LITERATURE REVIEW

Air Pollution and Lung Cancer

Ida Ayu Jasminarti Dwi Kusumawardani[1*], Putu Gita Indraswari[1], Ni Luh Gede Yoni Komalasari[2]
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Udayana University, Denpasar, Indonesia.
[2]Department of Cell Biology, Graduate School of Medicine, Dentistry, and Pharmaceutical Science, Okayama University, Okayama, Japan.

ARTICLE INFO

Article history:
Received 14 February 2023
Received in revised form
17 April 2023
Accepted 11 May 2023
Available online 31 May 2023

Keywords:
Air pollution,
Cancer,
Lung cancer,
PM2.5.

Cite this as:
Kusumawardani IAJ, Indraswari PG, and Komalasari NLGY. Air Pollution and Lung Cancer. *J Respi* 2023; 9: 150-158

ABSTRACT

Malignant lung cancer is the leading cause of cancer-related death worldwide. Smoking is the main risk factor for lung cancer. However, the International Agency for Research on Cancer (IARC) declared in 2013 that outdoor air pollution is a substance that is carcinogenic and contributes to lung cancer. This was supported by several studies which show an increased prevalence of adenocarcinoma, even in countries with a low prevalence of smokers. The presence of one or more substances in the air for longer periods or at higher concentrations than usual, which can potentially have negative effects, is called air pollution. Aside from carbon monoxide (CO), nitrogen dioxide (NO_2), lead, ozone (O_3), and sulfur dioxide (SO_2), particulate matter with <2.5 µm diameter (PM2.5) has been identified to be associated with the risk of lung cancer. The risk of lung cancer was higher after prolonged exposure to PM2.5 regardless of age, gender, and smoking history. Exposure to air pollution is a significant factor in the onset and progression of lung cancer. Oxidative stress, deoxyribonucleic acid (DNA) damage, inflammation, metabolism, epigenetic control, and signal transduction pathways are a few potential mechanisms of air pollution-induced lung cancer. Everyone, including the government and the general public, must implement strategies to stop the harmful effects of air pollution.

INTRODUCTION

The leading cause of death from cancer worldwide is lung cancer.[1] According to data from the International Agency for Research on Cancer (IARC), lung cancer affects 18% of people worldwide. According to the American Cancer Society, the highest number of cancer-related fatalities is caused by lung cancer, with approximately 350 deaths per day.[2] Based on data from the Ministry of Health of the Republic of Indonesia, lung cancer prevalence in men is 16.77%, and in women, it reaches 9.89%.[2,3]

Smoking is the primary cause of lung cancer in both men and women. Lung cancer is known to be influenced by several other factors, including air pollution. Since 2013, outdoor air pollution has been classified by the IARC as a substance that carcinogenic to human life.[4] This is supported by several studies which show an increased prevalence of adenocarcinoma, even in countries with a low prevalence of active smokers and passive smokers, such as Taiwan.[5]

Air pollution occurs due to the accumulation of many hazardous substances. All contaminants in the atmosphere, whether gases, particulate matter (PM), or biological particles, are considered sources of air pollution. These dangerous substances may be produced due to production processes, modernization efforts, or organic phenomena. Air pollution can be classified into physical, gas, chemical, and biological.[4]

PM, a type of physical pollution, comprises a variety of solid and liquid particles suspended in the air.

*Corresponding author: jasminarti@unud.ac.id

Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v9-I.2.2023.150-158

PM10 particles have a diameter of 10 micrometers or less, and PM2.5 particles are tiny and have 2.5 micrometers or less diameter.[6] This enables them to invade alveolar tissue and tiny airways. Benzene, dioxins, PAHs, other organic and inorganic compounds, and metals constitute the complex mixture that makes up atmospheric PM. According to a European cohort study, exposure to PM2.5 increases the risk of developing lung cancer, especially lung adenocarcinoma.[6] According to a different study, an increase in PM2.5 concentration every 10 g/m^3 will raise the risk of dying from lung cancer by 15–27%.[2]

Exposure to outdoor air pollution is an important and urgent health problem because it will continue to increase along with the development of the industrial sector and modernization and affect almost everyone. This review summarizes the mechanism of lung cancer due to air pollution, the association between lung cancer and air pollution, and recommendations for minimizing air pollution.

When one or more substances are present in air-safe levels for extended periods and potentially have negative effects, this is called air pollution.[2,4] Air pollution can be differentiated based on its source, chemical composition, and place of emission/release. There are two types of air pollution: primary and secondary. Primary pollutants are those released directly from specific atmospheric sources, such as sulfur dioxide (SO_2), carbon monoxide (CO), and PM. Meanwhile, secondary pollutants arise from chemical reactions between pollutants and gases, including ozone (O_3) and nitrogen dioxide (NO_2).[7]

Air pollutants can also be separated into outdoor and indoor air pollution. The following is a general classification of air pollution according to Bernstein, *et al*. (2019) (Table 1).[7] Physical, chemical, gaseous, and biological pollutants can all be classified as pollutants in outdoor air.[2] The classification of air pollutants, their types, physical form, and primary sources can be seen in Table 2.[2]

DEFINITION AND TYPES OF AIR POLLUTION

Table 1. Air pollution classification[7]

A. Primary – Secondary Pollutant
   1. Primary: Pollutants are released from the source into the atmosphere directly
   2. Secondary: Pollutants that arise in the air due to chemical reactions between gases and pollutants

B. Outdoor – Indoor Pollutant
   1. Indoor pollutants
      a. Sources: cooking, internal combustion, materials of the building, resuspension of particulates, air conditioners, cigarette smoke, space heaters, biological agents
      b. Products: combustion products, specific volatile organic compounds, CO, CO_2, microbiological agents, radon, organic dust, artificial fibers
   2. Outdoor pollutants
      a. Sources: industry, commercial activity, vehicle, urban activity, agriculture, plantation, natural process
      b. Products: SO_2, O_3, NO, PM, CO, specific volatile organic compounds

C. Gas – Particle Pollutant
   1. Gas: SO_2, CO, O_3, NO, specific volatile organic compounds
   2. Particles: Fine PM (2.5-10 microns; generally PM10), fine particle (0.1-2.5 microns; generally PM2.5), and ultrafine PM (size < 0.1 microns)

PM: Particulate matter; CO: Carbon monoxide; SO_2: Sulfur dioxide; CO_2: Carbon dioxide; NO: Nitrogen oxide; O_3: Ozone

Table 2. Classification of the primary pollutants by group, physical form, and resources[4]

Pollutants	Examples	Physical form	Main sources
Photochemical oxidant	Ozone	Gas	NO_X, VOCs, and CO, a natural process
Sulfur dioxide	SO_2	Gas	Burning of fossil fuels
Carbon monoxide (CO)	CO	Gas	Fossil fuel burning, oxidation from emissions of biogenic VOC
Nitrogen oxide (NO_X)	NO_2	Gas	Burning
Hazardous air pollutants (HAPs)	1,3-butadiene, benzene, formaldehyde acid	Gas	Incomplete combustion, chemical processing, use of solvents
Mercury (Hg)	Hg^0, methylmercury	Gas and particulate	Coal burning
Lead (Pb)	Pb	Particulate	Lead burning, lead treatment process
PM, including $PM_{2.5}$, PM_{10}, respirable PM total suspended particle (TSP)	Inorganic (sulfate) ions, metal oxides, and carbonaceous materials, including elemental carbon (EC) and OC	Particulate	Dust, burning of fossil fuels, burning of biomass fuels, biogenic emissions, use of fertilizers, conversion of gas to PM
Organic carbon (OC)	Hopane, sterane, polycyclic aromatic hydrocarbons (PAH), levoglucosan	Particulate	Combustion of fossil fuels and biomass, vegetative detritus, oxidation of gaseous organic compounds

Primary, secondary, and re-emission sources are the categories into which air pollution sources can be subdivided. From the direct emission source, the main source is derived. Re-emissions are pollutants that originate from primary or secondary pollutants that are deposited on the ground or water surface and then released back into the atmosphere. Secondary pollution results from precursor chemical reactions released from air pollution sources. The IARC has published IARC Monographs on the Identification of Carcinogenic Hazards to Humans, which international working groups made of independent scientists. They classified carcinogenic agents into groups based on evidence. Group 1 applies whenever there is sufficient evidence of carcinogenicity in humans. Agents included in Group 2A are probably carcinogenic to humans, while those of Group 2B are possibly carcinogenic. Agents not classifiable to their carcinogenicity to humans are included in Group 3. Table 3 shows outdoor agents defined and suspected as carcinogens.[4]

Table 3. Outdoor agents defined and suspected as carcinogens[4]

Agent	Group
Metal	
Asbestos	1
Arsenic and inorganic arsenic mixtures	1
Beryllium and beryllium mixture	1
Chrome	1
Cadmium and cadmium mixture	1
Lead mixture	2A/3
Silica dust	1
Nickel	2B/1
Organic chemistry	
Benzene	1
1,3-butadiene	1
Ethyl oxide	1
Formaldehyde	1
Halogenated chemical	
2,3,7,8-tetrachlorodibezo-para-dioxin	1
1,2,3-trichloropropane	2A
Ethylene dibromide	2A
Tetrachloroethylene	2A
Trichloroethylene	1
Vinyl fluoride	2A
Vinyl chloride	1
Vinyl bromide	2A
Polycyclic aromatic hydrocarbons	
1-nitropyrene	2A
6-nitrochrysene	2A
2-nitrotoluene	2A
Dibenz(a,h)anthracene	2A
Cyclopenta(cd)pyrene	2A
Benzo(a)pyrene	1
Mixture	
Indoor emissions from combustion, biogas fuel (mainly wood)	2A
Indoor emissions from coal, household burning	1
Emission from high temperature, frying	1
Product of carbonated drink	1
Creosote	2A
Coal tar pitch	1
Diesel engine muffler	2A
Polychlorinated biphenyl	1
Mineral oil	1
Polybrominated biphenyl	2A
Cigarette and secondhand smoke	1
Wood dust	1

Note: Carcinogens and suspected carcinogenic substances are included in Groups 1 and 2A

Photochemical oxidants are secondary pollutants formed when photochemical reactions occur in the atmosphere. These oxidants are continuously produced, interfering with chemical reactions and creating pseudo-steady state concentrations that are necessary for chemical processes and can be inhaled. These oxidants include reactive radicals, peroxyacetyl nitrate, acids, O_3, and hydrogen peroxide. Product of combustion, such as nitrogen oxides (NOx) and volatile organic compounds (VOCs), reacts chemically to produce O_3. The World Health Organization (WHO) stated that the average safe limit for O_3 exposure was 100 µg/m^3 per 8 hours.[4]

Atmospheric particles are related to their source, both the physical processes that shape them and the processes in the atmosphere that control and change the particles' size. Coarse particles (particles between 2.5 µm and 1.0 µm in diameter) are produced by physical processes, including soil and road dust resuspension, agricultural processing, vehicle abrasion (tire wear and brakes), and industrial process emissions.[4]

SO_2 is the product of atmospheric oxidation of a sulfur mixture which is emission from microbial activity in the sea and anaerobic degradation of organic matter. SO_2 emissions from Mount Merapi also affect SO_2 exposure in some locations, such as Japan and Mexico. However, in most areas, SO_2 emissions from natural materials are usually lower than anthropogenic emissions. In urban areas, SO_2 comes from combustion and metal production. In some areas where coal is burned for heating and cooking in the household environment, high exposure to SO_2 can occur. According to WHO, the average safe limit for SO_2 exposure is 500 µg/m3 every 10 days and 20 µg/m3 daily.[4,7]

CO is a gas that is tasteless, odorless, and colorless. This gas is generally caused due to imperfect combustion of carbon substances, predominantly produced by transportation (gasoline or diesel-powered vehicles) or biomass combustion activities. CO concentrations in rural areas generally come from biomass-burning activities because they are used for cooking and heating homes. Inhaled CO will enter the body and diffuse from the alveoli to the blood capillaries. In the erythrocytes, CO will bind with hemoglobin (Hb) with a high affinity to form carboxyhemoglobin (COHb). Hb has a 3-fold bond with CO compared to oxygen (O_2). The occurrence of competitive bonding between O_2 and CO will result in hypoxic conditions and a decrease in the oxidative phosphorylation process. Hence, adenosine triphosphate

(ATP) production will also decrease. COHb is not effective at delivering oxygen and can cause hypoxia.[4,7]

NO_2 is generally produced by burning fossil fuels, microbial activity in the soil, and biomass burning, with a small portion coming from lightning and stratospheric nitrous oxide (N_2O) oxidation. In urban areas, the burning of fossil fuels is the dominant source, in addition to power plants, engines with diesel fuel, and engines with gasoline fuel. Meanwhile, in the countryside, fuel combustion and microbial activity in the soil are the dominant sources of NOx. According to WHO, the average NO_2 exposure is 200 µg/m^3 per hour and 40 µg/m3 per year. NO_2 is also an oxidant pollutant. However, it is less reactive and less potent than O_3.[4,7]

Non-volatile metals are PM components of the atmosphere and can influence their biological activity. Apart from road emissions and electricity generation, industrial sources are the main origins of non-volatile metals. Atmospheric mercury concentrations are dominated by fuel combustion, generally coal.[4,7]

PM2.5

PM2.5 is a mixture of airborne liquid and solid particles with a diameter of less than 2.5 microns (µm). PM2.5 is one of the most important pollutants in deteriorating air quality, besides CO, NO_2, lead, O_3, and SO_2. Based on their size, PM can be classified into PM10, PM2.5, and PM1. Another name for PM10 is a coarse PM with a size of 2.5-10 micrometers (µm). The smaller the diameter of the dust particles, the more dangerous they are because they can enter the airways and reach the bronchioles and alveoli. Fine particulate is another name for PM2.5 with a diameter of 0.1 to 2.5 µm. Ultrafine particulate is another name for PM1, which has a diameter of 0.1 to 10 µm. PM with a diameter of ≥5 µm will settle in the nose, nasopharynx, trachea, and bronchial tree. PM with <2 µm diameter will be in the respiratory bronchioles and alveoli, while PM with a diameter of <0.5 µm generally does not settle in the respiratory tract and can be expelled again. How small is 2.5 µm? The average diameter of human hair is about 70 µm, making it 30 times larger than the fine particle (Figure 1). WHO recommended exposure limit for PM2.5 is 25 µm/m3 per day, an average of 10 µm/m3 per year.[7]

PM can come from various sources, such as combustion engines, industry, plants, home energy, burned biomass, crop cultivation, and dust. PM is also associated with various health problems, including cardiovascular, respiratory, endocrine, cancer, and others, even at low concentrations.[8]

The biggest threat to public health is PM as a risk factor. According to the Global Burden of Disease (2015), exposure to PM2.5 is the fifth biggest risk factor for death worldwide, accounting for 4.2 million deaths (7.6% of all fatalities). According to WHO, three billion people are exposed to indoor air pollution because of non-renewable fuels. Nine out of ten people in urban areas are exposed to outdoor air pollution containing high levels of PM2.5 (annual average concentration >10 g/m^3). The Air Quality Life Index (AQLI) estimates that every increase of 10 g/m^3 of PM2.5 over time reduces life expectancy by 0.98 years. Additionally, 0.22% of deaths from respiratory diseases and 0.29% of all deaths are increased with a 10 g/m^3 per day increase in PM2.5 concentration.[9]

PM can be found around 50-70% freely scattered in the air and the atmosphere for days or weeks. PM is considered the most harmful. A variety of toxic and dangerous substances can be absorbed by PM due to its large surface area. PM can enter the gas-blood barrier and travel deep into the lungs, where it can precipitate in the terminal bronchioles, alveoli, and the circulatory system (Figure 1).[9,10]

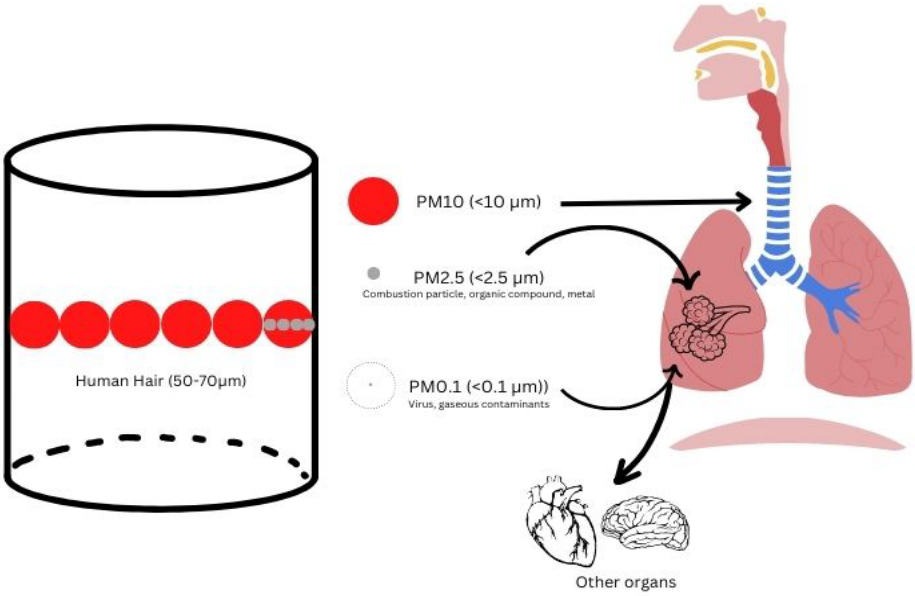

Figure 1. Particulate size, composition, and deposition in the lungs[10]

MECHANISM OF LUNG CANCER DUE TO AIR POLLUTION

The onset and progression of lung cancer are significantly influenced by exposure to air pollution. Oxidative stress, deoxyribonucleic acid (DNA) damage, inflammation, metabolism, epigenetic control, and signal transduction pathways are a few possible mechanisms for how air pollution causes lung cancer (Figure 2).[2,11] PM2.5 induces tumor suppressor gene inactivation and oncogene activation through DNA methylation and microRNA dysregulation in lung cancer. Alteration of tumor microenvironment is also detected in PM2.5-induced inflammatory cells (Figure 3).[6] These various mechanisms are described in Figure 2.

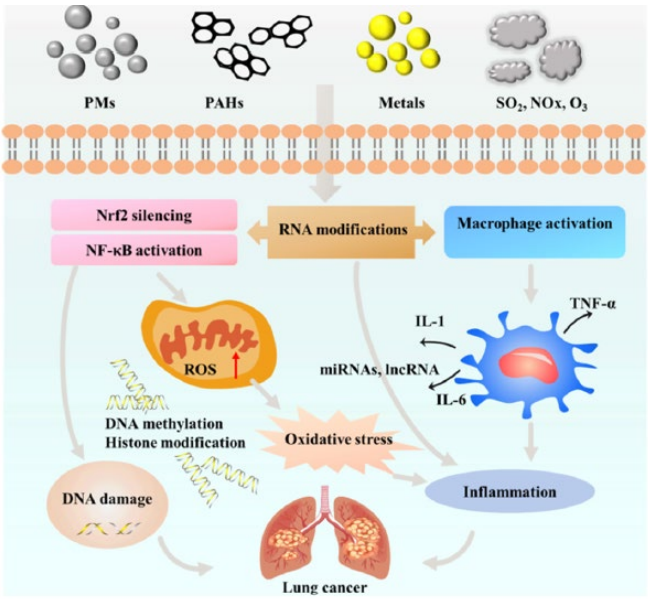

Figure 2. Mechanism of air pollution as a cause of lung cancer[2]

a. Oxidative Stress

When dangerous oxidants like free radicals and reactive oxygen species (ROS) are present, it causes oxidative stress. This stress causes cellular constituents like nucleic acids, proteins, and fats to oxidize, facilitating inflammatory cell invasion.[2]

Exposure to PM2.5 causes oxidative stress, antioxidant and inflammatory reactions, and changes in epithelial cell activity. The smaller size of the PM, the greater its ability to produce ROS and cause oxidative stress on bronchial epithelial cells. Epithelial cells that have been exposed to PM produce more ROS. The main mediators of the inflammatory effects of PM are the

nicotinamide adenine dinucleotide phosphate (NADPH) and oxidase of dual oxidase 1 (DUOX1). Through increased expression of DUOX1 in bronchial epithelial cells and both NADPH and DUOX1 from epithelial cells of the bronchial and alveolar levels, PM2.5 exposure increases cell oxidative stress. In addition, PM causes mitochondrial toxicity, which impairs oxidative phosphorylation in bronchial epithelial cells by increasing the production of ROS in the mitochondria, deregulating electron transport, reducing the potential of the mitochondria, and losing the ability to store energy.[10]

Activation of transcription factors like activator protein 1 (AP-1), NF-κB, mitogen-activated protein kinase (MAPK), and other enzymes are linked to ROS. Cigarettes and PM contain hydroxyl radicals, contributing to increased ROS production.[2] Apoptosis and mitochondrial dysfunction can be caused by defects of mitochondrial kinetic and an abundance of mitochondrial fragments. By inhibiting ATP synthesis and oxidative phosphorylation signaling pathways (downregulation of NDUF, ATP5F, UQCR, and COX7A; upregulation of CAPN1 and RELA), PM2.5 exposure causes necrosis of BEAS-2B cells. Additionally, PM2.5 participates in the autophagy of A549 cells, which can harm the lungs. PM2.5 can alter matrix metalloproteinases (MMPs), disrupt redox reactions, and cause oxidative stress in mitochondria after silencing Nrf2. Another crucial antioxidant enzyme, metallothionein protein (MT-1) 1, is upregulated when it binds to heavy metals (Figure 2).[2]

b. Inflammation

Pollutant exposure can also result in an inflammatory response. One example of an inflammatory marker that increases its expression due to exposure to fine particles is NF-kβ. In both in vitro and in vivo settings, it is known that the onset of acute inflammation is accompanied by an increase in the expression of chemokines, cytokines, and proteins (IL-1, TNF), as well as heme oxygenase-1 (HO-1) associated with angiogenesis and autophagy.[2] Another study found that 1-nitropyrene (1-NP) acute exposure increases levels of IL-1, TNF-α, IL-6, and Kc in lung tissue through NF-κB pathway activation. This causes inflammation by activating the ROS-mediated NLRP3 and TLR4/NF-B pathways. Pro-inflammatory cytokine (IL-1) is released because of PM2.5 exposure, which in turn increases the inflammatory response (Figure 2).[2]

c. DNA Damage

DNA damage occurs when the nucleotide sequence is altered during replication. It can lead to tumor suppressor gene inactivation or oncogene activation. The mutations involved in lung cancer pathogenesis are brought about by the accumulation of DNA damage over a long period. Exposure to PM2.5 can cause reverse transcription of p53, autophagy, and a sizable upregulation of vascular endothelial growth factor (VEGF), all of which can contribute to pulmonary vascular endothelial dysfunction and chronic inflammation. p53 mutations can also lead to abnormal cell growth, damage, and apoptosis, which will aid in the pathogenesis of lung cancer. Exposure to air pollution, especially c-PAH and B[*a*]P from PM2.5, can cause oxidative damage and DNA addition (Figure 3).[2]

d. Epigenetic Changes

Epigenetic changes are cellular responses that occur due to air pollution exposure and can be in the form of modification of non-coding RNA, DNA methylation, and modification of histones.[2,6] Micro RNA (miRNA) is contributed to the control of post-transcriptional gene expression, including differentiation, apoptosis, and proliferation. 25 miRNAs, including miR-21, miR-222, miR-155, miR-425, and miR-126-3p, which are significant regulators, promoters, or inhibitors of angiogenesis, inflammation, are linked to air pollution exposure and lung cancer (Figure 2).[2,6]

p53 regulatory gene is an important regulator in apoptosis, cell proliferation, and repair against cell damage. It contributes to lung cancer pathogenesis. In previous studies, it was known that PM2.5 exposure induces p53 mutations. Exposure to PM2.5 was able to induce p53 promoter methylation by increasing the level of DNA (cytosine-5)-methyltransferase 3β (DNMT3B) methylation, mediating the inactivation of p53 (Figure 3).[2,6]

Changes in chromatin structure and function are caused by histone modifications, which change how histone interacts with DNA and effector proteins. Histone H3 and H4 modifications are recognized as potential biomarkers of lung cancer. H3K27ac changes brought on by PM2.5 exposure are linked to the activation of immune cells and inflammatory responses. Increased methylation of H3K9 and H3K4 in the promoter region of IFN- and IL-6 has been linked to long-term PM2.5 exposure (Figure 3).[2,6]

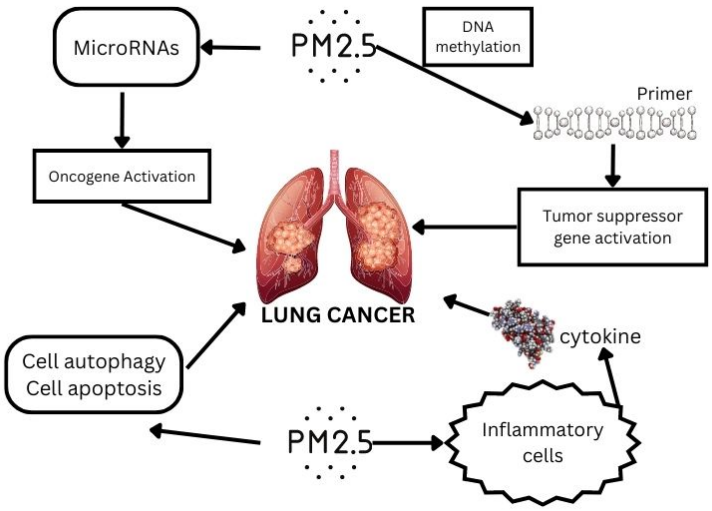

Figure 3. PM2.5 and its role in the pathogenesis of lung cancer[6]

PM2.5 AND LUNG CANCER

PM2.5 raises the risk of lung cancer. One study reported that lung cancer incidence increased 1.11 times (95% CI = 1.05–1.18) for every 10 units of increase in PM2.5 exposure.[10] Another study stated that a 1 μg/m^3 PM2.5 increase was linked to a higher incidence of lung cancer (OR adjusted = 2.394, 95% CI = 1.446–3.964).[12] A study by Hvidtfeldt, *et al*. (2021) also supports this, which discovered a higher risk of lung cancer at higher PM2.5 exposure (HR: 1.13, 95% CI: 1.05-1.23 per 5 g/m^3).[13] Even at PM2.5 concentrations below the values advised by Europe (25 g/m^3) and WHO (10 μg /m^3), exposure to PM2.5 over a long period is linked to lung cancer.

Exposure to PM2.5 is said to have a higher association with the incidence of adenocarcinoma than squamous cell carcinoma. A study conducted by Gharibvand in 2017 showed a 1.3-fold increased risk of adenocarcinoma (95% CI = 0.87–1.97) for every 10 units of PM2.5 increased.[14] Another study stated the same. There is an increased risk of adenocarcinoma along with increased exposure to PM2.5 per 1 μg/m^3.[12] A higher increased risk of adenocarcinoma was found in populations who spent more than one hour per day outdoors.[14] Increased PM2.5 levels are also said to increase the risk of having malignant pleural effusion (OR= 1.517; 95% CI = 1.082–2.127).[14]

The risk of mortality for patients with lung cancer related to PM2.5 exposure is 1.11 (95% CI: 1.05-1.18). Based on its geographic location, it is known that North America has the largest rank for mortality in lung cancer related to PM2.5 with an RR of 1.15 (95% CI: 1.07, 1.24), then Asia with an RR of 1.12 (95% CI: 0.94-1.35), and Europe with an RR of 1.05 (95% CI: 1.01-1.10). In the analysis of male and female subgroups, mortality caused by lung cancer related to PM2.5 was greater for males with an RR of 1.26 (95% CI: 1.15, 1.40) than for females with an RR of 1.17 (95% CI: 0.98, 1.39).[15]

Incidence of lung cancer associated with PM2.5 was found in Asia with an RR of 1.09 (95% CI: 1.03, 1.15), followed by North America with an RR of 1.06 (95% CI: 1.01, 1.11), then Europe with RR 1.03 (95% CI: 0.61, 1.75). Incidence of lung cancer linked with PM2.5 was higher in men with RR 1.23 (95% CI: 0.83-1.81) than in women with RR 1.15 (95% CI: 1.12-1, 18).[15]

Smoking is said to be related to death from lung cancer associated with PM2.5. The risk of death for former smokers was 1.46 (95% CI: 0.84, 2.55), while active smokers had a lower risk of death, 1.33 (95% CI: 1.20 - 1.49). The population who had never smoked had a risk of death of 1.16 (95% CI: 1.02, 1.33). Based on a meta-analysis conducted by Yu, *et al*. (2021), who reviewed 30 publications from Europe, United States, and Asia covering a total population of 30.8 million, it was found that the combined RR of change in lung cancer incidence or death is 1.16 (95% CI, 1.10-1.23) for every increase of 10- μg/m^3 in PM2.5 exposure.[16]

Based on a study by Myers, *et al*. (2021), it was found that there was an increase in the hazard ratio in patients who had never smoked to lung cancer incidence.[17] Their study found a significant association between lung cancer incidence in a non-smoker population and female with an OR of 4.01 (95% CI 2.76-5.82, $p < 0.001$). In the Asian population, when compared with the non-Asian population, the OR was found to be 6.48 (95% CI 4.42–9.50, $p < 0.001$), while PM2.5 exposure obtained OR 1.79 (95% CI 1.10-7.29, $p = 0.019$).[17]

Overall, the meta-analysis showed that exposure to PM2.5 over a lengthy period was associated with an

increased risk of lung cancer, even after variables for age, sex, and smoking were controlled. The ESCAPE study reported that PM2.5 exposure was only associated with the risk of lung adenocarcinoma.[16] In line with population growth and urbanization, it is important to perform further studies regarding air pollution as a determinant factor for lung cancer in non-smoker patients without any other risk factors.[17]

RECOMMENDATIONS REGARDING AIR POLLUTION

Various studies have demonstrated the harmful effects of air pollution in the last two decades. Recent studies have shown that those effects are not limited to exposure to high concentrations. Even low concentrations of exposure can be bad for health. Thus, strategies to prevent the harmful effects of air pollution need to be implemented. Reducing outdoor air pollutants, especially PM, requires the cooperation of many parties. The government as a policy maker plays a role in making good regulations regarding air pollution control, better coordination with academicians and organizations to deal with air pollution, improving air quality through various steps to reduce air pollution, monitoring air pollution, and increasing public awareness, as well as preparing the health service system.[7,18]

Apart from public policies regulated by the government, here are some recommendations for personal strategies that can be implemented to reduce the impact of air pollution (Table 4).[19–21]

Table 4. Personal strategies to minimize air pollution impacts[21]

	Intervention	Recommendation
1.	Use particulate respirator masks, such as N95 masks, when traveling to high air pollution area	C
2.	Avoid using motorized vehicles and choose cycling or walking	C
3.	Choose routes of travel with minimal air pollution exposure, such as routes with low traffic and open spaces, and delay traveling to high air pollution areas whenever possible	C
4.	Optimization of conditions when using motorized vehicles, such as closing the windows when driving and maintaining vehicle air filtration, and avoiding engine idling	D
5.	Exercise regularly and limit outdoor activities when air pollution is high	C
6.	Be wary of air pollution levels	D
7.	Use fuel that does not pollute the air	C/D
8.	Ensure household ventilation is adequate if possible	C
9.	Use portable air purifiers, increase ventilation, and reduce sources of household air pollution	C
10.	Treat respiratory diseases	D
11.	Modify your diet and take antioxidant or anti-inflammatory-rich supplements	D

SUMMARY

Exposure to air pollution is a significant factor in the beginning and progression of lung cancer. Over a long period, an increased risk of lung cancer is associated with exposure to PM2.5. Oxidative stress, DNA damage, inflammation, metabolism, epigenetic control, and signal transduction pathways are some of the potential mechanisms of air pollution-induced lung cancer. Strategies to prevent the harmful effects of air pollution need to be performed, especially in relation to lung cancer. Apart from making public policies by the government, personal strategic interventions need to be performed in an effort to minimize the impact of air pollution.

Acknowledgments
None declared.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
This study did not receive any funding.

Authors' Contributions
Concepting, preparing, and corresponding: IAJDK. Manuscript writing: IAJDK, PGI. Revising: IAJDK, PGI, NLGYK. All authors contributed and approved the final version of the manuscript.

REFERENCES

1. Thandra KC, Barsouk A, Saginala K, *et al*. Epidemiology of Lung Cancer. *Contemp Oncol (Poznan, Poland)* 2021; 25: 45–52.
2. Xue Y, Wang L, Zhang Y, *et al*. Air Pollution: A Culprit of Lung Cancer. *J Hazard Mater* 2022; 434: 128937.
3. Pangribowo S. *Beban Kanker di Indonesia*. Jakarta, https://www.studocu.com/id/document/universitas-udayana/antropologi-kesehatan/infodatin-kanker-2019/32696320 (2019).
4. (IARC) IA for R on C. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Outdoor Air Pollution (Volume 109)*. Lyon, https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Outdoor-Air-Pollution-2015 (2015).
5. Chen K-C, Tsai S-W, Shie R-H, *et al*. Indoor Air Pollution Increases the Risk of Lung Cancer. *International Journal of Environmental Research*

and Public Health; 19. Epub ahead of print 2022.
6. Li R, Zhou R, Zhang J. Function of PM2.5 in the Pathogenesis of Lung Cancer and Chronic Airway Inflammatory Diseases (Review). *Oncol Lett* 2018; 15: 7506–7514.
7. Susanto AD. *Pencegahan dan Penanganan Dampak Kesehatan Akibat Polusi Udara Luar Ruangan*. Jakarta, 2019.
8. Baghbeheshti M, Zolfaghari M, Rückerl R. Fine Particulate Matter (PM2.5) and Health Effects: An Unbridle Problem in Iran. *Galen Med J* 2017; 6: 81–94.
9. Chen R, Yin P, Meng X, *et al*. Fine Particulate Air Pollution and Daily Mortality: A Nationwide Analysis in 272 Chinese Cities. *Am J Respir Crit Care Med* 2017; 196: 73–81.
10. Yang L, Li C, Tang X. The Impact of PM2.5 on the Host Defense of Respiratory System. *Frontiers in Cell and Developmental Biology*; 8, https://www.frontiersin.org/articles/10.3389/fcell.2020.00091 (2020).
11. Thangavel P, Park D, Lee Y-C. Recent Insights into Particulate Matter (PM(2.5))-Mediated Toxicity in Humans: An Overview. *Int J Environ Res Public Health*; 19. Epub ahead of print June 2022.
12. Bai K-J, Ho S-C, Tsai C-Y, *et al*. Exposure to PM2.5 is Associated with Malignant Pleural Effusion in Lung Cancer Patients. *Ecotoxicol Environ Saf* 2021; 208: 111618.
13. Hvidtfeldt UA, Severi G, Andersen ZJ, *et al*. Long-Term Low-Level Ambient Air Pollution Exposure and Risk of Lung Cancer - A Pooled Analysis of 7 European Cohorts. *Environ Int* 2021; 146: 106249.
14. Gharibvand L, Lawrence Beeson W, Shavlik D, *et al*. The Association between Ambient Fine Particulate Matter and Incident Adenocarcinoma Subtype of Lung Cancer. *Environ Heal* 2017; 16: 71.
15. Huang F, Pan B, Wu J, *et al*. Relationship between Exposure to PM2.5 and Lung Cancer Incidence and Mortality: A Meta-Analysis. *Oncotarget*; 8, https://www.oncotarget.com/article/17313/text/ (2017).
16. Yu P, Guo S, Xu R, *et al*. Cohort Studies of Long-Term Exposure to Outdoor Particulate Matter and Risks of Cancer: A Systematic Review and Meta-Analysis. *Innov* 2021; 2: 100143.
17. Myers R, Brauer M, Dummer T, *et al*. High-Ambient Air Pollution Exposure among Never Smokers versus Ever Smokers with Lung Cancer. *J Thorac Oncol* 2021; 16: 1850–1858.
18. Turner MC, Andersen ZJ, Baccarelli A, *et al*. Outdoor Air Pollution and Cancer: An Overview of the Current Evidence and Public Health Recommendations. *CA Cancer J Clin* 2020; 70: 460–479.
19. Hoffmann B, Boogaard H, de Nazelle A, *et al*. WHO Air Quality Guidelines 2021–Aiming for Healthier Air for All: A Joint Statement by Medical, Public Health, Scientific Societies and Patient Representative Organisations. *International Journal of Public Health*; 66, https://www.ssph-journal.org/articles/10.3389/ijph.2021.1604465 (2021).
20. Sofia D, Gioiella F, Lotrecchiano N, *et al*. Mitigation Strategies for Reducing Air Pollution. *Environ Sci Pollut Res* 2020; 27: 19226–19235.
21. Carlsten C, Salvi S, Wong GWK, *et al*. Personal Strategies to Minimise Effects of Air Pollution on Respiratory Health: Advice for Providers, Patients and the Public. *Eur Respir J* 2020; 55: 1902056.