition of apoptosis, and the induction of cell proliferation in somatic cells. 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 the IARC as a causal agent (Group 1 carcinogen) for lung cancer. Despite this, the US Environmental Protection Agency (EPA), in its most recent review of the evidence on PM (the Integrated Science Assessment), found that the weight-of-evidence indicated that PM2.5 is only likely to be causal. Nonetheless, when the IARC conclusion was published, 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 caused by outdoor air pollution is challenging because there are typically numerous combustion sources with emissions, including both specific carcinogens and other agents, that may increase cancer risk. On the basis of understanding carcinogenesis and considering the agents known to be in air pollution, a linear nonthreshold relationship between exposure and risk can be reasonably assumed. From a regulatory perspective, this suggests that any exposure conveys some risk and that lowering exposure to the maximum extent feasible should be the goal.

A useful starting point for considering the management of cancer risk caused by air pollution is the definition of acceptable risk by Lowrance, who described it as a thing is safe if the risks are judged as acceptable. For lung cancer, using PM as the indicator of exposure, the risks have been quantified with sufficient certainty for carrying out a risk assessment, but any consensus societal judgment regarding 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 (see above). The global proportion of lung cancer deaths attributable to ambient PM2.5 is second only to that of tobacco smoking.

Interventions to reduce air pollution exposure may be considered at various scales, including the individual, community, industrial, and broader regional scales. 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 because adverse effects of air pollution have been demonstrated at levels well below current NAAQS and, for some adverse effects, including lung cancer, nonthreshold-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. Therefore, 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 findings to advocate for accurate air pollution monitoring, tighter air-quality management, and 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 to improvements in health. Further research to evaluate the effectiveness of specific interventions in low-income and middle-income countries, where air quality continues to worsen, is needed. 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. Effects in terms of reducing lung cancer incidence, as noted above, require long-term and sustained intervention over multiple years and decades. Although potential effects on cancer survival postdiagnosis have also been suggested, further research is required to evaluate the effects of reducing patient-level outdoor air pollution exposure on survival.

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. Specific interventions may relate to destination accessibility, employment distribution, residential density, availability and cost of parking, and enhancement of active travel networks. Interventions related to 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 effects of outdoor air pollution. The key role of the medical and health care community in raising public and patient awareness, including the monitoring of local air quality indices and guidelines, motivating action on air quality management, and involvement in the policy process, has been described.

The support of the medical and health care community in the further conduct of relevant etiological and innovative intervention studies is also needed. There is also increasing interest in the use of green spaces and green infrastructure in air pollution mitigation, although further research in terms of specific infrastructure deployment is needed to optimize health benefits, reduce unintended consequences, and develop evidence-based guidelines for implementation.

Individual-level interventions have also been described, including the use of personal respirators, although the effects on exposure and health are difficult to evaluate in the general population. Reductions in exposure to PM\textsubscript{2.5} and other particle pollutants have been reported in some studies, although the overall evidence remains inadequate. The use of personal respirators in combination with avoidance behavior, such as route selection, for example, has been recommended. Reductions in indoor levels of PM\textsubscript{2.5} have been observed with the use of some household filtration systems. 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 experienced the highest, although those results may not be applicable to other areas. Personal mobile monitoring technologies, including mobile phones, may support avoidance behaviors in the future.

Finally, the suggestion of possible greater-than-additive joint effects of cigarette smoking and PM\textsubscript{2.5} concentrations for lung cancer mortality may also suggest that public health efforts in tobacco control and air-quality management may result in greater-than-expected reductions in lung cancer rates because of the reduction in cases attributable to the interaction of both factors.

**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 multilevel 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 along with research on the effectiveness of specific interventions for cancer prevention, particularly in low-income and middle-income countries.

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