Review Article

Narrative review: association between lung cancer development and ambient particulate matter in never-smokers

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Objective: To review the association and pathophysiological link between lung cancer in never smokers and ambient particulate matter (PM).

Background: Although the association between exposure to PM and lung cancer development is well known, the pathophysiological background is yet to be studied in depth. Never smokers comprise a large proportion of newly diagnosed lung cancer cases and account for 25% of all cases. Considering the carcinogenic nature of ambient PM and the fact that many patients with lung cancer are never smokers, it is necessary to evaluate the interrelation and possible clinical background, in order to effectively prevent lung cancer development in this subgroup.

Methods: An online search of literature was conducted. The National Center for Biotechnology Information (NCBI), PubMed, Google Scholar, Cochrane Library and EMBASE were searched.

Conclusions: In never smokers, the risk of lung cancer was dose-dependent with the concentration of ambient air pollutants. Regarding the pathophysiological link, involvement of epithelial mesenchymal transition (EMT) and chronic inflammation has been mentioned, but further studies are necessary to enable therapeutic interventions to prevent cancer development. Considering the significant burden of PM on lung cancer development, both public and clinical approaches to cancer prevention are essential. To prevent lung cancer more effectively, clinicians should develop a more individualized approach in patients, focusing on gender and genetic background.

Keywords: Particulate matter (PM); lung cancer; never smoker; pathophysiology; carcinogenesis

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Background

Lung cancer is one of the leading causes of cancer-related deaths worldwide (1). Tobacco smoking is a well-known cause of lung cancer (2). Nevertheless, never smokers comprise a large proportion of newly diagnosed lung cancer cases and account for 25% of all cases (3). Recently, the proportion of never smokers among newly diagnosed lung cancer cases has been increasing steadily (4-7); in some countries, a considerable proportion of lung cancer seen among women were in never smokers (8-10). There are other factors associated with lung cancer development, such as exposure to secondhand smoke, radon, household fumes, occupational exposure to carcinogens, and infections (11,12). Above all, the World Health Organization (WHO) has classified air pollution as carcinogenic to humans (International Agency for Research on Cancer, Group 1), and many countries have monitoring systems to measure levels of ambient pollutants, such as respirable particulate

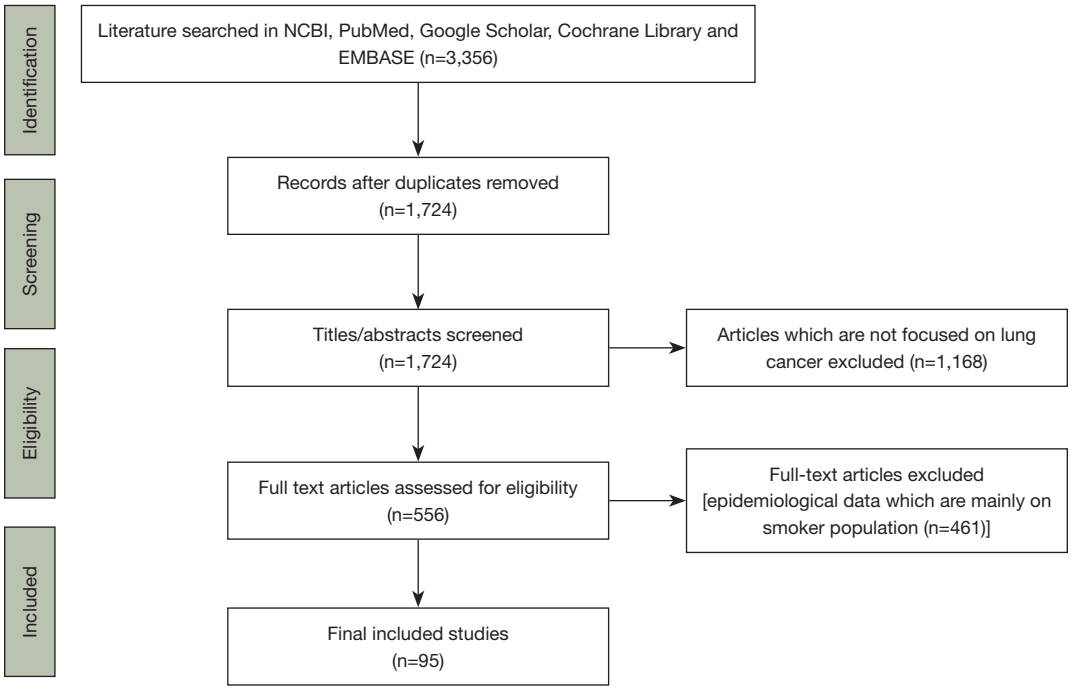

Figure 1 Literature review flow chart. A structured review of the literature (January 2014–February 2021) was performed.

matter (PM_{10}), fine PM ($PM_{2.5}$), NO_2, SO_2, and O_3 (13,14). PM is an airborne complex mixture of organic and inorganic particles, in both solid and liquid forms, present in the ambient atmosphere (15). Worldwide ambient $PM_{2.5}$, was estimated to have contributed to 14.1% of all lung cancer deaths in 2017 (16). Several studies have reported a strong association between long-term exposure to air pollution and lung cancer in the never-smoker population (17,18).

Although the association between exposure to PM and lung cancer development is well known, the pathophysiological background is yet to be studied in depth. Furthermore, the incidence and clinical characteristics of PM-related lung cancer differ depending on the region of residence and other epidemiologic factors such as sex (19,20).

Considering the carcinogenic nature of ambient PM and the fact that many patients with lung cancer are never smokers, it is necessary to evaluate the interrelation and possible clinical background, in order to effectively prevent lung cancer development in this subgroup. In this mini-review, the association and pathophysiological link between lung cancer in never smokers and ambient PM are assessed.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-655/rc).

Methods

Search strategy

An online search of literature was conducted. The National Center for Biotechnology Information (NCBI), PubMed, Google Scholar, Cochrane Library and EMBASE were searched for articles on association between PM and lung cancer in never smokers (*Figure 1*). All literature published in English between January 2014 and February 2021 were included. Various combinations of search texts were used. Search word 'particulate matter' and 'lung cancer' was combined with each of the following terms; 'ambient', 'pollution', 'carcinogenesis', 'indoor', 'never smoker', 'mechanism', 'concentration', 'air', 'sex', and 'development'.

Common constituents of PM

PM is a dispersed complex mixture of small particles and liquid droplets in air (21,22). It generally enters the human body through inhalation. PM with a relatively larger particle size is blocked in the nasal cavity and upper airway, while fine PM can penetrate deeper into the lower respiratory tract (23). PM is commonly characterized by size fractions into particles with diameter <10 μm (PM_{10}) and particles with diameter <2.5 μm ($PM_{2.5}$). PM_{10} is the largest inhalable

particle, while $PM_{2.5}$, known as fine PM, can be inhaled deep into the lung parenchyma and alveoli (24).

The chemical constituents of PM include nitrates, sulfates, ammonium, other inorganic ions, organic and elemental carbon, crustal material, metals, particle-bound water, and polycyclic aromatic hydrocarbons (PAHs) (25). The constituents of PM can differ depending on the region. In urban areas, incineration of wastes, traffic fumes, mining, and toxic material fuel from the incomplete combustion of biomass or oil fuel comprising metals and metalloids, contribute to PM (15). A study analyzing $PM_{2.5}$ components in four Canadian cities showed the presence of mineral dust, trace element oxides, transition metals, ammonium sulfate, black carbon, organic matter, and sea salts (26). These products generate reactive oxygen species (ROS) and activate inflammatory responses, resulting in subsequent genetic mutations in both somatic and germ cells, and altered gene expression, ultimately increasing the risk of cancer (14).

Epidemiologic background of PM as a cause of lung cancer

Association between ambient PM concentration and lung cancer development

A study has shown an association between exposure to PM and lung cancer risk in the never-smoker population, which may not be as strong as that in the smoker population (27). Epidemiological evidence showing the association is notable.

Considering that the pollutants causing ambient air pollution are diverse, studies focused on the evaluation of $PM_{2.5}$ and PM_{10}, which can be detected by air quality monitoring systems. Several large sized-population-based studies have been conducted to evaluate the association between lung cancer risk and PM (28-30). Notable prediction models for the prediction of lung cancer risk in never smokers included the level of PM as a risk factor (31).

The population data from various countries were evaluated for the severity of air pollution. Studies using nationwide data or large-sized cohorts from the North American population are notable. In a study using the National Health Interview Survey data, in which 341,665 never-smokers were surveyed from 1987 to 2014, an increase of 10 μg/m^3 in $PM_{2.5}$ was associated with an increased risk of all-cause mortality (HR =1.19; 95% CI: 1.06–1.33); an increase in $PM_{2.5}$ also showed a significant association with lung cancer-related mortality (HR =1.73; 95% CI: 1.20–2.49) after adjusting for multiple factors such as age, sex, and ethnicity (30). In another large study using Adventist Health and Smog Study-2 (AHSMOG-2) and US state cancer registries, a 10 μg/m^3 increment in $PM_{2.5}$, was significantly associated with incident lung cancer (HR =1.43; 95% CI: 1.03–2.00) after adjusting for sex, educational level, race, O_3 level, and smoking status. This result is notable because of the high proportion of never smokers in the cohort (80.8%) (28).

According to the Nurses' Health Study, $PM_{2.5}$ (per 10 μg/m^3) showed a significant association with lung cancer incidence after adjusting for age, time period, and geographic region (32). A 26-year prospective study on 188,699 lifelong never-smokers also showed that a 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with a small but measurable increase in lung cancer mortality. In overall patients, each 10 unit-increase in $PM_{2.5}$ was associated with a 15–27% increase in lung cancer deaths. This study is important because the heterogeneity in terms of smoking history was more controlled than that in other studies (33).

A plethora of evidence suggests a strong association between increased PM levels and lung cancer incidence; however, even at a relatively low level of $PM_{2.5}$, lung cancer may occur. In a study evaluating seven cohorts from across Europe, long-term exposure to ambient $PM_{2.5}$ was associated with lung cancer incidence, and it should be taken into account that the median annual exposure level of $PM_{2.5}$ was 15.5 μg/m^3, which is below the EU limit values. This finding was consistent in the never-smokers subgroup (HR =1.15; 95% CI: 1.01–1.31) (29).

Regarding association between lung cancer risk and PM_{10}, a study on Korean population including 908 lung cancer patient and matching controls showed that lung cancer incidence showed tendencies to increases with a ten-unit increase in PM_{10} (adjusted odds ratio of 1.09 95% CI: 0.96–1.23), and the associations were stronger among never smokers (34). In another study using the Nurses' Health study, incidence of lung cancer increases with a 10 unit increase in 72-month average PM_{10} (HR =1.04; 95% CI: 0.95–1.14). The associations appeared to increase in the never-smokers and former smokers (35). A meta-analyses of 18 studies showed the relationship of exposure to $PM_{2.5}$ and PM_{10} with incidence and mortality of lung cancer. The study analyzed lung cancer risk associated with $PM_{2.5}$ by smoking status. The risk was greatest for former smokers [1.44 (95% CI: 1.04–1.22)], followed by never-smokers [1.18 (95% CI: 1.00–1.39)], and then current smokers [1.06 (95% CI: 0.97–1.15)], showing that the risk is higher for the

never-smokers than for the current smokers (36).

Biochemical background of interrelationship between PM and lung cancer

Oxidative stress and inflammation

PM induces oxidative stress due to an imbalance in the oxidation and reduction status within the body. Excessive ROS impair cell function and induce cell death (37,38). In order to overcome the adverse effects of PM, the lungs have a unique protective system in which glutathione (GSH) plays an important role in neutralizing oxidative stress (39-41). The lungs are exposed to high concentrations of oxygen; hence, a balance between oxidants and antioxidants is critical. Excessive oxidative stress leads to chronic inflammation in the lung tissue, attracting diverse inflammatory cells, and subsequently DNA damage occurs, which in turn is associated with an increased possibility of lung cancer development (38,42).

Recent studies have reported new aspects of PM-related oxidative stress in the lung tissue. A study by Niu *et al.* (43), using human bronchial epithelial (HBE) cells, showed increased levels of ROS, malondialdehyde, and cellular heme oxygenase and decreased levels of GSH, after exposure to $PM_{2.5}$, reflecting the occurrence of oxidative stress in a dose-dependent manner. Quantitative analysis indicated that $PM_{2.5}$ caused a significant increase in malondialdehyde in a dose-dependent manner, while GSH was greatly reduced after exposure ($P<0.05$). PM-induced oxidative stress induces inflammatory reactions in the lung tissue through various pathways. Liu *et al.* (44) showed that oxidative stress induced by $PM_{2.5}$ increases intercellular adhesion molecule-1 expression (ICAM-1), which mediates inflammatory cells in the lung epithelial cells through the IL-6/AKT/STAT3/NF-κB signaling pathway. Wang *et al.* (45) demonstrated that PM exposure increased the levels of inflammatory cytokines and pro-inflammatory cytokines through ROS-mediated activation of MAPK and downstream NF-κB pathways. Hu *et al.* (46) showed that environmental levels of both $PM_{2.5}$ and total PAHs were significantly correlated with increased PAH metabolite levels in the urine of human subjects, while urinary metal metabolite levels were significantly correlated with oxidative stress biomarkers, suggesting a dose-dependent relationship between exposure to metal components and oxidative stress. In the study, $PM_{2.5}$ bound PAHs and metals showed significant exposure-response relationship with markers of oxidative stress, and it was illustrated that the levels of urinary metal metabolites such as 8-OHdG, 8-iso-PGF2α and MDA gradually elevated with increasing environmental $PM_{2.5}$ exposure.

Genotoxicity and malignant transformation

Damage to DNA, oxidative stress induced or not, is a significant contributing factor to cancer development (47). Accumulation of damaged DNA beyond the host's repair capability leads to irreversible changes, resulting in malignant transformations (1,48).

Air pollutants include several mutagenic carcinogens, such as PAHs (e.g., benzopyrene and polar compounds), sulfur-containing compounds (SO_3, H_2SO_4), dioxins, and 3-nitrobenzanthrone (49-52). Epigenetic changes in the genome are considered to mediate the effects of air pollutants on lung cancer development (53). Long-term exposure to the chemical constituents of PM ultimately generates genetic mutations and defects in gene expression (14), as proved in animal and *in vitro* experiments (54-56).

Niu *et al.* (43) showed that after exposure of 16 HBE to $PM_{2.5}$, the micronucleus rate was elevated, and various indicator proteins such as γ-H2AX and 8-OH-dG were remarkably enhanced, indicating subsequent DNA damage. In addition, the changes in the indicator proteins became more evident as the $PM_{2.5}$ levels increased.

Epithelial mesenchymal transition (EMT), which is involved in cancer progression and metastasis, is reportedly induced by $PM_{2.5}$, according to several *in vitro* studies (57). Guo *et al.* (58) showed that organic components from traffic-originated $PM_{2.5}$, promoted lung adenocarcinoma cell invasion and migration via the notch1 signaling pathway. HBE cell lines treated with $PM_{2.5}$ induced EMT, while involving metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) (59).

PM also affects the behavior of preformed cancer cells. Cancer cells exposed to $PM_{2.5}$ show active molecular signatures and cellular processes related to their invasive and proliferative properties (1,60). Similarly, Wei *et al.* (61) using the A549 cell model, showed that $PM_{2.5}$ exposure increases migration and invasion of cancer cells. Lu *et al.* (62) using A549 cells, showed that exposure to PM significantly suppresses miR-26a to upregulate lin-28 homolog B (LIN28B), subsequently upregulating interleukin 6 and signal transducer and activator of transcription 3. This process eventually contributes to EMT, cancer migration, and invasion. In another study using A549 cells and nude

mice, Xu *et al.* (63) showed that exosomes produced after exposure to $PM_{2.5}$, may promote the growth of lung tumor cells *in vitro* and *in vivo* via the Wnt3a/β-catenin pathway. Using the acute and chronic exposure model, Wei *et al.* (61) showed that $PM_{2.5}$ exposure enhanced cell migration and invasion of A549 cells and further induced EMT and cancer stem cell properties.

PM-related genotoxicity has also been observed in human subjects. In a study including 72 subjects from Taiwan, 8-oxo-7, 8-dihydro-2-deoxyguanosine (8-oxodG) and N7-methylguanine (N7MeG), which are biomarkers correlated with oxidative and methylated DNA damage, were longitudinally measured. N7-MeG levels had significantly increased with increasing $PM_{2.5}$, whereas 8-oxodG levels were positively correlated with N7-MeG levels (64). A study comparing traffic policemen and office policemen showed that increased cumulative intersection duty time was associated with increases in 8-hydroxy-20deoxyguanosine, tail DNA, micronucleus frequency, and a decrease in GSH. These findings support the hypothesis that longer exposure to air pollution can induce cumulative DNA damage (65). Alterations in DNA structure may increase the risk of cancer cell development. Among different mechanisms, epigenetic alterations involving DNA methylation and histone modification are involved in carcinogenesis by PAHs, the major component of PM (66). DNA methylation can prevent transcription of tumor suppressor genes, which can lead to development of cancer cells (67). Histone acetylation via histone acetyltransferases decreases histone protein affinity, facilitating DNA transcription process. Alterations in histone acetylation process may deter DNA transcription, increasing the chance of carcinogenesis (68).

However, until now, there has been no target pathway established, to enable therapeutic management and reduce cancer risk. Future studies that consider the chemical constituents of PM need to be conducted to clarify the pathophysiological mechanisms underlying the carcinogenesis of PM.

Possible genetic biomarkers predicting carcinogenesis

Evaluation of the association between genetic factors and risk of lung cancer among patients who are exposed to ambient PM is necessary, as we can focus on the group with certain genetic conditions, to prevent the risk of lung cancer more effectively.

In a study including 1,142 individuals from Taiwan, SOX_2 promoter methylation was shown to be a potential biomarker for industrial air pollution exposure and reflected a predisposition to cancer (69). Exposure to PM_{10} was shown to cause lung cancer development and the genetic changes subsequent to PM_{10} exposure were demonstrated *in vitro*, by Kang *et al.* (70). The lung epithelial cells were exposed to PM_{10} like fine dust, at a concentration of 50 μg/mL. After culture, the extracted RNA was subjected to next generation sequencing (NGS) and the genes that showed significant changes were validated by quantitative real-time polymerase chain reaction (qRT-PCR). The four upregulated genes were *CYP1A1*, *CYP1B1*, *LINC01816*, and *BPIFA2*. The study concluded that development of lung cancer due to PM_{10} exposure may involve the activation of *CYP1A1*, *CYP1B1*, and *LINC01816*, considering that *CYP1A1* and *CYP1B1* contribute to the development of lung cancer by metabolizing PCAH. Another study showed that telomere length in peripheral blood leukocytes is associated with lung cancer development and may be affected by exposure to coal smoke. Subjects were enrolled from the same province, and those in the tertile with the shortest telomere lengths had approximate four-fold increased risk of developing lung cancer (71).

Clinical characteristics of PM attributable to lung cancer

Influence on lung cancer pathologic type

Regarding the cancer types, several studies have shown a strong association between PM exposure and adenocarcinoma development (72,73). For each 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$, the risk of adenocarcinoma significantly increased (72). However, other factors such as smoking should be taken into account when discussing the association between ambient PM and specific pathologic subtypes; certain subtypes such as squamous cell cancer and small cell types are strongly linked to tobacco smoking.

Sex difference

It has been suggested that female patients with lung cancer have different etiologies and they should be regarded as a distinct entity (6,74). Furthermore, the proportion of smokers among female lung cancer patients is usually much lower than that in male patients, depending on the country of residence (75,76). Several studies, mainly from Asian countries, have shown that women may be more susceptible to air pollution in terms of lung cancer risk (77-79). A study

in China showed that PM_{10} is most closely related to lung cancer development, and women are more likely to develop lung cancer from air pollution than men. Data envelopment analysis effectiveness between air pollution and female patients was greater than that of male patients, showing that women are more susceptible to lung cancer caused by air pollution. Furthermore, when different groups of patients were compared, female non-smokers were at higher risk from air pollution induced lung cancer than male non-smokers (77). Regarding $PM_{2.5}$, the risk ratio for lung cancer was significantly higher among women than men. The study participants who were women were mainly never smokers compared to 48% of men who were smokers in the same province. The authors further discussed that this may be due to exposure to indoor cooking oil fumes (78). The difference in lung cancer risk based on sex, was also observed in a study on Korean metropolitan citizens who were exposed to PM_{10} for a long period, however, smoking status was not adjusted in the analysis (79).

Based on the presumption that ambient air pollution results in a higher risk of lung cancer development among women than men, several factors can be considered to be possible reasons. First, women have a smaller body mass than men. In a study based on nationwide data from Korea, low BMI (<18.5 kg/m^2) was a significant independent risk factor for a higher incidence of lung cancer among never-smoking women (80). Second, women may have additional risk factors associated with the development of lung cancer. In East Asia, women have a propensity to spend time cooking and are more likely to be exposed to increased levels of PM from burning fuels such as coal than men (81-86). It is difficult to separate the respective impacts of ambient air pollution and indoor pollution because the two factors often correlate with each other. However, in order to manage the risk factors more effectively, we believe that separate evaluation of ambient air pollution and indoor air pollution is important, and it can be achieved by utilizing the data of populations that show predominant exposure to either of the two factors.

Indoor air pollution

Most of the studies on PM have focused on ambient PM owing to the relative availability of level measurements. Indoor $PM_{2.5}$ consists of elemental carbon components that originate from smoldering combustion in contrast to the elemental carbon components from internal combustion engine exhaust soot, in outdoor $PM_{2.5}$, (87). Aside from second-hand and third-hand tobacco smoke, which are reported to significantly influence indoor PM levels (88), pollutants from indoor cooking are also a significant source of PM. Many studies have shown an association between indoor cooking and use of coal as a fuel within the house, with an increased risk of lung cancer development (81-86).

Most of the studies on association between indoor cooking and risk of lung cancer were conducted in East Asia, the majority of which were from China (89-92). Cooking oil fumes account for a significant proportion of indoor cooking-related PM (93). A case-control study from Taiwan, which was conducted on 1,302 lung cancer patients and the same number of matched healthy controls, showed a dose-response association between cooking fume exposure and lung cancer incidence. While long-term use of a fume extractor during cooking reduces the risk of lung cancer, cooking habits are also important factors affecting the risk of lung cancer (94). A meta-analysis including 23 observational studies and 9,411 lung cancer cases showed that the pooled odds ratio of cooking oil fume exposure was 1.98 (95% CI: 1.54–2.54; I^2 =79%) among the non-smoking female population, suggesting that cooking oil fumes are a risk factor for lung cancer in women. Similar to a previous study, poor ventilation and cooking methods such as stir frying, were considered to increase the risk of lung cancer (89). The chemical composition of $PM_{2.5}$ obtained from cooking oil fumes showed a distinction from $PM_{2.5}$ from other sources. $PM_{2.5}$ from cooking oil fumes include benzo(a)pyrene, benzo(a)anthracene, SO_4^{2-}, NO^{3-}, and NH_4^+, and have higher concentrations of five PAHs than that in $PM_{2.5}$ derived from other sources such as ambient air or incense burning (93,95,96). Liu *et al.* (93) further showed that $PM_{2.5}$ led to cell death, oxidative stress, apoptosis, and cell arrest in primary fetal alveolar cells.

Indoor air pollution, in which indoor cooking plays a major role, may contribute considerably to never-smoking female lung cancer, but epidemiological data supporting this hypothesis are still lacking. In both developing and developed countries, more studies should be conducted to clarify the pathophysiological link between indoor air pollution and the risk of lung cancer.

Cancer prevention and future direction

Efforts to prevent cancer attributable to PM may include measures such as avoiding outdoor activities when air quality is poor and wearing particle-filtering masks. Regarding indoor air pollution, it is necessary to remove

possible sources of indoor elemental carbon components through appropriate ventilation. However, a more large-scale, organized approach should be implemented. Public and government efforts to improve air quality are essential. Constant monitoring of hazardous airborne PM levels of different particle fractions and strict control over sources, such as incineration of wastes, traffic fumes, and combustion of biomass or oil fuel are necessary. In addition, more research should be conducted to determine how constituents of PM induce carcinogenesis and identify the subjects that have a high risk of developing lung cancer when exposed to PM. When conducting future research, regions where the study population reside should be considered as a major factor because concentrations of air pollutants, climate, racial differences, and cultural backgrounds may affect the impact of PM. For example, indoor air pollution due to indoor cooking, tends to be more severe in developing countries due to a lack of ventilation systems and indoor burning of biomass fuels (97,98). Other factors such as ultrafine PM (PM 0.1), which received relatively less clinical attention, should also be evaluated for pathological backgrounds leading to cancer development (24).

Since oxidative stress induced by PM is the major mechanism of lung cancer development, antioxidant usage could be a potential cancer prevention modality. It has been reported that carotenoids, vitamin C, and vitamin E have protective effects against lung cancer (99). Antioxidant products may have some benefit in decreasing the risk of lung cancer; however, evidence supporting the routine use of antioxidants among the population at risk is insufficient, and further studies are necessary (1).

Conclusions

In never smokers, the risk of lung cancer was dose-dependent with the concentration of ambient air pollutants. Considering the significant burden of PM on lung cancer development, both public and clinical approaches to cancer prevention are essential. To prevent lung cancer more effectively, clinicians should develop a more individualized approach in patients, focusing on gender and genetic background. The association between exposure to PM and lung cancer development has been well studied, even among never smokers. Regarding the pathophysiological link, involvement of EMT and chronic inflammation has been mentioned, but further studies are necessary to enable therapeutic interventions to prevent cancer development. Other factors that can aggravate the hazardous impact of ambient PM, such as indoor pollution, smoking, and other epidemiological factors, should also be controlled.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-655/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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