CA CANCER J CLIN 2020;70:460–479

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

Michelle C. Turner, PhD [1,2,3,4]; Zorana J. Andersen, PhD [5]; Andrea Baccarelli, MD, MPH, PhD [6]; W. Ryan Diver, MSPH [7]; Susan M. Gapstur, PhD [7]; C. Arden Pope, III, PhD [8]; Diddier Prada, MD, PhD [6,9]; Jonathan Samet, MD, MS [10]; George Thurston, ScD [11]; Aaron Cohen, DSc [12,13]

[1]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain; [2]Pompeu Fabra University, Barcelona, Spain; [3]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain; [4]McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario Canada; [5]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [6]Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, New York; [7]Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, Georgia; [8]Department of Economics, Brigham Young University, Provo, Utah; [9]National Cancer Institute, Mexico City, Mexico; [10]Colorado School of Public Health, Aurora, Colorado; [11]New York University School of Medicine, New York, New York; [12]Health Effects Institute, Boston, Massachusetts; [13]Institute for Health Metrics and Evaluation, Seattle, Washington.

Corresponding Author: Michelle C. Turner, PhD, Barcelona Institute for Global Health, Barcelona Biomedical Research Park (PRBB), Room 186, Doctor Aiguader, 88, 08003 Barcelona, Spain (michelle.turner@isglobal.org).

DISCLOSURES: Michelle C. Turner is funded by a Ramón y Cajal fellowship (RYC-2017-01892) from the Spanish Ministry of Science, Innovation, and Universities and is co-funded by the European Social Fund. Barcelona Institute for Global Health (ISGlobal) acknowledges support from the Spanish Ministry of Science and Innovation through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S) and support from the Generalitat de Catalunya through the Research Centers of Catalonia [CERCA] Program. George Thurston was supported in part by center grant ES 00260 from the National Institute of Environmental Health Sciences. The remaining authors report no conflicts of interest.

doi: 10.3322/caac.21632. Available online at cacancerjournal.com

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.**

Keywords: breast cancer, cancer survival, lung cancer, particulate matter

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.[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). 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.[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 (eg, sulfuric acid [H_2SO_4]) and nitrate (eg, 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 $PM_{2.5}$ 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 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[5,6], 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: $PM_{2.5}$, 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 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 SO_2 and NO_x 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.[7]

PM is commonly characterized according to the following size fractions:

- PM_{10} (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. PM_{10} also includes all the fractions described below:
- $PM_{2.5\text{-}10}$, also known as coarse fraction particles (PM with an aerodynamic diameter >2.5 μm but ≤10 μm);
- $PM_{2.5}$, 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, $PM_{2.5}$ 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 $PM_{2.5}$ contains 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, although some constituents, such as lead (Pb) concentration, have been separately regulated. Whereas UFPs usually make up only a small fraction of $PM_{2.5}$ mass, they 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.[8]

$PM_{2.5}$ 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

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 (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	
Suspended PM	
Fine PM ($PM_{2.5}$)	Outdoor: Fossil fuel combustion, gas-to-particle conversion, biomass burning
	Indoor: Biomass fuel combustion, tobacco smoking
Coarse PM ($PM_{2.5\text{-}10.0}$)	Outdoor: Dust storms, windblown soil, pollens
	Indoor: Mold spores, resuspended dust
Nitrogen dioxide (NO_2)	Outdoor: Fossil fuel combustion (eg, 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
	Indoor: Home applications of herbicides, insecticides, fungicides, etc
Ammonia	Outdoor: Livestock yards
	Indoor: Metabolic activity, cleaning products
Hazardous air pollutants (HAPs) (eg, benzene, 1,3-butadiene, formaldehyde, acids)	Outdoor: Incomplete combustion, chemical processing
	Indoor: Solvent use

Adapted from: World Health Organization (WHO) & Global Environment Monitoring System. Estimating Human Exposures to Air Pollutants. WHO Offset Publication No. 69. WHO; 1982[5]; 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.[6]

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).[9] Indeed, coal combustion has been found to account for approximately one-quarter of the world's emissions of both As and mercury (Hg).[10,11] $PM_{2.5}$ can remain in the atmosphere for days to weeks and travel through the atmosphere hundreds to thousands of kilometers[7]; 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, which is 4-fold greater than the WHO's health-based world air-quality guideline of 10 $\mu g/m^3$ (Fig. 1).[1,12] Ninety-two percent of the global population worldwide lives in areas where ambient $PM_{2.5}$ concentrations exceed the WHO

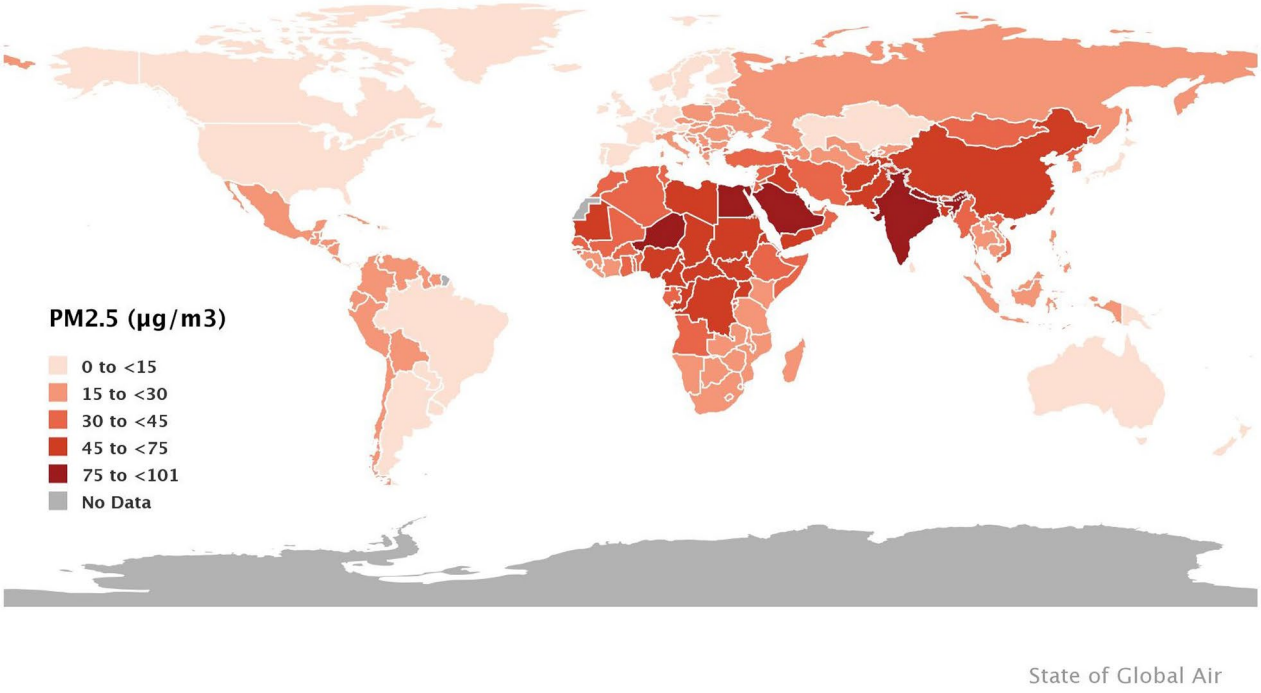

FIGURE 1. Average Annual Population-Weighted Fine Particulate Matter Concentrations in 2017. $PM_{2.5}$ indicates particulate matter (PM) particles ≤2.5 µm in aerodynamic diameter. Source: Health Effects Institute State of Global Air 2019.[12] Data source: Global Burden of Disease Study, 2017[1]; Institute for Health Metrics and Evaluation (IHME) Study, 2018.[13]

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/m^3. Among the 10 largest countries by population, population-weighted ambient $PM_{2.5}$ in 2017 varied by >12-fold, from 7 µg/m^3 in the United States to 91 µg/m^3 in India. For NO_2, 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.[14] 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 O_3 concentration worldwide was 57 ppb in 2017, which was unchanged from 1990.[12]

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.[15] In the United States, approximately 234,030 new lung cancer cases, and 154,050 deaths were estimated in the same year.[16] Lung cancer is highly fatal, with an overall 5-year survival rate of only 18%.[16] Rates of lung cancer incidence and mortality vary substantially within and between countries, depending

largely on historical patterns of cigarette smoking,[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/Polynesia, Eastern Asia, and Eastern Europe and, among women, in North America, Northern and Western Europe, and Australia/New Zealand.[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.[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.[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.[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.[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 $PM_{2.5}$ exposure, was particularly influential.[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[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.[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.[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 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations and, in 9 studies of PM_{10}, an 8% (95% CI, 0%-17%) increase in risk per 10 $\mu g/m^3$.[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 $\mu g/m^3$ $PM_{2.5}$) was observed with similar findings again in studies from different regions (Fig. 2).[18-20,29-60] When extrapolated to the global population-weighted mean annual average $PM_{2.5}$ concentration (46 $\mu g/m^3$) relative to the WHO health-based world air-quality guideline (10 $\mu g/m^3$), 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_2 exposure, a marker of traffic-related air pollution, for lung cancer mortality (relative risks [RRs], 1.04-1.05 per 10 $\mu g/m^3$), although results were attenuated somewhat in studies that adjusted for individual-level cigarette smoking status and were no longer significant.[61,62] Additional research in Asia and in other understudied and more highly polluted regions is needed,[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 $PM_{2.5}$ and lung cancer mortality among 635,539 US National Health Interview Survey (NHIS) participants (hazard ratio [HR] per 10 $\mu g/m^3$, 1.13; 95% CI, 1.00-1.26; n = 7420 lung

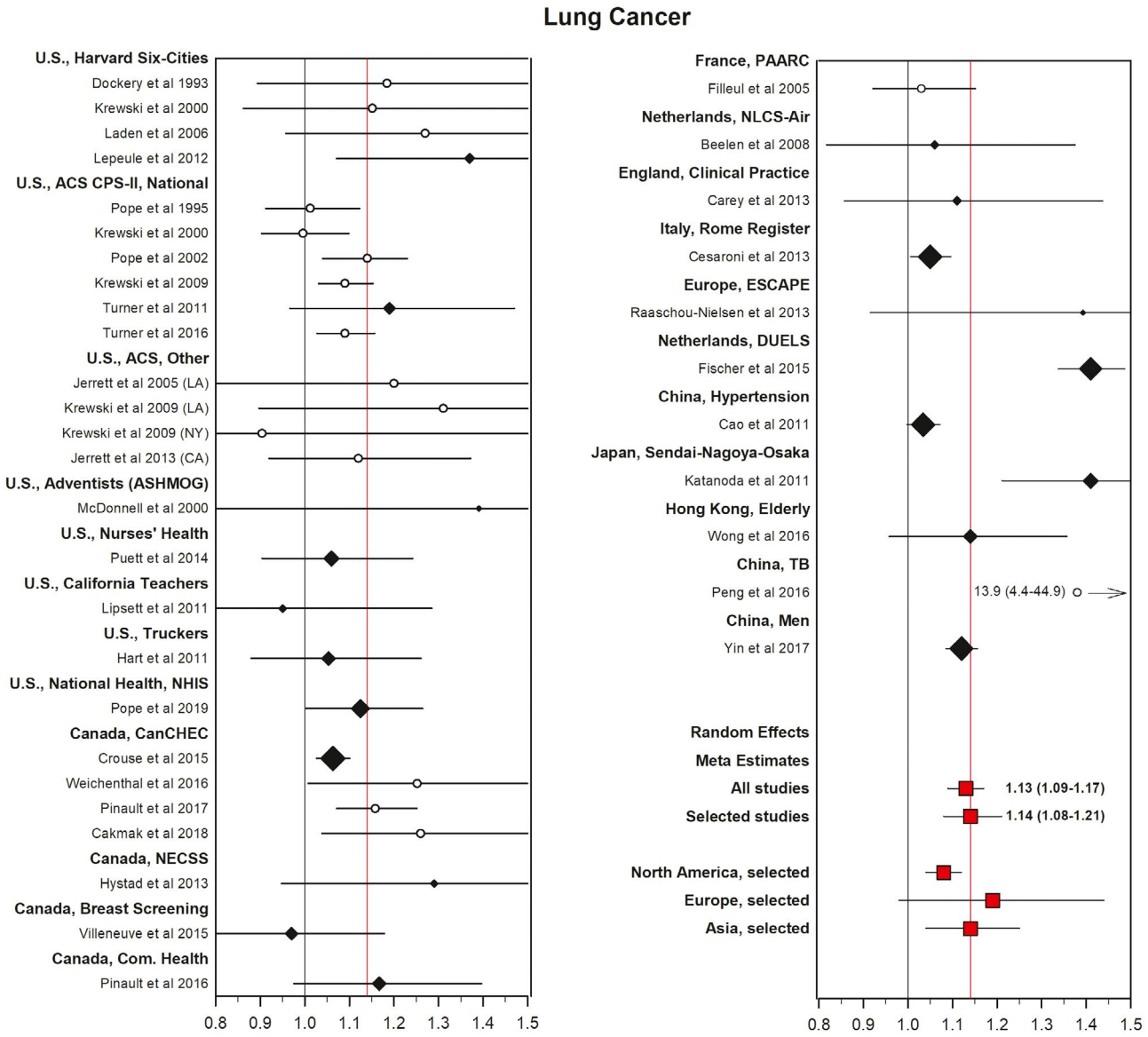

FIGURE 2. Estimated Adjusted Hazard Ratios (HRs) and 95% Confidence Intervals for Lung Cancer Mortality per 10 μg/m^3 Elevation in $PM_{2.5}$ From Multiple Cohort Studies. Black diamonds represent selected studies, with the size of the diamond proportional to the relative weight in the random effect estimate using selected studies. The red squares represent random effects meta-estimates. The black line is a reference line at an HR of 1.00. The red line is a reference line at an HR equal to the random-effects meta-estimate using the selected studies. ACS indicates American Cancer Society; ACS CPS II, American Cancer Society Cancer Prevention Study II; ASHMOG, Adventist Health Air Pollution Study; CanCHEC, Canadian Census Health and Environment Cohort; Com. Health, Community Health; DUELS, Dutch Environmental Longitudinal Study; ESCAPE, European Study of Cohorts for Air Pollution Effects; NECSS, National Enhanced Cancer Surveillance System; NHIS, National Health Interview Survey; NLCS-Air, Netherlands Cohort Study on Diet and Cancer-Air Pollution Study; PAARC, French Air Pollution and Chronic Respiratory Diseases study; $PM_{2.5}$, particulate matter particles ≤2.5 μm in aerodynamic diameter; TB, tuberculosis. Source: Modified and updated 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.[60] Reprinted under a CC BY-NC-ND 4.0 Creative Commons license.

cancer deaths).[63] 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.[64] 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.[65] 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.[66] 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

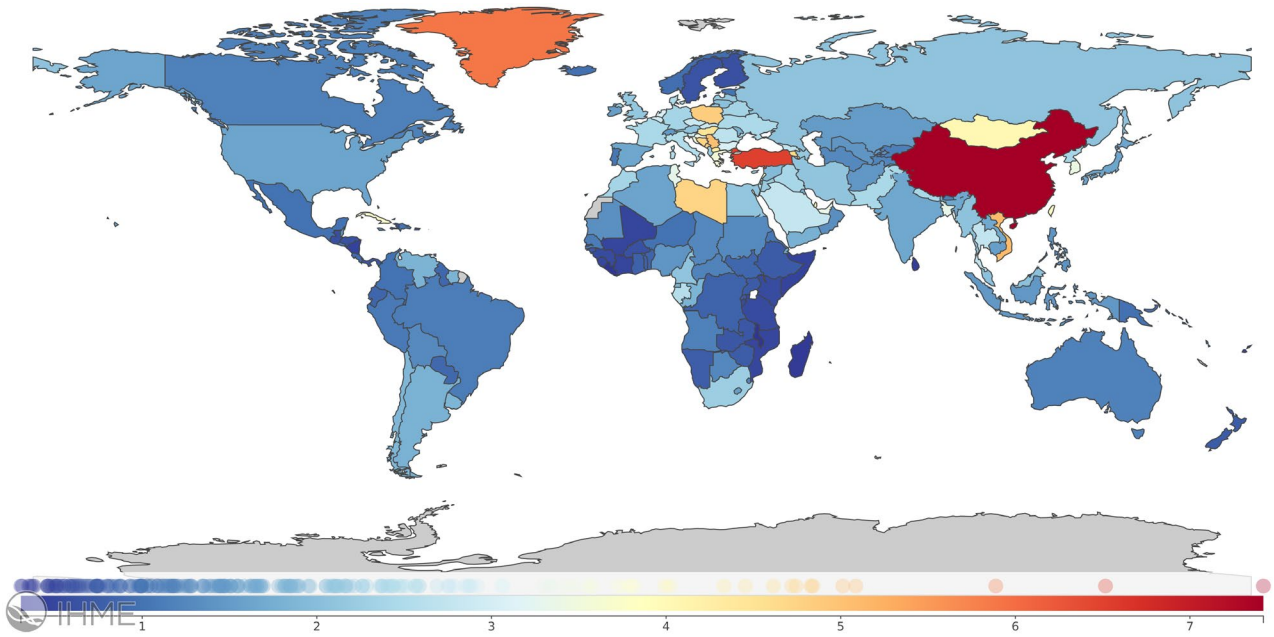

FIGURE 3. Global Age-Standardized $PM_{2.5}$-Attributable Trachea, Bronchus, and Lung Cancer Mortality Rates per 100,000 in 2017. $PM_{2.5}$ indicates particulate matter (PM) particles ≤2.5 μm in aerodynamic diameter. Source: Institute for Health Metrics and Evaluation (IHME). IHME Viz Hub. GBD Compare. University of Washington; 2020.[72]

mortality (HR per 10 μg/m^3 [60-month moving average], 1.33; 95% CI, 1.24-1.40).[67] There were also some significant adverse associations with O_3 and NO_2.[68,69] Although an analysis extended to 53 million Medicare beneficiaries reported no association of $PM_{2.5}$ and lung cancer mortality, there may have been confounding by cigarette smoking status in rural populations that were included.[70]

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 lung cancer deaths) in 2017, or 14.1% (95% 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,[71] 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 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).[72]

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.[73] 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,[28] results for both $PM_{2.5}$ and PM_{10} were somewhat stronger for adenocarcinoma (RR per 10 μg/m^3, 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 $PM_{2.5}$ 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 per 10 μg/m^3, 1.53; 95% CI, 0.93-2.53) and adenocarcinoma (HR per 10 μg/m^3, 1.44; 95% CI, 1.06-1.97).[74] 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 μg/m^3, 1.43; 95% CI, 1.11-1.84).[75] There was also an adverse association with adenocarcinoma (HR per 10 μg/m^3, 1.31; 95% CI, 0.87-1.97), which strengthened in participants who reported spending >1 hour per day outdoors.[76] There was also an adverse association of ambient PM_{10} 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/m^3, 1.28; 95% CI, 0.95-1.72), with somewhat stronger findings for squamous cell carcinoma (OR per 10 μg/m^3, 1.44; 95% CI, 0.90-2.29).[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/m^3, 1.14; 95% CI, 1.03-1.25).[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.[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/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.[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.[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.[44] 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.[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).[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.[82,83] There was also sufficient evidence in experimental animals for the carcinogenicity of condensates of gasoline engine exhaust.[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[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.[84] 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.[20] 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.[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.[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%).[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.[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.[23] Second-hand tobacco smoke has also been suggestively associated with many of these types of cancer.[73]

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.[87] 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.[17,82,88-91]

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.[6] 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 $PM_{2.5}$ and bladder cancer mortality (HR per 4.4 μg/m^3, 1.13; 95% CI, 1.03-1.23; n = 1324) but no association with NO_2 or O_3.[92] 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).[63] 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),[93] 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.[94] 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.[95]

Previous studies have suggested some adverse associations of both NO_2 and NO_x and breast cancer, with fewer clear associations with PM.[96] Among most recent studies, in an analysis of 47,433 women in the US Sister Study, there were adverse associations of both NO_2 (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 = 2848).[97] There were also adverse associations of $PM_{2.5}$ concentrations characterized by low S component fractions 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 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.[98] In an 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 meters of major roads, with stronger associations for NO_x and NO_2 among African American and Japanese American women overall.[99] 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, range 1.13-1.17) and the risk of incident premenopausal, but not postmenopausal, disease.[100,101] However, results from other recent studies have reported no clear associations with incident breast cancer risk.[66,102,103] 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.[104] 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.[105] Results of studies of mammographic density, a breast cancer risk factor, are also mixed.[106-108]

For other types of cancer, there are fewer studies and the results are also inconsistent. Although there was an adverse association of NO_x 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/m^3, 2.28; 95% CI, 1.25-4.19; n = 95),[109] the findings were not replicated in subsequent studies.[110,111] There was an adverse, but nonsignificant, 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 nonmalignant (n = 366), brain tumor incidence in the ESCAPE study, although there were no data on brain tumor histology or morphology.[112] An 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.[113] 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 tumor incidence in an 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 = 1400).[114]

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).[92] 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.[63] 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.[115,116] Total $PM_{2.5}$ and $PM_{2.5}$ S components were also associated with incident gastric cancer risk.[117,118] 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.[57] 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.[119] 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).[120] $PM_{2.5}$ was also related to reduced HCC survival.[121]

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.[92] 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.[122] 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.[63] 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.[123] Studies in Denmark have reported no clear associations of ambient air pollutant exposure and incident NHL,[109,124] although, in one study, significant adverse associations of primary carbonaceous and secondary organic aerosols were observed.[125] 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).[126]

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.[127] 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.[128]

Despite these limitations, there is some suggestive evidence for an adverse association of traffic-related air pollution and acute childhood leukemia.[6,129-133] 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.[6] 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.[130] 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.[132] 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.[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,[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.[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.[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.[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.[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).[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 $\mu g/m^3$, 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).[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.[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.[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.[143] Air pollution contains several mutagens and carcinogens, including PAHs (eg, benzo[a]pyrene and polar compounds),[144] dioxins,[145] sulfur-containing compounds (SO_3, H_2SO_4),[146] and 3-nitrobenzanthrone.[147] PAHs are a class of compounds associated with human cancer risk because of their ability to generate DNA adducts.[148] One meta-analysis has confirmed the nonlinear dose-response relationship between air pollution PAH and DNA adducts,[149] and several studies have indicated that carcinogen-DNA adducts are closely associated with cancer risk.[150-152] However, an individual's repair capacity may determine whether DNA adducts are eliminated by the repair machinery, potentially inducing DNA mutations.[153]

Gene mutations and gene silencing are particularly relevant during carcinogenic processes, when they can affect tumor suppressor genes (TSGs).[154] Several studies have shown that there are fractions of outdoor air that contain mutagenic particulate and volatile matter.[155] Also, mice exposed to industrial ambient air pollution showed higher heritable mutations at tandem-repeat DNA loci.[156] *TP53* is a TSG involved in cell proliferation, apoptosis, and damage repair, and its mutation/inactivation contributes to the pathogenesis of lung cancer.[157] Studies have shown that low-dose $PM_{2.5}$ may induce epigenetic silencing of *TP53* in human alveolar epithelial cells.[158] Remarkably, studies from Yu et al[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,[160] including changes to posttranslational modifications of histones,[161] 5-hydroxymethylation,[160] 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,[162] but DNA hypomethylation contributes to chromosome instability[163] and activation of retrotransposon sequences and repetitive elements such as LINE-1[164] and Alu.[165] DNA hypomethylation also affects

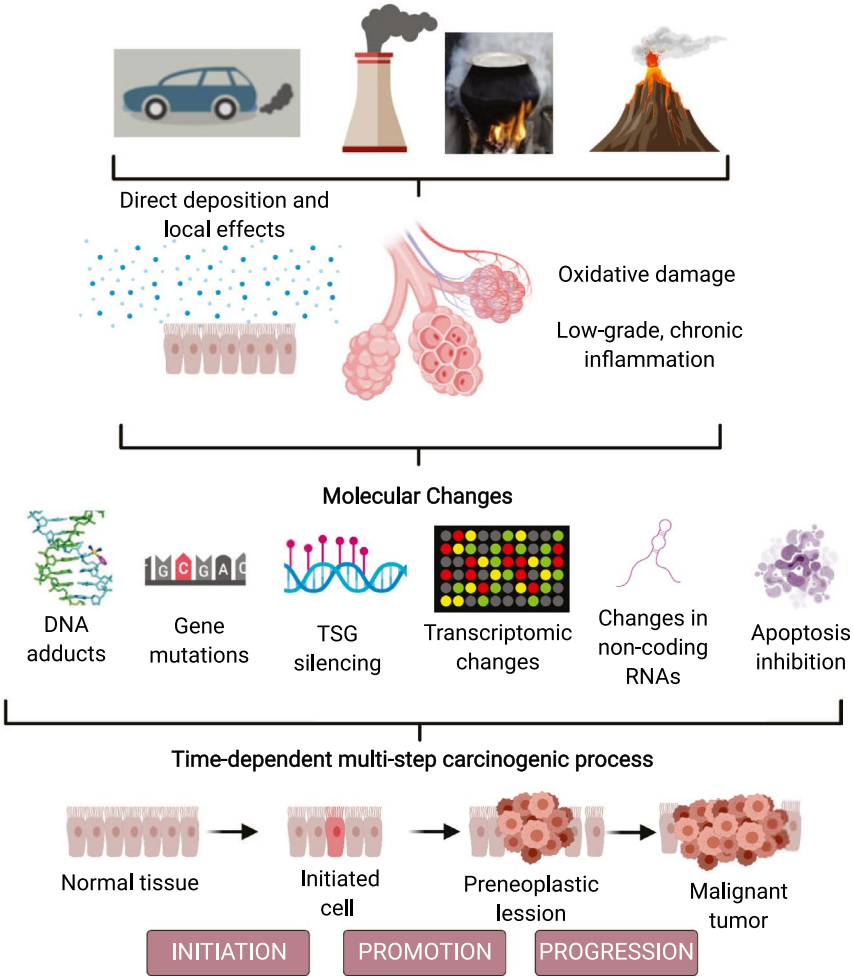

FIGURE 4. Air Pollution-Related Cancer: Potential Pathways and Mechanisms. TSG indicates tumor-suppressor genes.

critical chromosome regions, such as the subtelomeric and pericentromeric regions.[166] Exposure to ambient air pollution, whether short-term or long-term, is associated with abnormal DNA methylation.[167-169] 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 microRNAs (miRs), modifying cancer-related signaling pathways.[170] $PM_{2.5}$ 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.[171]

Transcriptional changes in miRs have also been described in human bronchial cells exposed to ambient $PM_{2.5}$, including the downregulation of miR-182 and miR-185, potentially deregulating oncogenes (*SLC30A1*, *SERPINB2*, and *AKR1C1*) and facilitating neoplastic transformation.[172] 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.[173] 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.[174] Several other studies have found that air pollution compounds induce the release of proinflammatory cytokines, including IL-6, TNF-α, and granulocyte-macrophage colony–stimulating factor, resulting in low-grade, chronic inflammation in the airway and throughout the body.[175-177] Another critical driver of carcinogenesis associated with air pollution is oxidative stress,[178] 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_3,[179] nitrogen oxides (NO and NO_2), and metals.[180] Early studies demonstrated that mouse fibroblasts exposed to ROS could lead to carcinogenic transformation of cells.[181] ROS are considered proneoplastic factors: they stimulate cell proliferation, invasiveness, angiogenesis, and metastasis, and they inhibit apoptosis.[182]

Air pollution-related carcinogenesis is expected to follow a multistep process that includes initiation, promotion, and progression (Fig. 4).[183] 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 oncogenes,[184] cell cycle alterations dependent on *TP53* activation,[185] activation of energetic dysregulation,[186] chromosome instability,[187,188] the inhibition of apoptosis,[189] and the induction of cell proliferation in somatic cells.[190] 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.[6] 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 $PM_{2.5}$ is only *likely to be causal*.[191] Nonetheless, when the IARC conclusion was published,[192] 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.[28,193,194] 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,[195] 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 $PM_{2.5}$ 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.[196] 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.[25,26,197-200] Further research to evaluate the effectiveness of specific interventions in low-income and middle-income countries, where air quality continues to worsen, is needed.[197] 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.[201,202] 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.[85]

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.[203] Specific interventions may relate to destination accessibility, employment distribution, residential density, availability and cost of parking, and enhancement of active travel networks.[204] 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.[199,205] 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,[202] motivating action on air quality management, and involvement in the policy process, has been described.[201,203,205,206] The support of the medical and health care community in the further conduct of relevant etiological and innovative intervention studies is also needed.[203] 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.[207]

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.[201,208] Reductions in exposure to $PM_{2.5}$ and other particle pollutants have been reported in some studies,[209] although the overall evidence remains inadequate.[208] The use of personal respirators in combination with avoidance behavior, such as route selection, for example, has been recommended.[208] Reductions in indoor levels of $PM_{2.5}$ have been observed with the use of some household filtration systems.[210,211] 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.[212] Personal mobile monitoring technologies, including mobile phones, may support avoidance behaviors in the future.[213]

Finally, the suggestion of possible greater-than-additive joint effects of cigarette smoking and $PM_{2.5}$ 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.[84]

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. ■

Acknowledgements: We thank Nathan Coleman for helpful comments on an earlier version of the article and Julia Knox for contributing to an earlier draft of the section on biological mechanisms.

References

1. Global Burden of Disease (GBD) 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1923-1994.
2. Lelieveld J, Evans J, Fnais M, et al. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature*. 2015;525:367-371.
3. Santos LR, Alves-Correia M, Camara M, et al. Multiple victims of carbon monoxide poisoning in the aftermath of a wildfire: a case series. *Acta Med Port*. 2018;31:146-151.
4. Thurston G. Outdoor air pollution: sources, atmospheric transport, and human health effects. In: Quah SA, Cockerham WC, eds. International Encyclopedia of Public Health. 2nd ed. 2017;367-377.
5. World Health Organization (WHO) & Global Environment Monitoring System. Estimating Human Exposure to Air Pollutants. WHO Offset Publication No. 69. WHO; 1982.
6. International Agency for Research on Cancer (IARC). Outdoor Air Pollution. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 109. IARC; 2013.
7. Lall R, Thurston G. Identifying and quantifying transported vs. local sources of New York City $PM_{2.5}$ fine particulate matter air pollution. *Atmos Environ*. 2006;40(suppl 2):S333-S346.
8. Leikauf GD, Kim SH, Jang AS. Mechanisms of ultrafine particle-induced respiratory health effects. *Exp Mol Med*. 2020;52:329-337.
9. National Research Council (NRC). Controlling Airborne Particles. The National Academies Press; 1980.
10. Matschullat J. Arsenic in the geosphere—a review. *Sci Total Environ*. 2000;249:297-312.
11. United Nations (UN). Global Mercury Assessment 2018. UN Environment Programme, Chemicals and Health Branch; 2019.
12. Health Effects Institute. State of Global Air 2019. Special Report. Health Effects Institute; 2019.

13. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington; 2018. Accessed August 5, 2020. http://vizhub.healthdata.org/gbd-compare
14. Geddes JA, Martin RV, Boys BL, van Donkelaar A. Long-term trends worldwide in ambient NO2 concentrations inferred from satellite observations. *Environ Health Perspect.* 2016;124:281-289.
15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424.
16. American Cancer Society. Cancer Facts & Figures 2018. American Cancer Society; 2018.
17. Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: an update from the IARC Monographs. *Occup Environ Med.* 2018;75:593-603.
18. Krewski D, Jerrett M, Burnett RT, et al. Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality. Health Effects Institute; 2009.
19. Turner MC, Krewski D, Pope CA III, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never smokers. *Am J Respir Crit Care Med.* 2011;184:1374-1381.
20. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol.* 2013;14:813-822.
21. Doll R, Hill AB. Smoking and carcinoma of the lung. *Br Med J.* 1950;2:739-748.
22. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Household Use of Solid Fuels and High-Temperature Frying. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 95. International Agency for Research on Cancer; 2006.
23. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. A Review of Human Carcinogens. Part E: Personal Habits and Indoor Combustions. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 100E. International Agency for Research on Cancer; 2009.
24. Chafe ZA, Brauer M, Klimont Z, et al. Household cooking with solid fuels contributes to ambient PM2.5 air pollution and the burden of disease. *Environ Health Perspect.* 2014;122:1314-1320.
25. Global Burden of Disease Major Air Pollution Sources (GBD MAPS) Working Group. Burden of Disease Attributable to Coal-Burning and Other Major Sources of Air Pollution in China. Special Report 20. Health Effects Institute; 2016.
26. Global Burden of Disease Major Air Pollution Sources (GBD MAPS) Working Group. Burden of Disease Attributable to Major Air Pollution Sources in India. Special Report 21. Health Effects Institute; 2018.
27. Health Effects Institute (HEI), Household Air Pollution-Ghana Working Group. Contribution of Household Air Pollution to Ambient Air Pollution in Ghana. Communication 19. Health Effects Institute; 2019.
28. Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. *Environ Health Perspect.* 2014;122:906-911.
29. Dockery DW, Pope CA, Xu X, et al. An association between air pollution and mortality in six US cities. *N Engl J Med.* 1993;329:1753-1759.
30. Krewski D, Burnett RT, Goldberg MS, et al. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Health Effects Institute; 2000.
31. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med.* 2006;173:667-672.
32. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect.* 2012;120:965-970.
33. Pope CA, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am J Respir Crit Care Med.* 1995;151:669-674.
34. Pope CA, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA.* 2002;287:1132-1141.
35. Turner MC, Jerrett M, Pope CA III, et al. Long-term ozone exposure and mortality in a large prospective study. *Am J Respir Crit Care Med.* 2016;193:1134-1142.
36. Jerrett M, Burnett RT, Ma R, et al. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology.* 2005;16:727-736.
37. Jerrett M, Burnett RT, Beckerman BS, et al. Spatial analysis of air pollution and mortality in California. *Am J Respir Crit Care Med.* 2013;188:593-599.
38. McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. Relationships of mortality with the fine and coarse fractions of long-term ambient PM 10 concentrations in nonsmokers. *J Expo Sci Environ. Epidemiol.* 2000;10:427.
39. Puett RC, Hart JE, Yanosky JD. Particulate matter air pollution exposure, distance to road, and incident lung cancer in the Nurses' Health Study cohort. *Environ Health Perspect.* 2014;122:926-932.
40. Lipsett LJ, Ostro LD, Reynolds P, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med.* 2011;184:828-835.
41. Hart JE, Garshick E, Dockery DW, et al. Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med.* 2011;183:73-78.
42. Pope CA, Lefler JS, Ezzati M, et al. Mortality risk and fine particulate air pollution in a large, representative cohort of US adults. *Environ Health Perspect.* 2019;127:077007.
43. Crouse DL, Peters PA, Hystad P, et al. Ambient PM2.5, O3, and NO2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census health and environment cohort (CanCHEC). *Environ Health Perspect.* 2015;123:1180-1186.
44. Weichenthal S, Crouse DL, Pinault L, et al. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). *Environ Res.* 2016;146:92-99.
45. Pinault L, Weichenthal S, Crouse DL, et al. Associations between fine particulate matter and mortality in the 2001 Canadian Census health and environment cohort. *Environ Res.* 2017;159:406-415.
46. Cakmak S, Hebbern C, Pinault L, et al. Associations between long-term PM2.5 and ozone exposure and mortality in the Canadian Census Health and Environment Cohort (CANCHEC), by spatial synoptic classification zone. *Environ Int.* 2018;111:200-211.
47. Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M. Long-term residential exposure to air pollution and lung cancer risk. *Epidemiology.* 2013;24:762-772.

48. Villeneuve PJ, Weichenthal SA, Crouse D, et al. Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. *Epidemiology.* 2015;26:536-545.
49. Pinault L, Tjepkema M, Crouse DL, et al. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environ Health.* 2016;15:18.
50. Filleul L, Rondeau V, Vandentorren S, et al. Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup Environ Med.* 2005;62:453-460.
51. Beelen R, Hoek G, van Den Brandt PA, et al. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect.* 2008;116:196-202.
52. Carey IM, Atkinson RW, Kent AJ, et al. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med.* 2013;187:1226-1233.
53. Cesaroni G, Badaloni C, Gariazzo C, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect.* 2013;121:324-331.
54. Fischer PH, Marra M, Ameling CB, et al. Air pollution and mortality in seven million adults: the Dutch Environmental Longitudinal Study (DUELS). *Environ Health Perspect.* 2015;123:697-704.
55. Cao J, Yang C, Li J, et al. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater.* 2011;186(2-3):1594-1600.
56. Katanoda K, Sobue T, Satoh H, et al. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in *Japan*. *J Epidemiol.* 2011;21:132-143.
57. Wong CM, Tsang H, Lai HK, et al. Cancer mortality risks from long-term exposure to ambient fine particle. *Cancer Epidemiol Biomarkers Prev.* 2016;25:839-845.
58. Peng Z, Liu C, Xu B, Kan H, Wang W. Long-term exposure to ambient air pollution and mortality in a Chinese tuberculosis cohort. *Sci Total Environ.* 2017;580:1483-1488.
59. Yin P, Brauer M, Cohen A, et al. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. *Environ Health Perspect.* 2017;125:117002.
60. 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.
61. Atkinson RW, Butland BK, Anderson HR, Maynard RL. Long-term concentrations of nitrogen dioxide and mortality. *Epidemiology.* 2018;29:460-472.
62. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. *Environ Health Perspect.* 2015;123:1107-1112.
63. Coleman NC, Burnett RT, Higbee JD, et al. Cancer mortality risk, fine particulate air pollution, and smoking in a large, representative cohort of US adults. *Cancer Causes Control.* 2020;31:767-776.
64. Hvidtfeldt UA, Geels C, Sorensen M, et al. Long-term residential exposure to PM2.5 constituents and mortality in a Danish cohort. *Environ Int.* 2019;133:105268.
65. Klompmaker JO, Hoek G, Bloemsma LD, et al. Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. *Environ Int.* 2020;134:105341.
66. Bai L, Shin S, Burnett RT, et al. Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the Ontario Population Health and Environment Cohort. *Int J Cancer.* 2020;146:2450-2459.
67. Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-term PM2.5 exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol.* 2017;186:961-969.
68. Eum KD, Kazemiparkouhi F, Wang B, et al. Long-term NO2 exposures and cause-specific mortality in American older adults. *Environ Int.* 2019;124:10-15.
69. Kazemiparkouhi F, Eum KD, Wang B, Manjourides J, Suh HH. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. *J Expo Sci Environ Epidemiol.* 2020;30:650-658.
70. Wang B, Eum KD, Kazemiparkouhi F, et al. The impact of long-term PM2.5 exposure on specific causes of death: exposure-response curves and effect modification among 53 million U.S. Medicare beneficiaries. *Environ Health.* 2020;19:20.
71. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of cause-specific mortality associated with $PM_{2.5}$ air pollution in the United States. *JAMA Netw Open.* 2019;2:e1915834.
72. Institute for Health Metrics and Evaluation (IHME). IHME Viz Hub. GBD Compare. University of Washington; 2020. Accessed April 29, 2020. vizhub.healthdata.org/gbd-compare/
73. US Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
74. Tomczak A, Miller AB, Weichenthal SA, et al. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. *Int J Cancer.* 2016;139:1958-1966.
75. Gharibvand L, Lawrence Beeson W, Shavlik D, et al. The association between ambient fine particulate matter and incident adenocarcinoma subtype of lung cancer. *Environ Health.* 2017;16:71.
76. Gharibvand L, Shavlik D, Ghamsary M, et al. The association between ambient fine particulate air pollution and lung cancer incidence: results from the AHSMOG-2 study. *Environ Health Perspect.* 2017;125:378-384.
77. Consonni D, Carugno M, De Matteis S, et al. Outdoor particulate matter (PM10) exposure and lung cancer risk in the EAGLE study. *PLoS One.* 2018;13:e0203539.
78. Moon DH, Kwon SO, Kim SY, Kim WJ. Air pollution and incidence of lung cancer by histological type in Korean adults: a Korean National Health Insurance Service health examinee cohort study. *Int J Environ Res Public Health.* 2020;17:915.
79. US National Academy of Sciences, Engineering, and Medicine. Using 21st Century Science to Improve Risk-Related Evaluations. The National Academies Press; 2017.
80. Thurston GD, Ito K, Lall R, et al. NPACT Study 4. Mortality and Long-Term Exposure to $PM_{2.5}$ and Its Components in the American Cancer Society's Cancer Prevention Study II Cohort. Research Report 177. In: Lippman M, Chen LC, Gordon T, Ito K, Thurston GD, eds. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components. Research Report 177. Health Effects Institute; 2013:127-166.
81. Raaschou-Nielsen O, Beelen R, Wang M, et al. Particulate matter air pollution components and risk for lung cancer. *Environ Int.* 2016;87:66-73.

82. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Diesel and Gasoline Engine Exhausts and Some Nitroarenes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 105. International Agency for Research on Cancer; 2014.
83. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst.* 2011;103:1827-1839.
84. Turner MC, Cohen A, Jerrett M, et al. Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in Cancer Prevention Study II. *Am J Epidemiol.* 2014;180:1145-1149.
85. Eckel SP, Cockburn M, Shu YH, et al. Air pollution affects lung cancer survival. *Thorax.* 2016;71:891-898.
86. Danesh Yazdi M, Wang Y, Di Q, Zanobetti A, Schwartz J. Long-term exposure to PM2.5 and ozone and hospital admissions of Medicare participants in the Southeast USA. *Environ Int.* 2019;130:104879.
87. Josyula S, Lin J, Xue X, et al. Household air pollution and cancers other than lung: a meta-analysis. *Environ Health.* 2015;14:24.
88. Guo J, Kauppinen T, Kyyronen P, et al. Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among Finnish workers exposed to diesel or gasoline engine exhaust. *Int J Cancer.* 2004;111:286-292.
89. Peters CE, Parent ME, Harris SA, et al. Occupational exposure to diesel and gasoline engine exhausts and the risk of kidney cancer in Canadian men. *Ann Work Expo Health.* 2018;62:978-989.
90. Rota M, Bosetti C, Boccia S, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. *Arch Toxicol.* 2014;88:1479-1490.
91. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Arsenic, Metals, Fibres and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100C. International Agency for Research on Cancer; 2012.
92. Turner MC, Krewski D, Diver WR, et al. Ambient air pollution and cancer mortality in the Cancer Prevention Study-II. *Environ Health Perspect.* 2017;125:087013.
93. Castano-Vinyals G, Cantor KP, Tardon A, et al. Air pollution and risk of urinary bladder cancer in a case-control study in Spain. *Occup Environ Med.* 2008;65:56-60.
94. Turner MC, Gracia-Lavedan E, Cirac M, et al. Ambient air pollution and incident bladder cancer risk: updated analysis of the Spanish Bladder Cancer Study. *Int J Cancer.* 2019;145:894-900.
95. Pedersen M, Stafoggia M, Weinmayr G, et al. Is there an association between ambient air pollution and bladder cancer incidence? Analysis of 15 European cohorts. *Eur Urol Focus.* 2018;4:113-120.
96. White AJ, Bradshaw PT, Hamra GB. Air pollution and breast cancer: a review. *Curr Epidemiol Rep.* 2018;5:92-100.
97. White AJ, Keller JP, Zhao S, Carroll R, Kaufman JD, Sandler DP. Air pollution, clustering of particulate matter components, and breast cancer in the Sister Study: a U.S.-wide cohort. *Environ Health Perspect.* 2019;127:107002.
98. Niehoff NM, Gammon MD, Keil AP, et al. Airborne mammary carcinogens and breast cancer risk in the Sister Study. *Environ Int.* 2019;130:104897.
99. Cheng I, Tseng C, Wu J, et al. Association between ambient air pollution and breast cancer risk: the Multiethnic Cohort Study. *Int J Cancer.* 2020;146:699-711.
100. Goldberg MS, Villeneuve PJ, Crouse D, et al. Associations between incident breast cancer and ambient concentrations of nitrogen dioxide from a national land use regression model in the Canadian National Breast Screening Study. *Environ Int.* 2019;133:105182.
101. Villeneuve PJ, Goldberg MS, Crouse DL, et al. Residential exposure to fine particulate matter air pollution and incident breast cancer in a cohort of Canadian women. *Environ Epidemiol.* 2018;2:e021.
102. Hart JE, Bertrand KA, DuPre N, et al. Exposure to hazardous air pollutants and risk of incident breast cancer in the Nurses' Health Study II. *Environ Health.* 2018;17:28.
103. Andersen ZJ, Ravnskjaer L, Andersen KK, et al. Long-term exposure to fine particulate matter and breast cancer incidence in the Danish Nurse Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2017;26:428-430.
104. Amadou A, Praud D, Coudon T, et al. Chronic long-term exposure to cadmium air pollution and breast cancer risk in the French E3N Cohort. *Int J Cancer.* 2020;146:341-351.
105. DuPre NC, Hart JE, Holmes MD, et al. Particulate matter and traffic-related exposures in relation to breast cancer survival. *Cancer Epidemiol Biomarkers Prev.* 2019;28:751-759.
106. DuPre NC, Hart JE, Bertrand KA, Kraft P, Laden F, Tamimi RM. Residential particulate matter and distance to roadways in relation to mammographic density: results from the Nurses' Health Studies. *Breast Cancer Res.* 2017;19:124.
107. Yaghjyan L, Arao R, Brokamp C, et al. Association between air pollution and mammographic breast density in the Breast Cancer Surveillance Consortium. *Breast Cancer Res.* 2017;19:36.
108. Huynh S, von Euler-Chelpin M, Raaschou-Nielsen O, et al. Long-term exposure to air pollution and mammographic density in the Danish Diet, Cancer and Health cohort. *Environ Health.* 2015;14:31.
109. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, et al. Air pollution from traffic and cancer incidence: a Danish cohort study. *Environ Health.* 2011;10:67.
110. Poulsen AH, Sorensen M, Andersen ZJ, Ketzel M, Raaschou-Nielsen O. Air pollution from traffic and risk for brain tumors: a nationwide study in Denmark. *Cancer Causes Control.* 2016;27:473-480.
111. Jorgensen JT, Johansen MS, Ravnskjaer L, et al. Long-term exposure to ambient air pollution and incidence of brain tumours: the Danish nurse cohort. *Neurotoxicology.* 2016;55:122-130.
112. Andersen ZJ, Pedersen M, Weinmayr G, et al. Long-term exposure to ambient air pollution and incidence of brain tumor: the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Neuro Oncol.* 2018;20:420-432.
113. Wu AH, Wu J, Tseng C, et al. Association between outdoor air pollution and risk of malignant and benign brain tumors: the Multiethnic Cohort Study. *JNCI Cancer Spectr.* 2020;4:pkz107.
114. Weichenthal S, Olaniyan T, Christidis T, et al. Within-city spatial variations in ambient ultrafine particle concentrations and incident brain tumors in adults. *Epidemiology.* 2020;31:177-183.
115. Raaschou-Nielsen O, Pedersen M, Stafoggia M, et al. Outdoor air pollution and risk for kidney parenchyma cancer in 14 European cohorts. *Int J Cancer.* 2017;140:1528-1537.
116. Pedersen M, Andersen ZJ, Stafoggia M, et al. Ambient air pollution and primary liver cancer incidence in four European cohorts within the ESCAPE project. *Environ Res.* 2017;154:226-233.
117. Nagel G, Stafoggia M, Pedersen M, et al. Air pollution and incidence of cancers of the stomach and the upper aerodigestive

tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Int J Cancer.* 2018;143:1632-1643.

118. Weinmayr G, Pedersen M, Stafoggia M, et al. Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE). *Environ Int.* 2018;120:163-171.
119. Pan WC, Wu CD, Chen MJ, et al. Fine particle pollution, alanine transaminase, and liver cancer: a Taiwanese prospective cohort study (REVEAL-HBV). *J Natl Cancer Inst.* 2016;108:djv341.
120. VoPham T, Bertrand KA, Tamimi RM, Laden F, Hart JE. Ambient $PM_{2.5}$ air pollution exposure and hepatocellular carcinoma incidence in the United States. *Cancer Causes Control.* 2018;29:563-572.
121. Deng H, Eckel SP, Liu L, Lurmann FW, Cockburn MG, Gilliland FD. Particulate matter air pollution and liver cancer survival. *Int J Cancer.* 2017;141:744-749.
122. Teras LR, Diver WR, Deubler EL, et al. Residential ambient benzene exposure in the United States and subsequent risk of hematologic malignancies. *Int J Cancer.* 2019;145:2647-2660.
123. Winters N, Goldberg MS, Hystad P, et al. Exposure to ambient air pollution in Canada and the risk of adult leukemia. *Sci Total Environ.* 2015;526:153-176.
124. Taj T, Poulsen AH, Ketzel M, et al. Long-term exposure to air pollution and risk of non-Hodgkin lymphoma in Denmark: a population-based case-control study. *Int J Cancer*. Published online March 16, 2020. doi:10.1002/ijc.32978
125. Taj T, Poulsen AH, Ketzel M, et al. Long-term exposure to $PM_{2.5}$ and its constituents and risk of non-Hodgkin lymphoma in Denmark: a population-based case-control study. *Environ Res.* 2020;188:109762. doi:10.1016/j.envres.2020.109762
126. Raaschou-Nielsen O, Ketzel M, Harbo Poulsen A, Sorensen M. Traffic-related air pollution and risk for leukaemia of an adult population. *Int J Cancer.* 2016;138:1111-1117.
127. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol.* 2017;18:719-731.
128. Spycher BD, Feller M, Roosli M, et al. Childhood cancer and residential exposure to highways: a nationwide cohort study. *Eur J Epidemiol.* 2015;30:1263-1275.
129. Boothe VL, Boehmer TK, Wendel AM, Yip FY. Residential traffic exposure and childhood leukemia: a systematic review and meta-analysis. *Am J Prev Med.* 2014;46:413-422.
130. Carlos-Wallace FM, Zhang L, Smith MT, Rader G, Steinmaus C. Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: a meta-analysis. *Am J Epidemiol.* 2016;183:1-14.
131. Filippini T, Heck JE, Malagoli C, Giovane C Del, Vinceti M. A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2015;33:36-66.
132. Filippini T, Hatch EE, Rothman KJ, et al. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. *Environ Health Perspect.* 2019;127:46002.
133. Sun XX, Zhang SS, Ma XL. No association between traffic density and risk of childhood leukemia: a meta-analysis. *Asian Pacific J Cancer Prev.* 2014;15:5229-5232.
134. Danysh HE, Mitchell LE, Zhang K, Scheurer ME, Lupo PJ. Traffic-related air pollution and the incidence of childhood central nervous system tumors: Texas, 2001-2009. *Pediatr Blood Cancer.* 2015;62:1572-1578.
135. Ghosh JK, Heck JE, Cockburn M, Su J, Jerrett M, Ritz B. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. *Am J Epidemiol.* 2013;178:1233-1239.
136. Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environ Health Perspect.* 2013;121:1385-1391.
137. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A. Residential exposure to traffic in California and childhood cancer. *Epidemiology.* 2004;15:6-12.
138. von Ehrenstein OS, Heck JE, Park AS, Cockburn M, Escobedo L, Ritz B. In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. *Environ Health Perspect.* 2016;124:1093-1099.
139. Kumar SV, Lupo PJ, Pompeii LA, Danysh HE. Maternal residential proximity to major roadways and pediatric embryonal tumors in offspring. *Int J Environ Res Public Health.* 2018;15:505.
140. Lavigne E, Belair MA, Do MT, et al. Maternal exposure to ambient air pollution and risk of early childhood cancers: a population-based study in Ontario, Canada. *Environ Int.* 2017;100:139-147.
141. Ou JY, Hanson HA, Ramsay JM, et al. Fine particulate matter air pollution and mortality among pediatric, adolescent, and young adult cancer patients. *Cancer Epidemiol Biomarkers Prev*. Published online May 13, 2020. doi:10.1158/1055-9965.EPI-19-1363
142. Pitot HC. The molecular biology of carcinogenesis. *Cancer.* 1993;72:962-970.
143. Brauer M, Avila-Casado C, Fortoul TI, Vedal S, Stevens B, Churg A. Air pollution and retained particles in the lung. *Environ Health Perspect.* 2001;109:1039-1043.
144. Castano-Vinyals G, D'Errico A, Malats N, Kogevinas M. Biomarkers of exposure to polycyclic aromatic hydrocarbons from environmental air pollution. *Occup Environ Med.* 2004;61:e12.
145. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and health impacts of air pollution: a review. *Front Public Health.* 2020;8:14.
146. Yamagishi K, Onuma K, Chiba Y, et al. Generation of gaseous sulfur-containing compounds in tumour tissue and suppression of gas diffusion as an antitumour treatment. *Gut.* 2012;61:554-561.
147. Arlt VM. 3-Nitrobenzanthrone, a potential human cancer hazard in diesel exhaust and urban air pollution: a review of the evidence. *Mutagenesis.* 2005;20:399-410.
148. Moorthy B, Chu C, Carlin DJ. Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicol Sci.* 2015;145:5-15.
149. Peluso M, Ceppi M, Munnia A, Puntoni R, Parodi S. Analysis of 13 (32)P-DNA postlabeling studies on occupational cohorts exposed to air pollution. *Am J Epidemiol.* 2001;153:546-558.
150. Dunn BP. Carcinogen adducts as an indicator for the public health risks of consuming carcinogen-exposed fish and shellfish. *Environ Health Perspect.* 1991;90:111-116.
151. Peluso M, Airoldi L, Armelle M, et al. White blood cell DNA adducts, smoking, and NAT2 and GSTM1 genotypes in bladder cancer: a case-control study. *Cancer Epidemiol Biomarkers Prev.* 1998;7:341-346.
152. Tang D, Santella RM, Blackwood AM, et al. A molecular epidemiological case-control study of lung cancer. *Cancer Epidemiol Biomarkers Prev.* 1995;4:341-346.
153. Demetriou CA, Vineis P. Carcinogenicity of ambient air pollution: use of biomarkers, lessons learnt and future directions. *J Thorac Dis.* 2015;7:67-95.

154. Wang LH, Wu CF, Rajasekaran N, Shin YK. Loss of tumor suppressor gene function in human cancer: an overview. *Cell Physiol Biochem.* 2018;51:2647-2693.

155. Claxton LD, Matthews PP, Warren SH. The genotoxicity of ambient outdoor air, a review: Salmonella mutagenicity. *Mutat Res.* 2004;567:347-399.

156. Somers CM, Yauk CL, White PA, Parfett CL, Quinn JS. Air pollution induces heritable DNA mutations. *Proc Natl Acad Sci U S A.* 2002;99:15904-15907.

157. Deben C, van den Bossche J, van der Steen N, et al. Deep sequencing of the TP53 gene reveals a potential risk allele for non-small cell lung cancer and supports the negative prognostic value of TP53 variants. *Tumour Biol.* 2017;39:1010428317694327.

158. Zhou W, Tian D, He J, et al. Repeated PM2.5 exposure inhibits BEAS-2B cell P53 expression through ROS-Akt-DNMT3B pathway-mediated promoter hypermethylation. *Oncotarget.* 2016;7:20691-20703.

159. Yu XJ, Yang MJ, Zhou B, et al. Characterization of somatic mutations in air pollution-related lung cancer. *EBioMedicine.* 2015;2:583-590.

160. Sanchez-Guerra M, Zheng Y, Osorio-Yanez C, et al. Effects of particulate matter exposure on blood 5-hydroxymethylation: results from the Beijing Truck Driver Air Pollution Study. *Epigenetics.* 2015;10:633-642.

161. Gondalia R, Baldassari A, Holliday KM, et al. Methylome-wide association study provides evidence of particulate matter air pollution-associated DNA methylation. *Environ Int.* 2019;132:104723.

162. Clark SJ, Melki J. DNA methylation and gene silencing in cancer: which is the guilty party? *Oncogene.* 2002;21:5380-5387.

163. Zhang W, Klinkebiel D, Barger CJ, et al. Global DNA hypomethylation in epithelial ovarian cancer: passive demethylation and association with genomic instability. *Cancers (Basel).* 2020;12:764.

164. Ponomaryova AA, Rykova EY, Azhikina T, et al. Long interspersed nuclear element-1 methylation status in the circulating DNA from blood of patients with malignant and chronic inflammatory lung diseases. *Eur J Cancer Prev*. Published online June 8, 2020. doi:10.1097/CEJ.0000000000000601

165. Ye D, Jiang D, Zhang X, Mao Y. Alu methylation and risk of cancer: a meta-analysis. *Am J Med Sci.* 2020;359:271-280.

166. Prada D, Gonzalez R, Sanchez L, Castro C, Fabian E, Herrera LA. Satellite 2 demethylation induced by 5-azacytidine is associated with missegregation of chromosomes 1 and 16 in human somatic cells. *Mutat Res.* 2012;729:100-105.

167. Baccarelli A, Wright RO, Bollati V, et al. Rapid DNA methylation changes after exposure to traffic particles. *Am J Respir Crit Care Med.* 2009;179:572-578.

168. Guo L, Byun HM, Zhong J, et al. Effects of short-term exposure to inhalable particulate matter on DNA methylation of tandem repeats. *Environ Mol Mutagen.* 2014;55:322-335.

169. Tarantini L, Bonzini M, Apostoli P, et al. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. *Environ Health Perspect.* 2009;117:217-222.

170. Hesselbach K, Kim GJ, Flemming S, et al. Disease relevant modifications of the methylome and transcriptome by particulate matter ($PM_{2.5}$) from biomass combustion. *Epigenetics.* 2017;12:779-792.

171. Deng X, Feng N, Zheng M, et al. $PM_{2.5}$ exposure-induced autophagy is mediated by lncRNA loc146880 which also promotes the migration and invasion of lung cancer cells. *Biochim Biophys Acta Gen Subj.* 2017;1861:112-125.

172. Liu C, Guo H, Cheng X, et al. Exposure to airborne PM2.5 suppresses microRNA expression and deregulates target oncogenes that cause neoplastic transformation in NIH3T3 cells. *Oncotarget.* 2015;6:29428-29439.

173. Li X, Lv Y, Gao N, et al. MicroRNA-802/Rnd3 pathway imposes on carcinogenesis and metastasis of fine particulate matter exposure. *Oncotarget.* 2016;7:35026-35043.

174. Ding X, Wang M, Chu H, et al. Global gene expression profiling of human bronchial epithelial cells exposed to airborne fine particulate matter collected from Wuhan, China. *Toxicol Lett.* 2014;228:25-33.

175. Zhou Z, Liu Y, Duan F, et al. Transcriptomic analyses of the biological effects of airborne PM2.5 exposure on human bronchial epithelial cells. *PLoS One.* 2015;10:e0138267.

176. Baulig A, Blanchet S, Rumelhard M, Lacroix G, Marano F, Baeza-Squiban A. Fine urban atmospheric particulate matter modulates inflammatory gene and protein expression in human bronchial epithelial cells. *Front Biosci.* 2007;12:771-782.

177. Gualtieri M, Mantecca P, Cetta F, Camatini M. Organic compounds in tire particle induce reactive oxygen species and heat-shock proteins in the human alveolar cell line A549. *Environ Int.* 2008;34:437-442.

178. Strzelczyk JK, Wiczkowski A. Oxidative damage and carcinogenesis. *Contemp Oncol (Pozn).* 2012;16:230-233.

179. Yang W, Omaye ST. Air pollutants, oxidative stress and human health. *Mutat Res.* 2009;674:45-54.

180. Solleiro-Villavicencio H, Rivas-Arancibia S. Effect of chronic oxidative stress on neuroinflammatory response mediated by CD4(+) T cells in neurodegenerative diseases. *Front Cell Neurosci.* 2018;12:114.

181. Zimmerman R, Cerutti P. Active oxygen acts as a promoter of transformation in mouse embryo C3H/10T1/2/C18 fibroblasts. *Proc Natl Acad Sci U S A.* 1984;81:2085-2087.

182. Halliwell B. Oxidative stress and cancer: have we moved forward? *Biochem J.* 2007;401:1-11.

183. Puisieux A, Pommier RM, Morel AP, Lavial F. Cellular pliancy and the multistep process of tumorigenesis. *Cancer Cell.* 2018;33:164-172.

184. Bai J, Meng Z. Effect of sulfur dioxide on expression of proto-oncogenes and tumor suppressor genes from rats. *Environ Toxicol.* 2010;25:272-283.

185. Abbas I, Verdin A, Escande F, et al. In vitro short-term exposure to air pollution PM2.5-0.3 induced cell cycle alterations and genetic instability in a human lung cell coculture model. *Environ Res.* 2016;147:146-158.

186. Reyes-Caballero H, Rao X, Sun Q, et al. Air pollution-derived particulate matter dysregulates hepatic Krebs cycle, glucose and lipid metabolism in mice. *Sci Rep.* 2019;9:17423.

187. Santibanez-Andrade M, Quezada-Maldonado EM, Osornio-Vargas A, Sanchez-Perez Y, Garcia-Cuellar CM. Air pollution and genomic instability: the role of particulate matter in lung carcinogenesis. *Environ Pollut.* 2017;229:412-422.

188. Taghizadeh S, Najmabadi H, Kamali K, Behjati F. Evaluation of chromosomal aberrations caused by air pollutants in some taxi drivers from two polluted districts of urban Tehran and its comparison with drivers from rural areas of Lahijan: a pilot study. *J Environ Health Sci Eng.* 2014;12:144.

189. Dagher Z, Garcon G, Billet S, et al. Activation of different pathways of apoptosis by air pollution particulate matter (PM2.5) in human epithelial lung cells (L132) in culture. *Toxicology.* 2006;225:12-24.

190. Novack L, Yitshak-Sade M, Landau D, et al. Association between ambient air pollution and proliferation of umbilical cord blood cells. *Environ Res.* 2016;151:783-788.

191. US Environmental Protection Agency (EPA). Integrated Science Assessment (ISA) for Particulate Matter. EPA; 2019.

192. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol.* 2013; 14:1262-1263.

193. Burnett R, Chen H, Szyszkowicz M, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A.* 2018;115:9592-9597.

194. Pope CA 3rd, Burnett RT, Turner MC, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. *Environ Health Perspect.* 2011;119:1616-1621.

195. Lowrance WW. Of Acceptable Risk; Science and the Determination of Safety. William Kaufmann; 1976.

196. Annesi-Maesano I. The air of Europe: where are we going? *Eur Respir Rev.* 2017;26:170024.

197. Burns J, Boogaard H, Polus S, et al. Interventions to reduce ambient air pollution and their effects on health: an abridged Cochrane systematic review. *Environ Int.* 2020;135:105400.

198. Correia AW, Pope CA, Dockery DW, Wang Y, Ezzati M, Dominici F. The effect of air pollution control on life expectancy in the United States: an analysis of 545 US counties for the period 2000 to 2007. *Epidemiology.* 2013;24:23-31.

199. Glazener A, Khreis H. Transforming our cities: best practices towards clean air and active transportation. *Curr Environ Health Rep.* 2019;6:22-37.

200. Pope CA, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med.* 2009;360:376-386.

201. Schraufnagel DE, Balmes JR, De Matteis S, et al. Health benefits of air pollution reduction. *Ann Am Thorac Soc.* 2019;16:1478-1487.

202. Guan WJ, Zheng XY, Chung KF, Zhong NS. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. *Lancet.* 2016;388:1939-1951.

203. Sallis JF, Bull F, Burdett R, et al. Use of science to guide city planning policy and practice: how to achieve healthy and sustainable future cities. *Lancet.* 2016;388:2936-2947.

204. Giles-Corti B, Vernez-Moudon A, Reis R, et al. City planning and population health: a global challenge. *Lancet.* 2016;388:2912-2924.

205. Vardoulakis S, Kettle R, Cosford P, et al. Local action on outdoor air pollution to improve public health. *Int J Public Health.* 2018;63:557-565.

206. Wang L, Zhong B, Vardoulakis S, et al. Air quality strategies on public health and health equity in Europe—a systematic review. *Int J Environ Res Public Health.* 2016;13:1196.

207. Kumar P, Druckman A, Gallagher J, et al. The nexus between air pollution, green infrastructure and human health. *Environ Int.* 2019;133:105181.

208. French Agency for Food, Environmental and Occupational Health & Safety (ANSES). Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the "Assessment of the Expected Health Benefits of Anti-Pollution Respirators." French Agency for Food, Environmental and Occupational Health & Safety; 2018.

209. Pacitto A, Amato F, Salmatonidis A, et al. Effectiveness of commercial face masks to reduce personal PM exposure. *Sci Total Environ.* 2019;650:1582-1590.

210. Fisk WJ, Chan WR. Health benefits and costs of filtration interventions that reduce indoor exposure to PM2.5 during wildfires. *Indoor Air.* 2017;27:191-204.

211. Huang G, Zhou W, Qian Y, Fisher B. Breathing the same air? Socioeconomic disparities in PM2.5 exposure and the potential benefits from air filtration. *Sci Total Environ.* 2019;657:619-626.

212. de Nazelle A, Bode O, Orjuela JP. Comparison of air pollution exposures in active vs. passive travel modes in European cities: a quantitative review. *Environ Int.* 2017;99:151-160.

213. Nyarku M, Mazaheri M, Jayaratne R, et al. Mobile phones as monitors of personal exposure to air pollution: is this the future? *PLoS One.* 2018;13:e0193150.