LITERATURE REVIEW

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THE IMPACT OF AIR POLLUTION ON THE OCCURRENCE OF LUNG CANCER: A LITERATURE REVIEW

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# ABSTRACT

Combustion of fossil fuels, industrial emissions, biomass and waste combustion results in an increase in the amount of harmful substances such as sulfur dioxides, nitrogen oxides, carbon monoxide, ozone, particulate matter or aromatic hydrocarbons in the environment. The air full of pollutants that we all breathe affects our respiratory and cardiovascular systems and is also a factor leading to the development of cancer. The polluted air we breathe in every day drives the influx macrophages that release inflammatory mediators such as interleukin-1 $\beta$ , accelerating the expansion of cells with EGFR mutations. Overexpression mutated EGFR gene is characteristic of non-small cell lung cancer. Adenocarcinoma is one of the most common lung cancers. It accounts for 40% of all types of lung cancer.

In the European Union, Bulgaria and Poland are among the most polluted countries, while Sofia, Nicosia and Warsaw are the three most polluted capitals. Solid particles suspended in the air have been recognized by the International Agency for Research on Cancer (IARC) as a factor group I carcinogen. The concentration of PM10 measured at regional background stations, i.e. outside the direct impact of traffic pollution and outside city centers, in Poland is almost the highest in Europe and amounts to over  $60 \ \mu g/m^3$  with the standard up to  $20 \ \mu g/m^3$ . An adult person inhales 10-12 m3 of air per day, and with it inhales the pollutants contained in it into the body.

The aim of our work was to examine the correlation between air pollution and lung cancer and to conclude that anyone may be at risk.

**Methods:**We analyzed scientific papers on lung cancer and its correlation with the occurrence of air pollution. We searched pubmed and specialized literature for information.

**Conclusions:** There is a strong correlation between air pollution and the occurrence of lung cancer. Due to increasing air pollution, we can expect an increase in the number of patients suffering from this cancer. Air pollution in Poland is at a very high level. It is known that lung cancer is the most common cancer causing death in the Polish population, both among women and men. In 2019, the National Cancer Registry reported 22,271 people diagnosed with lung cancer in Poland. Therefore, this challenge needs to be addressed.

Keywords: lung cancer, air pollution, carcinogenesis, respiratory system, nicotinism, climate change

### INTRODUCTION

Air is an essential element of life, and its quality and components determine the health and proper functioning of the entire ecosystem. It consists of a mixture of various gases, such as nitrogen, oxygen and carbon dioxide, and others in trace amounts. [1,11] The composition of the atmosphere has changed gradually over the past millions of years, but it was especially influenced by the outbreak of the industrial revolution that took place in Europe and North America, as well as by the dynamic economic development of the last 50 years.

Highly industrialized and urbanized areas have a direct impact on the level of air pollution, and thus the quality of life of the inhabitants. An adult person inhales 10-12 m3 of air per day, and with it the pollutants penetrate into the body. [11]

Air pollution is defined as an excessive concentration of foreign matter in the air that is harmful to human health. According to WHO data in 2012, one in nine deaths was related to air pollution. Therefore, it can be considered that it is one of the most important environmental factors contributing to the loss of health and life. It should be emphasized that the inhabitants of Africa, Asia and the Middle East live in an environment with a higher intensity of air pollution than other regions of the world. [1,28]

In the European Union, Bulgaria and Poland are among the most polluted countries, while Sofia, Nicosia and Warsaw are the three most polluted capitals. Seven of the ten most polluted cities in the European Union and 33 cities from the group of 50 with the most polluted air are located in Poland. In 2015, the city with the highest average annual PM2.5 concentration in the European Union was Żywiec, and in previous years, e.g. Pszczyna. [11]

After the smoking, air pollution is the second leading cause of lung cancer [2]. Lung cancer is estimated as the most common cancer causing male and female death in Poland. In 2019, Polish National Cancer Registry reported 22,271 lung cancer cases. Therefore, we need to raise awareness on air pollution as a cause of lung cancer risk. [32].

# METHODS

We have carefully analyzed pubmed articles and specialist literature. Our goal was to familiarize the reader with both the problem of air pollution and its impact on lung cancer. The review of the works was carried out in a critical and detailed manner so as to elaborate on this issue as accurately as possible.

# **RESULTS AND DISCUSSION**

### **AIR POLLUTION**

The composition of polluted air is not constant, it varies seasonally and is related to industrial activities, transport, as well as prevailing winds and seasons. The sources of pollutant emissions are both natural processes and anthropogenic activities. Taking into account natural changes in the environment, their concentration depends on the amount of pollutant emissions into the atmosphere, but also on specific weather situations, e.g. winter anticyclonic atmospheric circulation, with low air temperature, low wind speed and lack of precipitation. From the beginning of the increased development of urbanization, human activity has a significant impact on the level of air pollution. The combustion process has the greatest impact, especially the combustion of fossil fuels and biomass - agricultural waste and waste from urban areas, as well as the resuspension of surface dust and construction works. [1,29]

CONVENTIONAL AIR CONTAMINANTS	UNCONVENTIONAL AIR CONTAMINANTS
Sulphur dioxide	Asbestos
Nitrogen Oxides (NO, NO2)	Mercury
Carbon Monoxide (CO)	Beryllium
Ozone	
Particulate Matter (PM 10, PM 2.5)	
Aromatic Hydrocarbons	
Lead	

Air pollution can be divided into conventional and unconventional.

Conventional pollution includes compounds such as:

#### **SULPHUR DIOXIDE**

It is a by-product of burning fossil fuels and leads to acidification of the air, becoming the main component of London Fog and acid rain. It is an easily soluble gas, and in the secretions of the mucous membranes it is transformed into toxic sulfuric acid, which is aspirated through the bronchial tree and the alveolar space of the lungs. The concentration of sulfur dioxide in low, average concentrations causes adaptation in healthy organisms, while long-term exposure leads to chronic inflammation of the respiratory tract in adults and children and immune deficiency. [1,11]

### NITROGEN OXIDES (NO, NO2)

The main source of nitrogen oxides in the air are road transport (diesel engines), locally used heating systems (ovens, gas cookers) or high-temperature processes used in power plants. They are an important component of acid rain and smog. Nitrogen oxides reduce the immune capacity of the lungs and reduce the ability to properly ventilate, which promotes chronic bacterial inflammation, and in children causes an increase in the frequency of asthmatic conditions. When inhaled in doses exceeding 6 mg m-3, it causes pulmonary edema, but in concentrations several dozen times lower, in cities, it does not pose a threat to humans. [1,11]

#### **CARBON MONOXIDE (CO)**

Its main sources are internal combustion engines and combustion of fossil fuels. Residents of city centers during rush hours are particularly exposed to its aspirations. Due to its high affinity for hemoglobin, it forms with it toxic carboxyhemoglobin deprived of the ability to transport oxygen, thus leading to oxygen deficit. It penetrates into the body both through the respiratory tract, as well as the skin and mucous membranes. [11]

#### OZONE

A highly reactive compound that irritates the airways of the lungs and disrupts the natural defenses of the airways.

It is formed under the influence of ultraviolet radiation during the oxidation of exhaust gas components (NOx, CO, CH4). It is the main component of the so-called photochemical smog characteristic of temperatures above 25°C and in cities with heavy traffic. Even low concentrations of O3 cause degeneration of epithelial cells in the respiratory tract, leading to an increase in non-specific reactions, bronchospasm and hyperactivity of the lungs, increasing the susceptibility of lung tissue to other pollutants - sulfuric acid, nitrogen oxides or allergens. [1,11]

#### PARTICULATE MATTER (PM 10, PM 2.5)

Their source is fireplaces, wood and coal-fired stoves, tobacco smoke, as well as diesel engine oil and car exhaust fumes. Their concentration increases during the abrasion of asphalt, car tires and metals, as well as in the vicinity of construction sites. High content during periods of higher temperatures is associated with wind transport from unvegetated areas. According to the US Environmental Protection Agency (EPA), the standard concentration of particulate matter suspended in the air is 265  $\mu$ g/m3, but there are no standards for their concentration in rooms. Normal concentrations range from 500  $\mu$ g/m3 in bars and public buildings to around 50  $\mu$ g/m3 in homes.

The incidence of respiratory diseases due to dust aspiration increases in elderly people suffering from asthma, and in children who breathe 50% more air per kilogram of body weight than adults. [1,11]

### (PM 10)

Dusts with grain diameter <10  $\mu$ m.

Their basic ingredient is carbon. Larger particles are retained in the nasal cavity and throat, while particles smaller than 5  $\mu$ m can penetrate deep into the respiratory system. [1,11]

#### (PM 2.5)

Particles with a diameter of 2.5  $\mu$ m and less. Due to their smaller diameter, they have a greater pathogenic potential than PM10 particles. They also differ from them in chemical composition - they contain proportionally more water and acid-forming substances, such as sulphates and nitrates, as well as trace amounts of metals. These small particles easily penetrate buildings and are relatively evenly dispersed in urban agglomerations. [1,11]

#### **AROMATIC HYDROCARBONS**

They are widely present in the environment and can be generated by various processes such as fossil fuel combustion, chemical industry, biomass combustion, and also as components of some products such as tobacco smoke.

Aromatic hydrocarbons are an important component of air pollution and are considered harmful to human health and the environment. They are also considered carcinogenic and can contribute to various diseases, including respiratory diseases. The impact of VA on human health depends on the length and intensity of exposure, as well as other factors such as age, gender, genetics, and overall health. [11]

### LEAD

Lead is a heavy metal that is present in the atmosphere as a component of air pollution. Exposure to lead in the air can be harmful to human health. Lead is neurotoxic and can affect brain development and the nervous system, especially in children. It can lead to lower IQ, learning difficulties, behavioral problems and affect psychomotor development. The most important source of lead emissions into the atmosphere used to be the burning of gasoline containing lead compounds, but thanks to the introduction of bans on the use of leaded gasoline, lead emissions from this source have been significantly reduced. [1]

Unconventional pollution includes:

#### ASBESTOS

Asbestos, also known as crystalline asbestos, is a group of natural fibrous minerals. Due to its unique properties such as strength, resistance to heat and chemical corrosive agents, asbestos has been widely used in industry and construction.

Asbestos is also a dangerous air pollutant. When asbestos-containing materials are damaged or destroyed, asbestos fibers can be released into the air as dust or fibres. These fine particles inhaled by humans are deposited in the lungs.

Exposure to asbestos can lead to a variety of diseases, including lung cancer, pleural cancer, and asbestosis (asbestosis). These diseases have long latency periods, and the first symptoms may not appear until many years after exposure. [1]

#### MERCURY

Mercury belongs to the group of heavy metals. It can be emitted into the air as a result of natural processes such as volcanic eruptions, but the main source of mercury pollution in the air is human activities, in particular the burning of fossil fuels containing this substance. Mercury is present in the atmosphere in the form of volatile organic mercury compounds (LVOCs) and mercury vapor. They settle on the surface of the earth, and exposure to them has harmful effects on health. Mercury is neurotoxic and can affect the nervous system, especially in fetuses and young children. It can lead to brain damage, cognitive impairment, learning disabilities, and other health problems. [1,5]

#### BERYLLIUM

Beryllium as a mineral is not a direct source of air pollution, but beryllium mining and processing can cause it. During mining, dust containing heavy metals and other toxic substances may enter the environment. When processing beryllium, such as grinding or polishing, it is possible to release fine dust that causes beryllium. The disease is caused by an allergic reaction in the body that attacks the airways, causing coughing, shortness of breath, chest pain, and weight loss. In more severe cases, the disease can develop into a chronic form that leads to scarring of the lungs and severe breathing problems. [1]

Air pollution is a global environmental problem that has a negative impact on environment, human and animal health. The main source of air pollution is emissions related to human activities, such as fossil fuel combustion, industrial emissions, transport, biomass and waste combustion. Substances formed in these processes affect air quality, causing smog, acidification of rain, the formation of the ozone hole, and also negatively affect the functioning of the respiratory and cardiovascular systems and lead to the development of various diseases, including cancer. [11,28,29,30]

### AIR POLLUTION AND MUTAGENESIS

Disturbances in the expression of genes that regulate the cell cycle play a key role in each neoplastic transformation. In this article, we want to pay special attention to the impact of air pollution on mutagenesis of proto-oncogenes and tumor suppressor genes, which have a direct effect on cancer.

Air pollution is a mixture of a large number of chemical compounds, mainly from due to vehicle traffic, heating systems and industrial plants. Such a mixture includes, among others particulate matter (PM2.5), carbon monoxide, ozone, nitrogen dioxide and sulfur dioxide, while PM contains chemicals such as benzene, formaldehyde and polycyclic aromatic hydrocarbons. Solid particles suspended in the air have been recognized by the International Agency for Research on Cancer (IARC) as a factor group I carcinogen. PM2.5 significantly increases the number of interstitial macrophages in lungs that release interleukin-1 $\beta$ , initiating inflammation on the surface of pneumocytes.[31] EGFR receptors are located on the surface of alveoli and are responsible for transmitting signals from the extracellular space to the inside of the cell, affecting proliferation, differentiation, ability metastasis and apoptosis. The polluted air we breathe in every day drives the influx macrophages that release inflammatory mediators such as interleukin-1 $\beta$ , accelerating the expansion of cells with EGFR mutations [9]. This mutation causes continuous stimulation of tyrosine kinase and transmission of a signal into the cell further, uninterrupted proliferation and consequently, to the development of cancer. Overexpression mutated EGFR gene is characteristic of non-small cell lung cancer and it occurs with the greatest frequency in the squamous type.[14]

Polycyclic aromatic hydrocarbons (PAHs) in particulate matter suspended are considered the most carcinogenic and toxic substances for organism. One of the chemical compounds included in their composition is benzo(a)pyrene. It was considered as an indicator of the entire group of PAHs, due to the degree of carcinogenicity impact and prevalence in the environment. Source of polycyclics aromatic hydrocarbons is the process of incomplete combustion of compounds organic, e.g. using coal and biomass for heating households, uncontrolled burning of waste and tobacco smoke or car exhaust fumes. Polycyclic aromatic hydrocarbons form a permanent connection with DNA, thanks to which have the ability to accumulate in the body. The mechanism of carcinogenesis is complex and still being studied [11].

It can be concluded that the emergence of toxic compounds in cells, such as pneumocytes, allows the formation of adducts with DNA, which very negatively affects the replication of the cells of the organism exposed to these relationships. After an incorrect course of repair processes, permanent ones occur mutational changes that may cause the initiation and progression of the process. As a consequence, it is a long-term carcinogenic effect. The process malignant transformation can occur through the activation of proto-oncogenes or inactivation of tumor suppressor genes. PAHs have the ability to induce mutations in within the p53 tumor suppressor gene, causing its inactivation. The inactivation does not result in elimination of cells with DNA damage, thus inducing carcinogenesis. In employees occupationally exposed to PAHs, tobacco smokers and in areas with high rates of air pollution, there is an increase susceptibility to the formation of DNA-PAH adducts, which makes them a risk group for cancer.[31]

Cigarette smoke contains about 4,000 chemical compounds that are products of pyrolysis of tobacco and tissue paper at 600 - 1000oC, among them the presence of very highly carcinogenic nitrosamines and about 153 different PAHs, including the most toxic: benzo[a]pyrene and dibenzo[a,h]anthracene. They are also found in cigarette smoke catechols, compounds with carcinogenic properties that increase carcinogenic activity polycyclic aromatic hydrocarbons.[11]

Polycyclic aromatic compounds can contribute to the occurrence of various types of lung cancer, both nonsmall cell and small cell. Non-small cell lung cancer is the most common type of lung cancer, accounting for approximately 85% of cases. It consists of three main subtypes: squamous cell carcinoma, carcinoma adenocarcinoma and large cell carcinoma. Polycyclic aromatic compounds can be risk factor for these subtypes of lung cancer.

Small cell lung cancer accounts for about 10-15% of all lung cancer cases. Mostly it is strongly associated with smoking, but exposure to some compounds carcinogens such as PAHs may also increase the risk of its occurrence. However, it is important to understand that lung cancer is a multifactorial disease and exposure to polycyclic aromatic hydrocarbons, which are part of the air pollution is just one of many risk factors.

# TYPES OF LUNGS CANCER

There are several types of cancer, each of which is characterized by certain different properties, which also translates into their treatment.

# ADENOCARCINOMA

It is the most common lung cancer and is not as strongly correlated with smoking as other cancers. It is relatively common in women. It is located in the small airways, so it occupies the peripheral parts of the lungs. [23] This makes it less likely to be detected by sputum examination. [13] It is characterized by slow local development, but quickly infiltrates the pleura. Due to the rich vascularity of this tumor, distant metastases occur rapidly, including m. to the brain. [13]

# SQUAMOUS CELL CARCINOMA

It is a cancer in which we observe a very high correlation with smoking. It is more common in men. It is located recessed. [23] It is more common in the elderly. [13]

# LARGE CELL CARCINOMA

Its location may vary. [23] Large cells of this tumor sometimes show features of neuroendogenous differentiation.

Adenocarcinoma, squamous cell and large cell carcinomas belong to a larger group of so-called non-small cell carcinomas and together account for up to 85% of all lung cancers. [23]

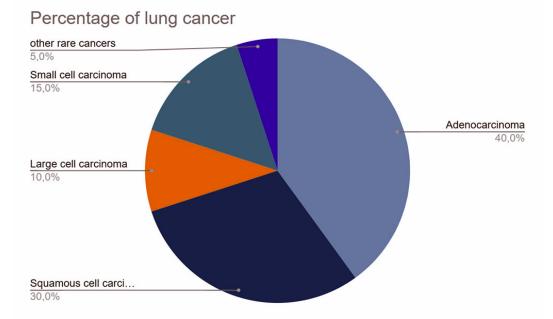
Surgical treatment is the basic method of treating non-small cell carcinomas. When patients do not qualify for surgical treatment, we use radiotherapy, and when the process is disseminated - chemotherapy [23]

# SMALL CELL CARCINOMA

It is a cancer strongly associated with smoking. Mainly located in the hive. It is characterized by aggressive growth and early dissemination to lymph nodes and distant organs, most patients already have metastases at the time of diagnosis. In the course of this neoplasm, paraneoplastic symptoms are common, e.g. hypercalcemia, SIADH, Cushing's syndrome, carcinoid syndrome, Lambert-Eton syndrome, dermatomyositis. This is due to the fact that this cancer originates from cells with neuroendocrine activity. [13]

The basic method of treatment is chemotherapy. If the tumor is limited, radiotherapy is additionally used. [23]

Despite the constant development of lung cancer diagnostics and therapy, patient survival is still unsatisfactory due to the diagnosis of this cancer at an advanced stage of development and the lack of radical treatment. [14]. The 5-year survival rate is about 15%. [14]



# HOW CAN THE PROBLEM OF POLLUTION BE REDUCED?

Reduction of pollution can occur in many ways, but legal regulations imposed by the government should play a major role. An example can be the reduction of air pollution during the 2008 Olympic Games in China by the government. Such actions led to a decrease of asthma-related outpatient visits by 41.6% compared to the period before the start of the games. This demonstrated that even in highly polluted cities, positive effects can be achieved for individuals suffering from asthma. [12]

In rural areas of Mexico, a randomized trial using properly vented wood-burning stoves compared to open fires showed a reduction in the decline of forced expiratory volume in 1 second and an improvement in respiratory symptoms when proper stoves were used. [16] It was also found that masonry stoves reduce carbon monoxide exposure by half and result in a lower rate of pneumonia diagnoses. [22]

The movement of light and heavy vehicles generates up to 50% of pollution on highways and 30-40% in urban areas. It has been demonstrated that the use of electric vehicles powered by fuel cells or batteries

leads to a 25% reduction in NOx and a 17% reduction in PM2.5. [4]

Urban forests and green roofs can contribute to air purification. Vegetation removes pollutants in several ways: by absorbing gaseous pollutants, capturing suspended particles, and breaking down organic compounds such as aromatic hydrocarbons. [20] The development of urbanization has led to a prevalence of concrete in most cities, resulting in limited space for planting trees. Building roofs, which often comprise nearly half of the city's area, provide an opportunity for vegetation growth. [7] Two thousand square meters of uncut grass on a green roof can remove up to 4000 kg of PM. [8]

Other ways to reduce pollution include transitioning to renewable energy (solar, wind), improving building insulation, increasing the amount of forests, nuclear energy, and carbon dioxide sequestration. [18]

Air purifiers can decrease both outdoor and indoor air pollution. The most effective and efficient filters are MERV and HEPA filters.[26] Research conducted in homes of children with asthma has shown that portable HEPA air purifiers are more effective than filters found in central ventilation systems. [3]

Tobacco smoke contributes to air pollution, especially when smoking tobacco products indoors. [15]

Higher cigarette consumption accelerates lung cancer incidence by 20-30 years. Additionally, among lung cancer patients, 90% are smokers. The risk of lung cancer development depends on the age of starting tobacco use, the number of pack-years, and the type of cigarettes smoked. The earlier one starts smoking, the higher the risk of lung cancer. Similarly, a higher pack-year index is associated with a higher risk of cancer development. This risk is slightly lower for filtered cigarettes, cigars, or pipes. Studies have shown that the duration of smoking in years is more significant than the number of cigarettes smoked per day. Passive smokers also have an increased risk. [10]

Nicotine itself is not carcinogenic but has an addictive potential, which drives continued smoking. However, nicotine metabolites are carcinogenic. In high concentrations, nicotine damages DNA and can induce apoptosis in healthy cells. Furthermore, nicotine can inhibit the anti-tumor immune response by affecting antigen presentation and dendritic cell activity, increasing the production of pro-inflammatory cytokines, and intensifying oxidative stress. In vitro studies have shown that nicotine reduces the anti-proliferative and pro-apoptotic effects of cytostatics and radiotherapy, potentially leading to a worse response to cancer treatment in smokers or those using nicotine-containing products. Nicotine metabolites include N-nitrosonornicotine (NNN), responsible for stomach and esophageal tumors, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), one of the most carcinogenic substances, as well as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a carcinogenic NNK metabolite in the lungs. [17]

Tobacco smoke, aside from nicotine, contains around 7000 toxic substances, several dozen of which are proven carcinogens. Carcinogens are produced during the combustion of tobacco, which occurs at the end of a cigarette and takes place at temperatures exceeding 750°C, as well as during pyrolysis at slightly lower temperatures ranging from 300-700°C. These substances can act through active molecules formed by metabolizing on the bronchial mucosa surface. They can also directly bind to receptors, leading to apoptosis or angiogenesis. Furthermore, cigarette smoke exhibits irritating properties, resulting in an increased susceptibility to respiratory infections and local weakening of defensive reactions, potentially promoting carcinogenesis. [27,19]

The most dangerous substances present in very high concentrations in tobacco smoke include: benzo(a)pyrene, nitrosoamine, naphthalene, pyrene, naphthylamine, methanol, acetone, hydrogen cyanide, toluidine, ammonia, urethane, arsenic, cadmium, polonium, phenol, butane, vinyl chloride, dibenzacridine, toluene, and carbon monoxide. The main carcinogenic agents in tobacco smoke are polycyclic aromatic hydrocarbons and volatile N-nitrosoamines, whose metabolites exhibit strong toxicity. [25,22]

Intermediate metabolites of benzo(a)pyrene bind to DNA in the guanine position, increasing the risk of carcinogenic mutations at that site. (5) Nitrosamine induces DNA damage and inhibits its repair. [24]

### CONCLUSIONS

Air is a fundamental element of life and its quality and composition play a key role in the proper functioning of our body and the entire ecosystem. Contaminated air inhaled by us every day can lead to the deterioration of our health. Harmful substances in the air irritate the respiratory tract, cause degeneration of epithelial cells lining the respiratory tract and disrupt the body's natural defenses. A strong link between carcinogenic processes and low air quality will cause an increase in the number of cancers in the near future, e.g. lungs or pleura. Lung cancer is estimated as the most common cancer causing male and female death in Poland. In 2019, Polish National Cancer Registry reported 22,271 lung cancer cases. Therefore, we need to raise awareness on air pollution as a cause of lung cancer risk.

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