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Review Article

# Deteriorating Situation of Smog in Pakistan and its Association with Lung and Skin Cancer

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## ABSTRACT

The first mention of smog dates back to 1952, when smog from excessive burning of coal, led to a national disaster in London, caused not only breathing problems, but also many injuries due to poor visibility. Since urbanization and globalization have intensified, many places on the planet have faced this not only environmental and socio-economic problem, but also a significant health problem on a regular basis. Pakistan currently ranks third out of 118 countries in terms of worsening smog exposure. It is well known that air pollution can cause many pathological conditions, but the greatest concern at the present time is the increase in the incidence of cancer in smog-affected regions. The prevailing conditions here are a variety of lung tumors, mainly lung adenocarcinoma, and skin cancer. This review summarizes current data and at the same time demonstrates the need for specific, precise further studies.

**Keywords:** Air quality index; PM10; PM2.5; PM1; Smog in Pakistan; Lung cancer; Skin cancer

## INTRODUCTION

Air pollution levels in metropolitan cities resulting in smog are significantly toxic to humans and lead to severe acute and chronic illnesses, lower quality of life and reduced life expectancy [1]. On a global scale, smog has been reported quite frequently in many of the world's biggest cities [2]. According to the world air quality report 2021, the Air Quality Index (AQI) is calculated from the average of all pollutant concentrations measured over a full hour, a full 8 hours or a whole day) and PM2.5 air pollution (particulate matter with a diameter of 2.5 micrometers or less) in Pakistan in 2021 received an average AQI of 156, which is 13.4 times higher than the annual WHO air quality standard value. It is well documented that since 2013 this level of air pollution in Pakistan has been getting worse every year, mainly due to industrialization and increased consumption of fossil fuels and vehicle emissions [3]. The citizens of Pakistan have been observing smog regularly in different cities since 2016 [4]. Thus, Pakistan is ranked third out of 118 countries in 2021 after Bangladesh and Chad in terms of air pollution [5].

It has been established by numerous studies that smog, which represents an extreme degree of air pollution and is visible even to the naked eye, leads to a variety of acute and chronic diseases [6]. Health problems due to smog can arise even in a short time. Short-term exposure in children leads to acute infections of the lower respiratory tract and exacerbation of asthma attacks [7]. Long-term exposure causes chronic obstructive pulmonary disease and other respiratory diseases such as pneumonia, chronic obstructive bronchitis and emphysema. The most vulnerable parts of the body, which can accumulate micro particles and contact with chemicals mucous of the airway, eyes and skin, are at risk of cancer development [8-10]. The rate of oncological conditions is steadily increasing in the parts of the globe with a high concentration of PM2.5 and smog itself. Therefore it is justified to review current data for a better understanding of the possible association between smog, lung, and skin cancer. We analysed the most relevant literature from 1995 to 2023 to summarize the current data on the properties of smog in Pakistan and its association with lung and skin cancer.

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# LITERATURE REVIEW

## Causes of air quality deterioration and its hazards in Pakistan

It has been observed that the incidence of smog in the urban areas of Pakistan has been increasing over the past few years [11]. According to the world air quality report for the period from 2017 to 2021, the level of PM2.5 in the air of Faisalabad and Lahore decreased to 70 μg/m$^3$ and 80 μg/m$^3$ respectively in 2020, after which it jumped again. In Karachi and Rawalpindi, it increased steadily during the biennium under review, but at a lower concentration. Islamabad showed no significant difference and had an average annual PM2.5 level of 40 μg/m$^3$ over those 4 years. In Muridke alone, over the last two years of the period, the concentration has almost halved (Figure 1).

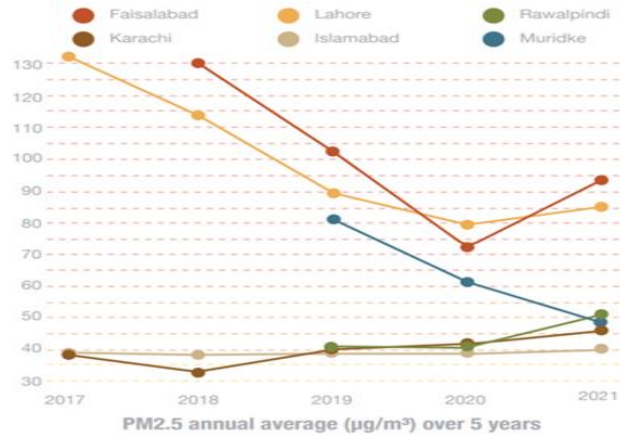


**Figure 1:** The dynamics of PM2.5 concentration from 2017 to 2015, according to world air quality report 2021.

The current state of air quality, according to official data at Lahore, Mirpur Khas and Bahawalpur, where AQI reaches a level of more than 180 (Table 1). Thus, even without a statistical analysis of the most recent years, an increase in the level of air pollutants in Pakistan is evident.

**Table 1:** Air quality in different cities of Pakistan on January 19th 2023.

| City | Air quality index |
|---|---|
| Peshawar, Khyber Pakhtunkhwa | 193 |
| Lahore, Punjab | 188 |
| Mirpur Khas, Sindh | 181 |
| Bahawalpur, Punjab | 180 |
| Karachi, Sindh | 177 |
| Faisalabad, Punjab | 173 |
| Islamabad, Islamabad | 161 |
| Rawalpindi, Punjab | 157 |
| Muridke, Punjab | 155 |
| Abbottabad, Khyber Pakhtunkhwa | 61 |

The factors contributing to the formation of smog in Pakistan can be divided into two large groups internal, reflecting the environmental impact in the country itself, and global, resulting from the impact on the planet as a whole by natural and geographical factors, regardless of human activities. The burning of crop by-products, coal and garbage is indeed widespread in Pakistan and has been identified as the main reason why sulphur dioxide has become a major component of smog here [12]. Emissions from transport are put forward as the next main reason for the deterioration of the state of atmospheric air, since the number of vehicles has recently increased significantly [13-15]. The growth of factories and the lack of cleaning technology add to the lion's share of air pollution, along with growing urbanization [16]. Poor sanitation and smoking can be classified as additional individual and modified aggravating factors [17]. Global causes, since deforestation worsens general atmospheric conditions and, in turn, has more or less severe impacts on certain regions of the planet, including Pakistan [18]. Deforestation, urbanization and industrialization of nearby countries can also be considered as cross border pollution and this is also the case in Pakistan [19]. The absence of rain also contributes to the condensation of particles in the air, so global warming also in general has a direct negative effect on this particular situation [20]. The survey showed that 58.5% of Pakistani men believe that the main cause of smog was the constant increase in deforestation; while the majority (63%) of Pakistani women answered that the increase in the number of cars was the main reason. Physicians and medical students in Pakistan, unlike the general population, have a good understanding of the factors associated with smog, its impact on health and necessary preventive measures.

According to the literature, there are two types of smog in terms of composition classical and photochemical smog. Particulate matters have a strong effect on the respiratory system and other parts of the body in contact with them through their chemical compounds. Most authors divide these dust particles by size and action into three large groups: PM10-2.5 μm, PM2.5 μm and PM1 μm (Table 2). PM2.5 is considered the most common and dangerous for human health, globally it is a risk factor for death of the fifth rank. It has been proven that every 10 $\mu g/mm^3$ increase in fine PM leads to an increase in all-cause mortality by 4%, cardiopulmonary mortality by 6%, and lung cancer mortality by 8%. Along with PM2.5, classical smog is a combination of the following free or bounded chemicals: Sulphur dioxide, nitric oxide, smoke, water droplets, carbon dioxide, carbon monoxide and nitro phenols. Many cohort studies show consistency between results and offer conclusions considering certain air pollutants and PM2.5 as carcinogenic. Sulphur dioxide, nitrogen oxides and carbon monoxide have also been identified as the main components of smog and are well-established oncogenes. Nitro phenols are also hazardous pollutants found in various environmental matrices, including ambient fine PM2.5. However, the specific role and circumstances in which these chemicals act as oncogenes require further study. There are also singular studies showing no association between certain types of pollutants and certain cancers. So, for instance, a Danish study using data from three prospective cohort studies found no clear association between environmental NOx emissions and lung carcinoma incidence. In photochemical smog, the major pollutants (in the form of volatile organic compounds and nitrogen oxides) mix and react with oxidizers. This increases the oncogenic potential and the range of possibly affected tissues.

**Table 2:** Comparison of the effects of particular matters.

| | PM10-2.5 | PM2.5 | PM1 |
|---|---|---|---|
| Penetration | Mostly caught in the upper respiratory tract. | More dangerous to health because of greater ability to penetration into the lower respiratory tract. | Pass through the blood-air barrier, penetrate into the blood vessels and thus can have a negative effect by a direct mechanism. |
| Composition | Inorganic ions, incl. residues of nitric including potassium and sodium cations, carbon, nitrophenols and hydrochlorio acids, as well as alkali metals, ammonium ions, organic and elemental. | | Trace elements of As, Cd, Co, Cr, Hg, Mn, Ni, Pb, Sb and Se. |
| Influence | Upper and lower respiratory tract oncogenesis. | 4% increase in all-cause mortality, a 6% increase in cardiopulmonary mortality, and an 8% increase in lung cancer mortality. | Widespread oncogenesis, direct chemical action due to dissolution. |
| Gender predisposition for adverse effects | Almost the same in most publications, where women have a higher with the exception of some regional data risk | | The effect on lung cancer incidence in women was greater for PM1, followed by PM2.5 and PM10. |

## Smog associated lung cancer

Asthma was rated as the top acute condition for 72.5% of men and 79% of women in high smog areas, and bronchitis was the next most common health problem. Smog inhalation irritates the respiratory mucosa and causes sore throat and spasmodic cough, but prolonged exposure directly increases mortality, mainly due to the development of lung cancer. In developed countries, it is the third most common type of cancer following breast and prostate, but it accounts for the largest proportion of all cancer related deaths (22%). There are two most common types of lung tumors associated with smog, lung adenocarcinoma and squamous cell carcinoma, which differ in their histopathological variants. These histopathological subtypes have diagnostic, prognostic, therapeutic, and demographic features. Several articles have shown an association between PM2.5 and other malignancies such as small cell lung cancer, pleural mesothelioma and glandular lung cancer (usually associated with tuberculosis). The lung epithelium is sensitive to endogenous and exogenous oxidants contained in air pollutants. Atmospheric PM2.5 is also associated with a high risk of developing various forms of lung tumors of varying degrees. Understanding the histological, molecular and genetic diversity of a tumor is crucial not only for diagnosis and treatment but also for understanding the main environmental causes of its formation.

The great concern is the temporary increase in the incidence of lung adenocarcinoma namely in smog related conditions since the annual age adjusted incidence rates of it increase by 2.8% in women and by 1.3% in men everywhere. An elevation of the lung adenocarcinoma risk was identified with an increase in the condensation of atmospheric PM2.5 for every 10 $\mu g/m^3$. Some studies have found a positive association between environmental PM2.5 and lung adenocarcinoma with $O_3$ exposure for every 10 $\mu g/m^3$ increment in PM2.5. This effect may also explain the high association of lung adenocarcinoma with skin cancers. The risk was also higher among those patients who spent more than 1 hour per day outdoors, as well as a 31% increase in lung adenocarcinoma associated with a gradual increase in environmental PM2.5 concentrations among non-smokers. The conducted analysis in this study also demonstrated that the risk was even higher among smokers who quit smoking more or less 10 years ago. Several studies suggested that patients with lung adenocarcinoma tended to be older, used to smoke, had less education, spent more time outdoors, drank more alcohol, and lived at the same address for a long time. They were also more likely to have quit smoking very recently, used to be heavy smokers, and often reported advanced non-melanoma skin cancer.

Some recent studies have shown that women are at a more significant risk of developing squamous cell lung cancer due to exposure to PM2.5. This article also shows that nitric dioxide plays a leading role in the development of squamous cell carcinoma. The other sources point to the impact of ozone on the development of that type of lung cancer. The long term exposure to those components of smog induces the formation of squamous metaplasia-a pre-neoplastic lesion in that case.

The exact carcinogenic components and mechanism of carcinogenesis under smog conditions are currently being studied. There are some remarkable works demonstrating the results of experiments and being close to the understanding of lung cancer associated with smog. Smog in a chamber with cell culture on a medium disrupts cell proliferation, destroys the phospholipid cell membrane, which, in turn, leads to cell death by necrosis with the activation of enzymes that quantify the number of dead cells nearby. Some experimental studies have demonstrated that exposure of rats to PM2.5 leads to an increase in the concentration of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNFα) and Interleukins: 6 (IL6) and 8 (IL8). Confocal microscopy of cell culture after smog exposure also demonstrated obvious changes in the cell nuclei, which may indirectly indicate the affected genetic material, allow genomic instability and make it prone to oncogenic transformation. Polycyclic aromatic hydrocarbons, common smog and tobacco smoke carcinogens, and PM2.5 are also responsible for the development of primary lung cancer. Tobacco and occupational inhalation or smog inhalation requires cellular remodelling and adaptation of basal cells either in the terminal respiratory unit or in the respiratory epithelium, followed by hyperplasia of vimentin positive cells and TTF1 bronchial positive cells pre-neoplastic lesion, as shown in carcinomas resulting from a molecular transformation in less mature cells, and then in multipattern carcinomas and pleomorphic carcinomas. Other authors have associated tobacco with intra-tumoral heterogeneity, as they have identified EGFR mutation heterogeneity depending on the type of adenocarcinoma and smoking patterns. Carcinogens may play a role in determining heterogeneity because some lung carcinomas are more commonly diagnosed in smokers or ex-smokers, such as small cell lung carcinoma and squamous cell carcinoma, while some other carcinomas, such as adenocarcinoma, are diagnosed in non-smokers.

There are also data demonstrating a large role of genetic predisposition to lung cancer in the same environmental conditions as high frequency of EGFR mutations and low frequency of KRAS mutations. This proves the complexity of the course of lung cancer in areas associated with smog, its multifactorial nature and subsequent clinical heterogeneity. Different patterns of molecular expression are associated with a different mode of occurrence as well as different prognoses.

Numerous sources conclude that there is a lack of information on the exact measures to prevent smog related cancers, sometimes even citing contradictory materials. Therefore, at the moment it is difficult to give certain recommendations to ordinary citizens. Television reports, social media and institutional education campaigns, tobacco cessation campaigns may be the most effective means of raising smog awareness among the general population, as well as those who may not be aware of all the factors that contributed to its occurrence. While much further research into smog related malignancies continues and ways to deal with the sources of smog are being developed, the healthcare system must focus on early diagnosis of lung cancer in smog areas. As one of the solutions currently adopted in developed countries where the incidence of lung pathologies

is increasing, lung cancer screening using low dose computed tomography may be useful for Pakistan.

# DISCUSSION

## The oncogenic effect of smog on the skin

Unaffected skin is not as sensitive to smog components as mucous membranes. However, there are reports of skin diseases (atopic dermatitis, acne, and psoriasis, skin cancers) associated with smog due to its severe cytotoxicity, carcinogenetic effects. Most skin diseases are usually caused by exposure to PM10 and PM2.5. Electron microscopic analysis showed that most of the solid particles are able to penetrate deep into the skin tissue. Similar to lung cancer, PMs not only play a role in skin cancer, but genes are also major components that lead to skin diseases due to changes in their expression due to exposure to PM. PM-related signalling pathways have been reported to be associated with changes in the skin barrier.

Photochemical smog has a greater effect on the skin than classical smog. It causes more prominent oxidative stress and, hence, severe cytotoxicity, which contributes to damage to less sensitive tissue such as skin upon prolonged exposure. When key chemical air pollutants receive ultraviolet energy, some of them are converted into oxidizing agents such as hydroxyl or ozone, and subsequently can be deposited in the deep layers of the skin and trigger oncogenesis in skin cells.

The risk of skin cancer from PM exposure is not fully understood. It appears that the particle size of PM 10 is too large to affect the skin directly, and there is no clear significant association between PM 10 and skin cancer incidence in epidemiological studies. However, there is a positive correlation between urban PM 2.5 exposure and non-melanoma or melanoma skin cancers, mostly due to increased oxidative stress and subsequent mutations.

Skin damage due to PM exposure has currently become an important issue, but the underlying mechanism of signalling changes in PM-induced skin diseases is not fully understood and its correlation in clinical practice is not clear.

# CONCLUSION

Smog has a significant negative influence, bringing not only severe chronic pathologies and also high socio-economic costs, but at the same time is one of the modifiable factors leading to the development of killing respiratory diseases. The most evident link, according to the majority of publications, is between smog and lung adenocarcinoma. However, the high heterogeneity of lung cancer due to smog requires a large number of studies to identify a specific causal relationship between a certain influencing factor and a certain type of pathology. Thus, the heterogeneity of lung cancer is an important fact for understanding the aetiology, pathogenesis, carcinogenesis, pathological diagnosis, selection of tissues for molecular diagnostics and making therapeutic decisions. Comprehension of a specific carcinogenic factor in the smog is critical and it is essential to be aware of the implications and future developments in this area. Skin cancer could be also related to PMs, but there is still not enough data to make a clear link.

Early detection programs for lung cancer should be widely implemented in smog-affected areas until the exact etiological components are fully understood and necessary preventive measures eradicate them. Further research into chronic PMs exposure is needed, especially under experimental conditions, as lungs and skin *in vivo* are more complex than the *in vitro* system used in most scientific studies.

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