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BRN Rev. 2024;10(1):16-29

BRN Reviews

REVIEW ARTICLE

Air pollution and lung cancer

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ABSTRACT

Outdoor air pollution and particulate matter (PM) in outdoor air is a major cause of lung cancer. The purpose of this article is to review the current knowledge regarding the effects of outdoor air pollution on lung cancer development and progression. There is clear and substantial evidence of a link between outdoor ambient air pollution and lung cancer. There is an interplay between environmental exposure and host factors, especially in those with genetic risk. PM can promote development and progression of lung cancer through inflammatory and immune mechanisms on pre-existing oncogenic mutations, by altering the lung microbiome and through metabolic perturbations. There is an urgent need to support efforts to improve air quality by reducing fossil fuel use. Health professionals and policy decision makers play an important role in supporting continued advances in research and implementation of measures to reduce the adverse health effects of outdoor air pollution.

Keywords: Air pollution. Lung cancer. Particulate matter.

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Received: 12-12-2023
Accepted: 06-03-2024
DOI: 10.23866/BRNRev:2024-M0103
www.brnreviews.com

INTRODUCTION

Background

Lung cancer continues to be the most diagnosed cancer and the leading cause of cancer death globally with over 1.8 million deaths a year[1]. At 20% or less, the five-year net survival for lung cancer is among the lowest of all types of cancer[2]. While tobacco smoking has been the major cause of lung cancer, increasing evidence indicates that air pollution and its major component, particulate matter (PM), is the second-highest specific cause of lung cancer in many countries in Central and Eastern Europe, Southeast, East, Central and South Asia, Latin America, North Africa and the Middle East[3]. In some East Asian countries, the incidence of lung adenocarcinoma has been increasing over time, despite a steady decline in male smoking since the 1990s and a constant low smoking rate among females[4], with over 50% of lung cancers now from people who have never smoked[4]. In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution and PM in outdoor air as carcinogenic to humans (Group 1) and causes of lung cancer[5-7]. A Global Burden of Disease Study in 2019 estimated that the percentage of global lung cancers attributable to different risk factors was 62.4% for smoking, 15.3% for PM air pollution, 5.8% for second-hand smoke, and 4% for household air pollution from use of solid fuels for cooking, pointing to the importance of PM in the development of lung cancer[8].

Objective

The purpose of this narrative review is to review the current knowledge regarding the effects of ambient air pollution on lung cancer development and progression relevant to health professionals and policy makers to mitigate the harms.

METHODS

An English language literature search of PubMed, Cochrane Library and Web of Science was conducted using the keywords related to air pollution and lung cancer. The date of last search was October 31, 2023.

MAIN FINDINGS

Epidemiologic evidence

Results of epidemiologic studies considered as part of the IARC evaluation (above) consistently demonstrated positive associations of both outdoor air pollution and PM in outdoor air and lung cancer risk in a range of cohort and case-control studies from different continents, including studies in people who have never smoked[5-7,9,10]. In one large cohort (n = 188,699 enrolled in 1982) of never-smoking individuals in the Cancer Prevention Study-II (CPS-II), the association between long-term ambient PM with an aerodynamic diameter < 2.5 microns ($PM_{2.5}$) and lung cancer mortality was studied[11]. Mean Metropolitan Statistical Area (MSA) $PM_{2.5}$ concentrations were determined for each participant based on central monitoring data. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a 15%-27% increase in lung cancer mortality. The findings contributed to addressing concerns regarding potential residual confounding by cigarette smoking in previous work and strengthened evidence for an association.

Among more recent studies, the "Effects of Low-level Air Pollution: a Study in Europe" (ELAPSE) collaboration pooled data from 307,550 participants in seven cohorts from Europe to examine in more detail the shape of the exposure-response relationship at low exposure levels. The median (Q1, Q3) annual (2010) exposure level of $PM_{2.5}$ was 15.4 µg/m^3 (12.8, 17.3). A positive association with lung cancer incidence was observed, including an estimated linear or supra-linear association with no threshold, at chronic exposure levels below the current European Union (EU) air quality limit of 25 µg/m^3 and possibly the 2005 World Health Organization (WHO) air quality guideline (AQG) of 10 µg/m^3 [12]. There were no associations with other pollutants (NO_2, BC or O_3). In an analysis of $PM_{2.5}$ elemental components, there were positive associations of lung cancer incidence with a range of components, including biomass (K), oil burning (Ni, V) and secondary inorganic aerosols (S)[13]. Another study in a low air pollution area in Australia also reported positive associations of both PM and BC and lung cancer incidence in a cohort of older men[14].

In registry-based studies, there were positive associations with lung cancer incidence in the county-level ecological analysis of > 1 million lung cancer cases in the Surveillance, Epidemiology, and End Results (SEER) program data[15]. Primary time-independent models using average incidence rates from 1992-2016 and average $PM_{2.5}$ from 1988-2015 were estimated. The incident rate ratio per 10-µg/m^3 increase in $PM_{2.5}$, for lung cancer was 1.19 (95% CI: 1.09, 1.30)[16]. In an analysis of lung cancer incidence in the U.S. Medicare cohort, there were significant positive associations of long-term $PM_{2.5}$ and NO_2 concentrations and a marginal positive association with particle radioactivity (PR) in multi-pollutant modeling[16]. There were stronger associations of $PM_{2.5}$ and PR observed among men, older participants, black participants, and those residing in lower-income areas. Positive associations for $PM_{2.5}$ and NO_2 were also observed at levels below current U.S. national air quality standards. Potential limitations include a lack of individual-level risk factor data and generalizability to the broader elderly population. There were no associations between $PM_{2.5}$ and lung cancer mortality in analysis of national population-based cohorts in Canada[17].

Analysis in the California Multiethnic Cohort sought to examine racial/ethnic differences in lung cancer risk[18]. The study included 2,796 incident lung cancer cases between 1993-2013. Latino (41%) and African American (32%) participants comprised the majority of the included study population and more often lived in lower socioeconomic status (SES) areas with higher ambient air pollution concentrations. The study observed positive associations of several ambient air pollutants and lung cancer incidence overall, and stronger associations with NO_x and NO_2 among participants residing in lower SES areas.

Findings from analysis of six cohorts from the Asia Cohort Consortium, including data on over 340,000 participants from Bangladesh, India, Iran, Japan, Korea, and Taiwan, observed positive associations of satellite-based NO_2 (HR per 10 ppb = 1.13, 95% CI 1.01-1.26) but not $PM_{2.5}$ concentrations, and lung cancer mortality[19]. The study contributes to fill important data gaps in regions with fewer previous studies.

In the UK Biobank, analysis sought to examine if ambient air pollutants modified genetic susceptibility to lung cancer based on polygenic risk score data of 18 SNPs[20]. Overall, there were significant positive associations of $PM_{2.5}$, $PM_{10,}$ NO_2, and NO_x and lung cancer incidence, with the greatest relative increases among those with high genetic risk. In a case-control study in Taiwanese females who had never smoked, GWAS identified SNPs and $PM_{2.5}$ were found to improve lung cancer risk prediction more than clinical demographic data alone[21]. Findings of an additive interaction between ambient air pollution and genetic risk suggest that efforts to reduce ambient air pollution concentrations will further benefit those with a higher genetic susceptibility.

Less is known regarding ultrafine PM (< 0.1 microns in diameter) (UFP) for lung cancer. Recent findings from the Los Angeles Ultrafines Study, including 45,012 participants and 1,770 lung cancer cases, showed a modest positive association of 10-year lagged historical residential ambient UFP number concentrations with lung cancer risk overall, and somewhat stronger associations for adenocarcinoma, particularly among men[22]. In an analysis of 10.8 million adults including 71,622 lung cancer deaths, the Dutch national cohort reported significant positive associations between annual average UFP and lung cancer mortality[23].

Specific sources of air pollutants

Outdoor air pollution derives from a range of anthropogenic and natural sources. Few studies have examined specific outdoor air pollution sources or components in relation to lung cancer risk[13,24]. Recently, due to climate changes, and with increases in the frequency and magnitude of wildfires, there is an emerging literature on human health impacts of wildfire smoke on the general population. Wildfire smoke impacts respiratory health more than fine particles from other sources due to the presence of more polar organic compounds[25] and is threatening to erase the progress to improve air quality. Findings from a recent population-based cohort study in Canada have also pointed to long-term exposure to wildfires and increased lung cancer incidence[26]. In an analysis of the 1996 Canadian Census Health and Environment Cohort followed to 2015, excluding participants who lived in major cities, there was a 4.9% (95% CI 3%-7%) increased risk of lung cancer incidence for participants exposed to wildfires based on area burned within 50 km of the residence in the previous 10 years compared to unexposed populations. Findings were similar for a 20 km radius. Further work to develop more refined estimates of wildfire smoke exposure and its constituents was recommended.

In addition to general population exposure to wildfire smoke, there is also occupational exposure among wildland firefighters. Although occupational exposure as a firefighter was recently classified as "carcinogenic to humans" (Group 1) by an IARC Working Group, with sufficient evidence for mesothelioma and bladder cancer, there was no clear epidemiological evidence for an association with lung cancer – though there remain potential methodological concerns related to negative confounding with lower rates of cigarette smoking among firefighters than the general population[27]. Firefighters are exposed to a range of combustion products, building materials, asbestos, diesel

engine exhaust (below), and other hazardous agents. There were few studies of cancer risk among wildland firefighters with and without using respirators, though concentrations of $PM_{2.5}$ in the range of 0.25-1.0 mg/m^3 in breathable air were described[28].

Diesel engine exhaust was classified as a Group 1 human carcinogen for lung cancer in 2012[29]. Consistent positive findings were observed across a range of studies in different industries, with well-characterised exposures, many adjusting for cigarette smoking[30]. In a recent extended follow-up of the Diesel Exhaust in Miners Study, doubling the number of observed deaths, findings of increased lung cancer mortality were sustained, with an SMR of 1.24 (95% CI 1.13-1.37), and 1.26 (95% CI 1.11-1.42) among workers who ever worked underground[31]. In a nested case-control analysis, there were stronger adverse associations in the previous 10-19 year exposure time window, sustained adverse associations for 20+ years following cessation of exposure, as well as a plateau/decline in risk in the most exposed workers[32]. An overview of occupational agents of relevance for lung cancer can be found in Loomis et al[33].

In 2020, opium consumption was classified as a Group 1 human carcinogen for lung cancer[35]. A meta-analysis estimated an approximate three-fold increase in lung cancer risk associated with a history of ever opium consumption[36].

There is little known regarding potential interactions of outdoor air pollution with other agents. In one study, it was estimated that 14% (95% CI 00-25%) of lung cancer mortality in the CPS-II was due to the interaction of ambient $PM_{2.5}$ concentrations and cigarette smoking[34].

Measurement of air pollutants

Exposure assessment in previous epidemiological studies of ambient air pollution and lung cancer risk has been conducted using a range of methods, often estimated at the residential address for single- or multiple-years, and either averaged for fixed time periods near cohort baseline or end of follow-up or updated in analysis over follow-up time in a time-dependent manner. Cohort participants are typically followed up for long periods of time, often decades, for studies of cancer occurrence with differing trends in ambient air pollution concentrations observed in different geographic regions. In one study, it was estimated that the global mean urban $PM_{2.5}$ concentration was 35 ug/m^3 in 2019 overall, with large regional differences in concentration trends from 2000 to 2019, with the largest increases observed in cities in South-East Asia and the largest decreases in cities in Africa[37].

Among studies considered as part of the 2013 IARC evaluation[38], ambient air pollution concentrations were generally estimated using measured central outdoor monitoring data, modeled based on atmospheric transport or land-use regression models or using satellite-based approaches (where measurement data may be limited or unavailable)[20]. For studies of lung cancer survival, due to the relatively short survival period from diagnosis, ambient air pollution estimates at finer scales of temporal resolution have been used (monthly or seasonal values rather than annual estimates)[39,40].

Models for ambient air pollution exposure estimation are being continually advanced and refined. In the recent ELAPSE study, hybrid Europe-wide models were developed

combining monitoring, land use data, satellite observations, and dispersion model estimates at the participant residence at a 100 m by 100 m geographic scale for the year 2010 (towards the end of follow-up), and were applied to the residential address of cohort participants at baseline[12]. The models were validated to ensure the stability of the spatial structure at different points in time[41]. Yearly pollutant concentrations were also estimated using back-extrapolation methods from 2010 to the cohort recruitment year. For some cohorts, sensitivity analysis taking into account residential mobility patterns over time was performed.

In one recent US study, comparisons of nine $PM_{2.5}$ concentration models were performed using different geophysical chemical transport models, interpolation methods, a satellite-derived aerosol optical depth-based method, a Bayesian statistical regression model, and data-rich machine learning methods[42]. At regional and national scales, the nine models provided broadly consistent estimates. Another previous study compared the use of ground-based to remote sensing $PM_{2.5}$ exposure metrics[43]. Recently, multi-year annual average $PM_{2.5}$ estimates by source and composition concentration were described at the US census tract level[44]. There is also increasing interest in better characterizing UFPs, through the development of emission inventories and systematic monitoring and modelling[45]. A high spatial resolution land-use regression model for urban UFPs in Shanghai, China was recently described[46].

With the advent of exposome methods, there have been increasing efforts in characterizing personal air pollution exposure, including specific constituents of $PM_{2.5}$[47]. Though such measurements are usually performed on the time scale of days to weeks, such studies provide useful information to understand assumptions of and agreement with outdoor exposure estimates for different pollutants and exposure circumstances[38]. In one study based on agent-based modeling and personal sensors, large differences in $PM_{2.5}$ inhalation between housemates and neighbours were observed[48]. Another recent study applied an automated classification of time-activity-location patterns to improve the estimation of personal exposure to air pollution[49]. Personal ambient air pollution exposures are influenced by outdoor and indoor sources, time-activity patterns, and commuting behavior, though there are few studies of lung cancer with such detailed data[50]. In the UK Biobank, there was an increased lung cancer risk among those commuting by public transportation (HR = 1.58, 95% CI 1.08-2.33) compared with automobile use, but not for other commuting modes[51]. The association with public transportation use was stronger among those residing in higher NO_2 areas.

Environmental carcinogens and tumorigenesis

A clinical study in Canada compared the demographic and clinical features of lung cancer patients who had never smoked versus those who had ever smoked. Using individual assessment of cumulative exposure to outdoor $PM_{2.5}$ quantified with a high spatial resolution global exposure model over a period of 20 years prior to their cancer diagnosis, a significantly higher cumulative outdoor $PM_{2.5}$ exposure was observed among those who had never smoked[52]. The latter were more likely females (70.5% versus 48.2%, $p < 0.001$),

who were significantly younger (66.5 years versus 69.2 years, p = 0.0001), with adenocarcinoma, more frequently East Asian (67.8% versus 16.7% p < 0.001), born outside of Canada (80.4% versus 37.4%, p < 0.001), better educated, less likely to have chronic obstructive pulmonary disease, or a family history of lung cancer and lower exposure to secondhand smoke. Workplace exposure to known occupational carcinogens such as asbestos, chromium, nickel, arsenic or polycyclic hydrocarbons were infrequent[52]. Therefore, lung tumors from patients who have never smoked may provide insights into the effects of air pollution exposure on lung cancer development and progression.

Several large genomic and proteomic studies have been conducted in lung cancer patients who have never smoked using whole exome sequencing, RNA sequencing, and proteome analyses[53-57]. Many carcinogens do not cause a detectable DNA mutational signature in tumors following exposure[58,59]. Although oncogenic driver mutations such as EGFR mutation are more prevalent in patients who have never smoked, no dominant carcinogenic signal of mutations deriving from exogenous sources have been identified aside from those with indoor radon exposure[60,61]. Oncogenic driver mutations such as EGFR mutations can be present in non-tumor tissue in 19% of the patients who have never smoked in whom the same mutations were not selected during NSCLC tumorigenesis[57]. KRAS mutations were also found in 38% of healthy lung tissue from people without lung cancer who had never smoked[57]. Females are more likely to have an EGFR mutation in healthy non-tumor lung tissue[57]. A mutational signature that is more commonly found in tumors from patients who had never smoked is SBS18 (single base substitutions 18, damage by reactive oxygen species, Catalogue of Somatic Mutations in Cancer)[61,62]. Mutational signatures linked to nitrated polycyclic aromatic hydrocarbons (Nitro-PAH), and polycyclic aromatic hydrocarbons (PAH) which are constituents of $PM_{2.5,}$ have been identified in lung adenocarcinomas of never smokers in several studies[53-55,59]. Nitro-PAHs and PAHs are formed from incomplete combustion of fossil fuels and biomass. Important sources include diesel exhaust from vehicles, industrial processes, and forest fires[26,28,63,64]. Nitro-PAH can be present in very fine particles down to the size of < 1 µm which can then accumulate in the distal airways over time[65]. In a human bronchial epithelial malignant transformed cell model, $PM_{2.5}$ exposure was found to activate APOBEC3B and other oncogenes and lead to APOBEC mutational signatures. In 1,117 non-small cell lung cancers (NSCLCs) from patients across four different geographic regions, a significantly higher prevalence of APOBEC mutational signatures was found in NSCLCs from non-smoking versus smoking Chinese patients, but this difference was not observed in the TCGA Caucasian cohort[66]. The mutational signature associated with direct exposure to tobacco smoking (SBS4) was not observed or observed in very low frequency[53-57,67]. Endogenous processes such as SBS8 (linked to nucleotide excision repair deficiency and late replication errors[68,69], SBS6, 15, 21, 26, 44 (defective DNA mismatch repair), and SBS1 (age-associated)[53,54] predominate over exogenous processes. The sum of these data suggests that the effect of air pollution is likely to be related to an interplay between environmental exposure and host factors in keeping with a study using the UK Biobank data that showed long-term exposure

to air pollution may increase the risk of lung cancer, especially in those with high genetic risk (above)[56].

Recently, a non-mutagenic mechanism whereby air pollutants such as $PM_{2.5}$ promote tumorigenesis through pre-existing oncogenic mutations accumulated in the aging process was proposed by Swanton and colleagues[57,70,71]. Using data from 5 cohorts from England, South Korea, Taiwan, Canada and the UK Biobank, which contain 440,466 individuals of White and Asian ancestries, a significantly higher incidence of lung cancer with EGFR mutation was observed with higher $PM_{2.5}$ exposure. The frequency of EGFR-driven lung cancer cases was 73% after three years of high air pollutant exposure compared to 40% with low exposure ($p = 0.03$). This association was not observed after 20 years of high compared with low cumulative exposure. The result suggested that three years of high $PM_{2.5}$ exposure may be sufficient for EGFR-driven lung cancers to arise[57].

Using genetically engineered mouse models of lung adenocarcinoma with oncogenic human $EGFR^{L858R}$ expression, intratracheal instillation of fine PM before or after oncogene induction was found to promote carcinogenesis without enhancing mutagenesis with short-term exposure[57]. A competent immune system was required for tumorigenesis. An enhanced and sustained increase in interstitial alveolar macrophages with an increase in PD-L1 expression was observed after PM exposure. There was upregulation of genes known to regulate macrophage recruitment, including those that encode interleukin-1β (IL-1β), GM-CSF, CCL6 and NF-κB and the epithelial-derived alarmin IL-33. There was also upregulation of genes previously associated with AT2 progenitor cell states. AT2 cells are thought to be the cell of origin of lung adenocarcinoma[72]. In a 3D organoid system, PM exposure in macrophages alone was found to be sufficient to increase organoid formation efficiency of EGFR mutant AT2 cells compared to control and the use of IL-1β antibody Canakinumab, during PM exposure could attenuate tumor formation[57]. The study indicates macrophages are a key source of IL-1β in response to PM and IL-1β signaling is required for the promotion of PM-mediated EGFR-driven lung adenocarcinoma[57].

Patients with lung cancer who have never smoked are usually younger than those who have smoked[52]. The source of EGFR or KRAS mutant clones in normal lung tissue cannot be explained by the effect of aging alone. The possibility that $PM_{2.5}$ and other air pollutants cause premature aging in lung cells in susceptible individuals similar to the heightened risk of chronic obstructive pulmonary disease (COPD) in people living with human immunodeficiency virus[73] is an interesting hypothesis that requires investigation such as by measuring the epigenetic age using the Horvath clock and the methylation telomere length estimator[74,75]. Exposure to traffic air pollutants during infancy was found to have an impact on lung function up to adolescence suggesting a long-lasting effect[76]. Potential long-lasting detrimental effects from exposure to air pollutants during infancy or childhood resulting in the development of mutant clones should be considered in future studies. In addition, as discussed above[23-33], $PM_{2.5}$ is comprised of a complex mixture of chemical species from diverse sources[23-33,77,78], each potentially having different effects on lung carcinogenesis. Global spatial variation in $PM_{2.5}$

composition may explain the differences in the molecular alterations in lung adenocarcinoma between countries[79]. In vitro and animal studies need to be done with $PM_{2.5}$ from different sources to examine their mutagenic effects in addition to tumor promotional effects.

Chronic exposure to environmental air pollutants such as $PM_{2.5}$ can also promote lung cancer development or progression through alteration of the lung microbiome. There is increasing evidence that the commensal microbiota in the body, such as the lungs, regulate many important physiological functions including the metabolism and immune system and that certain microbes and microbiome dysbiosis are correlated with development and progression of lung cancer[80-83]. Recent studies have demonstrated the importance of the interplay between tumors and bacterial symbiotes. For example, the local microbiome can stimulate Myd88-dependent IL-1β and IL-23 production from myeloid cells, inducing proliferation and activation of Vγ6+Vδ1+ γδ T cells to produce IL-17 and other effector molecules to promote inflammation and lung tumor cell proliferation[84]. In a study that had paired malignant and non-malignant lung tissue from the same lobe or segment from 75 patients with lung cancer, the lung tumor microbiome was found to be specifically enriched in bacteria that produce L-methionine – an essential amino acid for tumor cell growth and a precursor to S-adenosyl methionine for DNA methylation that cannot be synthesized by mammalian cells[85]. Very recently, intratumor mycobiome such as Aspergillus sydowii was found in patients with lung adenocarcinoma[86]. In three different syngeneic lung cancer mice models, A. sydowii was found to promote lung tumor progression by IL-1β secretion via β-glucan/Dectin-1/CARD9 pathway, resulting in expansion and activation of myeloid-derived suppressor cells, suppressed activity of cytotoxic T lymphocyte cells and accumulation of PD-1+ CD8+ T cells. Human tumors enriched in A. sydowii were associated with immunosuppression and poor outcome[86]. Exposure to PM can alter the lung microbiome. In a study by Yu and colleagues using the patients' residential address during the year prior to surgical resection of their lung tumors to estimate PM_{10} air particulate exposure, the lung microbiome alpha diversity was found to increase with environmental exposures to PM_{10} air particulates[87].

Metabolic perturbations associated with air pollution exposure that may play a role in mediating lung cancer development were recently studied using blood samples collected from participants in the CPS-II and CPS-III. Gammaglutamyglutamine and gamma-glutamylmethionine were found to be significantly associated with CO, NO_2, and PM_{10} exposure and lung cancer incidence[88]. Metabolomic alterations associated with air pollution exposure and lung cancer development need further investigations.

Clinical implications

The lung cancer promotion effect of PM exposure has important clinical implications. There is an emerging literature on the impacts of outdoor air pollution on survival in lung cancer patients. In an analysis of 352,053 California lung cancer patients, exposure to higher levels of ambient $PM_{2.5}$, $PM_{10,}$ and NO_2 were associated with poorer survival

following diagnosis, particularly among those with early-stage adenocarcinoma. The median survival for patients with early-stage lung cancer was 2.4 years for those with high $PM_{2.5}$ exposure (≥ 16 μg/m^3) and 5.7 years for those with low $PM_{2.5}$ exposure (< 10 μg/m^3)[89]. Another study including 252,123 lung cancer patients from the Pennsylvania Cancer Registry, observed the strongest adverse impacts with NO_2 for deaths two-year post-diagnosis, and among those with localized disease. There were also adverse impacts of $PM_{2.5}$, O_3, and PM_{10}[90]. Another US study sought to examine the impact of wildfire exposure on postoperative long-term overall survival in a cohort of 466,912 non-small cell lung cancer patients[91]. Associations of active wildfire detected at the zip code of residence at different times after surgery (ranging from 0-12 months) were examined. Overall, there were adverse associations among patients exposed to wildfires within three months (HR = 1.43, 95% CI 1.41-1.45), from 4-6 months (HR = 1.39, 95% CI 1.37-1.41), and from 7-12 months (HR = 1.17, 95% CI 1.15-1.19) following hospital discharge for stage I to III resection compared to unexposed patients. In a study of 11 million Medicare beneficiaries in the South-Eastern U.S., adverse associations of both long-term $PM_{2.5}$ and O_3 exposures with a first hospital admission for lung cancer were observed, indicating potential impacts on disease exacerbation[92]. In US SEER data from the years 2000-2016, the relevance of county-level long-term ambient $PM_{2.5}$ concentrations for mortality in a cohort of 5,591,168 total cancer patients and 2,318,068 five-year cancer survivors was assessed[93]. There was a weak adverse association for all-cause mortality (HR per 10 ug-m^3 = 1.01, 95% CI 1.00-1.03), but stronger associations for other mortality endpoints including COPD, cardiovascular, and influenza and pneumonia, ranging from 10% to 55% increases in mortality risk. Stronger adverse cardiopulmonary mortality associations were also observed among those who received chemotherapy or radiation treatments. The adverse effect of air pollution exposure on survival, treatment complication and second primary lung cancer in lung cancer patients receiving treatment may be analogous to patients who continue to smoke[94]. The effectiveness of the use of HEPA air filtering devices at home and wearing N95 face mask outdoors or the use of IL-1β inhibitor[95] as a short-term measure to mitigate the effect of $PM_{2.5}$ during periods of high pollution level such as during forest fire smoke season requires further study.

From a chemoprevention perspective, identification of microbiome specific to lung cancer in relation to $PM_{2.5}$ and other air pollutants exposure may uncover the pathways and microenvironment changes driving tumor formation and progression. Significant changes in the lung microbiome of airways can occur several years before lung cancer diagnosis[96]. Modulation of the lung microbiome as a chemopreventive intervention needs to be explored.

Prediction of lung cancer risk associated with air pollution exposure

While validated lung cancer risk prediction model such as the PLCOm2012 work well for identifying high-risk individuals who have ever smoked to guide selection of individuals for CT screening and is being used in screening programs in Canada and the UK[97,98], the

PLCOm2012 and other risk prediction models exclude important established risk factors, such as outdoor air pollution. The current PLCOm2012 model has the following predictors: age, race/ethnicity, education (estimator of socioeconomic circumstance), body mass index, history of COPD, personal history of cancer, family history of lung cancer, smoking status (current versus former), smoking intensity (cigarettes per day), smoking duration and smoking quit-years in former smokers. For people who have never smoked, without the addition of blood biomarkers such as carcinoembryonic antigen (CEA), alpha-fetal protein, single nucleotide polymorphisms (SNPs) or spirometry data, the accuracy of these prediction models was modest[99]. A risk prediction model that includes air pollution exposure may help to identify never or light smoking individuals with sufficient lung cancer risk, who would benefit from thoracic CT screening. However, inclusion of air pollution exposure into a lung cancer risk prediction model requires defining the relevant exposure interval. For example, shorter-term measurement of the previous three-year exposure to reflect possible tumor promotion effects of PM is less challenging than assessing the effects of air pollution since birth because accurate measurement of PM and other air pollutants are not available before the 1980's. Since exposure to traffic-related air pollution in infancy is negatively associated with FEV1 in adolescence, with an additional negative effect from later exposures[76], spirometry measurement may be a simple and cost-effective means to improve the accuracy of lung cancer risk prediction in never smokers and light smokers[100]. The addition of genetic factors may improve lung cancer risk prediction further[20,21].

Public health recommendation

It has been clearly recognized that outdoor air pollution is a major worldwide public health challenge requiring multiple multi-level public health and policy interventions for lung cancer prevention[101]. There are a range of opportunities for engagement of the medical and health community in the area of outdoor air pollution which have been described in a recent review by the International Association for the Study of Lung Cancer Early Detection and Screening Committee[102]. They include increasing awareness by health care community and patients that exposure to air pollution is the second largest risk factor for lung cancer, advocating for enhanced environmental policies to decrease fossil fuel emissions and use clean, sustainable energy instead; restricting air emission targets to the lowest levels as recommended by the WHO, and support further research into the pathophysiological and carcinogenetic effects of $PM_{2.5}$ and other pollutants on human health.

In terms of guidelines and regulatory approaches, in 2021, the WHO released new AQGs, lowering the threshold for recommended annual mean concentrations of $PM_{2.5}$ from 10 $\mu g/m^3$ to 5 $\mu g/m^3$ and of NO_2 from 40 $\mu g/m^3$ to 10 $\mu g/m^3$ [103]. The updated AQGs were based on systematic reviews of the evidence, including long-term $PM_{2.5}$ and PM_{10} and lung cancer[104]. In Europe, there has been detailed debate regarding the proposal for revision of the 2008 EU Ambient Air Quality Directives (AAQDs) in terms of potential alignment with the updated WHO AQGs[45,105,106]. In 2022, the European Commission published a proposal for revision of the AAQDs which included new annual limit values for $PM_{2.5}$ and NO_2 of

10 µg/m^3 and 20 µg/m^3 respectively by the year 2030, among other updates[107,108]. The proposal was later updated in 2023 to include full alignment with the WHO AQGs by the year 2035[45].

CONCLUSION

There is clear and substantial evidence of a link between outdoor ambient air pollution and lung cancer. There is an urgent need to support efforts to improve air quality. Health professionals and policy decision makers play an important role in supporting continued advances in research and implementation of measures to reduce the adverse health effects of air pollution.

DISCLOSURES

SL receives research funding from the Terry Fox Research Institute, the Lotte and John Hecht Memorial Foundation, the BC Cancer Foundation and the VGH-UBC Hospital Foundation.

MCT is funded by a Ramón y Cajal fellowship (RYC-2017-01892) from the Spanish Ministry of Science, Innovation and Universities and co-funded by the European Social Fund. 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 CERCA Program.

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