

Long Term Impact of Occupational Exposure to Fine Particulate Matter on the Incidence of Rare Histological Subtypes of Lung Cancer

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Abstract: Chronic occupational exposure to fine particulate matter (PM_{2.5}) has been linked to an elevated risk of respiratory diseases, but the association between this exposure and the incidence of rare histological types of lung cancer has not yet been sufficiently studied. The current retrospective cohort study assesses the association between cumulative occupational exposure to PM_{2.5} and the incidence of rare lung cancer subtypes among industrial workers. Information on occupational health, occupational exposure measurements, and regional cancer registry data obtained in 2006-2023 have been used for the analysis. This study covers 6,500 employees of mining, construction, and metalworking industries. Exposures of individuals were determined from PM_{2.5} measurements in the workplace and the use of job-exposure matrices. Rare lung cancer events were documented from histopathology reports and categorized based on standardized tumor classification. Over a median follow-up of 13.4 years, 226 lung cancer events were documented, with 39 rare histology types (17.3%). The highest PM_{2.5} exposure group had an increased risk of rare lung cancer compared to the lowest PM_{2.5} exposure group (HR = 1.79; 95%CI: 1.18–2.71; p = 0.004). From the continuous exposure model, there was increased risk for each 10 µg/m³ increase in cumulative exposure to PM_{2.5}. It can be concluded that long-term exposure to PM_{2.5} at workplaces increases the incidence of rare lung cancer subtypes.

Keywords: Fine Particulate Matter (PM_{2.5}), Occupational Exposure, Rare Lung Cancer Subtypes, Histological Variants of Lung Cancer, Environmental Carcinogenesis, Occupational Health Risk, Air Pollution and Cancer.

1. INTRODUCTION

Air pollution is hazardous for workers' health in various ways and particularly in those industries where there is higher generation of air pollutants like in mining, construction, metallurgical processing, manufacturing industries, where workers are exposed to high particulate matter concentrations. Fine particulates (PM_{2.5}) are particles whose aerodynamic diameter is less than 2.5 micrometres, and therefore, they can penetrate deeper into the airways and reach up to the alveoli of the lungs [1]. These particles, after deposition, lead to chronic inflammatory reaction, oxidative stress, and cell damage, all of which are

mechanisms leading to cancer development [2]. Increasing epidemiologic studies have reported an association between increased risk of respiratory diseases and lung cancer and exposure of workers to PM_{2.5} over time. Cohort studies have found a link between long-term exposure to airborne particulate matter and increased risk of lung cancer, especially in cases where there is combustion and industrial emissions [3]. Furthermore, recent studies have shown that the interaction between the carcinogenic effect of particulate matter and genetic exposure, as well as lifestyle factors such as smoking, can amplify the risk, thus making it harder to determine the risk in the work environment [4]. The findings emphasize the importance of conducting additional research regarding the health impacts of exposure to particulates in the occupational setting. Analysis of long-term

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occupational exposure demands systematic examination of complex data from the field of health and the environment [5].

Lung cancer is a heterogeneous disease because it has many types of histology that each has its unique pathology and molecular biology. While common histologic types like adenocarcinoma and squamous cell carcinoma make up the bulk of lung cancer cases, rare histologic variants, including large cell carcinoma, adenosquamous carcinoma, and sarcomatoid carcinoma, make up a small fraction of lung cancers and have distinct pathology. These rare forms constitute a small number of all lung cancer cases, but their diagnosis can be challenging due to their unpredictability. The study of histopathology plays a vital role in distinguishing these rare forms because they have biological behavior, prognosis, and therapeutic response different from common forms. Environmental and occupational exposure have become more widely appreciated as possible sources of rare tumors. Nevertheless, there is not much knowledge on this subject compared to common lung cancers. Therefore, it is essential to understand these differences in order to classify diseases and environmental factors for these rare tumors. Several long-term exposure studies have shown that there is a dose-response relationship between exposure to particulate matter and lung cancer [6].

The above analytical framework, as shown in Figure 1, can help explain the connection between occupational exposure to fine particulate matter and the development of rare types of lung cancer. This starts with the workplace and emissions of the particulates, followed by the measurement of exposure

via workplace and environmental sampling. The particulates are then measured in terms of exposure levels for individual workers. This exposure level data is 'splashed' with the data from the worker population, which includes demographic data and occupational history, as well as medical data and cancer registry data that includes histology findings. After putting together all this data, the analysis will be done to look at the development of diseases and the occurrence of rare cases of lung cancer among the occupationally exposed workers.

The repeated testing is one way of showing the impact of work and environmental conditions in causing cancer. Most of the mechanisms that cause cancer take a long time to incubate, and repeated exposure to particulates such as PM2.5 will affect the process of DNA repair, inflammation, and tumorigenesis [2]. There have been epidemiological studies conducted recently that show that exposure to particulate matter can not only increase the probability of lung cancer but may even contribute to the less common types of cancer as well. Population-based and cohort studies also provide evidence that chronic exposure to fine and ultrafine particles is related to the risk of various forms of cancer, which supports the hypothesis that airborne particulate pollution has more general carcinogenic consequences [7]. Therefore, the analysis of the chronic occupational effects of PM2.5 can provide useful information regarding environmental determinants of the rare types of lung cancer and aid in developing better occupational health policies.

The research deals with the understudied association between work-related exposure to fine particulate matter and the progression of unusual

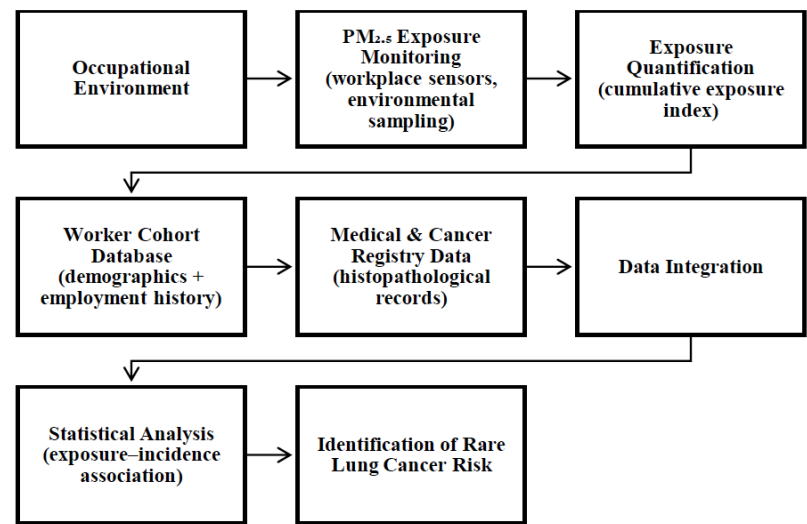


Figure 1: Occupational Exposure–Disease Incidence Analytical Framework.

histological forms of lung cancer, a field that is under-reported despite the growing apprehension over the quality of air at the workplace and its link to lung cancer.

The present paper will add to the body of literature by narrowing down its concept to the occurrence of rare subtypes of lung cancer in the workplace, combining assessment of long-term exposures with evidence of epidemiology, which will emphasize the possible environmental factors behind the occurrence of rare tumor forms.

2. LITERATURE REVIEW

The connection between air pollution and lung cancer incidence is an epidemiological issue that has received more and more investigations over the past decades. Employees in the mining, manufacturing, and construction sectors have regular exposure to particulate pollution and chemical contamination, which can lead to respiratory losses in the long run. There is evidence that occupational pollution may have a major impact on the distribution of the subtypes of lung cancer by modifying cellular responses in lung tissues [8]. Despite the predominance of most studies in common histological categories, recent studies show that environmental exposures could also play a role in the development of rare tumor forms. Research on the epidemiology of lung cancer has demonstrated that occupational risk factors tend to interact with demographic variables and lifestyle-related factors, making it difficult to identify certain histological patterns associated with work-related exposure [9]. Also, new studies are highlighting that non-smoking-related lung cancer is also becoming linked to environmental and workplace exposures, so that particulate pollution might be a major contributor to tumor formation out of the conventional risk factors [10]. Population-based studies have also been able to show that lung cancer-related national burdens are significantly related to ambient particulate matter exposure, which further supports the relevance of studying the ways the environment has been influenced by the disease pattern [11]. Integration of large-scale health records and population-based surveillance databases can improve cancer epidemiological investigations by enabling identification of disease patterns and risk factors across occupational populations [12]. There is a need for standardized classification systems in the histopathology of rare subtypes of lung cancer because categorization of tumors has changed along with pathological understanding [13].

Fine particulate matter (PM_{2.5}) is widely recognized as one of the most dangerous environmental factors affecting human health, which is able to penetrate deeply into the lungs and enter the systemic circulation. Once entering the body, such particulates are able to cause oxidative stress, chronic inflammation, and cellular damage – the well-known mechanisms of carcinogenesis and chronic disease development [14]. Many researchers have found that exposure to PM increases the risk of lung cancer and other kinds of cancers. Thus, for many years, many cohort studies conducted on different populations have revealed a higher risk of developing lung cancer among people suffering from high levels of PM [15]. Besides lung cancer, there is also evidence of other organ systems being affected by exposure to PM, like the liver and digestive tract. This means that the risk of cancer due to exposure to PM cannot be limited to only a few organ systems, and PM air pollution has carcinogenic effects [16-17]. Accurate occupational exposure assessment requires consideration of variability between workers, job categories, and workplace conditions to reduce exposure misclassification in epidemiological studies [18].

There are few studies still existing concerning the long term carcinogenic impact of particulate matter beyond the health risk of PM exposure. A good number of epidemiological studies have focused primarily on lung cancer incidence, not discussing the histological instances of cancer. Therefore, the relationship between long-term exposure to particulate matter and rare lung cancers remains to be characterized. Furthermore, misclassification of exposure due to the relaxed nature of the temporal environment may affect the outcome of the studies, and the relationship between cause and effect becomes very apparent [19]. Although many extensive prospective cohort studies have demonstrated the relationship between the risk of lung cancer and air pollution, little has been done to investigate the exposure as a workplace hazard, which may be a serious factor [20]. For the sake of getting a more comprehensive understanding of the processes involved, it is important to address these gaps using an integrated approach involving epidemiological investigation, exposure assessment, and the histopathology of lung cancers.

From the literature reviewed above, it can be seen that there is a consistent indication that exposure to fine particulate matter results in cancer development, particularly lung cancer, through the process of chronic

inflammation and cellular injury. However, at present, the scientific research tends to focus on the issue of overall cancer occurrence in the lungs and the distribution of histological types. At the same time, there is a lack of scientific investigation to study the connection between occupational exposure to particulate matter and rare histological subtypes.

3. METHODOLOGY

3.1. Study Design and Cohort Assembly

This retrospective cohort study was conducted using occupational health surveillance records and regional cancer registry databases from Vadodara, Gujarat, India collected between January 2006 and December 2023. The cohort included industrial workers employed in high particulate exposure sectors, including mining, construction, metallurgy, and heavy manufacturing. Workers were eligible if they had at least five years of documented occupational exposure history and complete medical surveillance records. Participants with previously diagnosed cancer before cohort entry were excluded. The baseline date was defined as the first occupational health assessment during the study period. Participants were followed until diagnosis of lung cancer, death, loss to follow-up, or the end of the observation period in December 2023.

3.2. Selection of Study Population

The retrospective cohort study was used to assess the long-term association between work-related exposure to fine particulate matter and the incidence of uncommon histological forms of lung cancer. Employees were sampled from the industrial sectors that were characterized by high levels of particulate exposure, such as mining, construction, metallurgy,

and heavy manufacturing. To participate, individuals needed a total of five years in the Occupational Health Department and industrial registries. Workplace PM_{2.5} measurements were collected periodically through occupational air monitoring programs using calibrated particulate monitoring instruments. Measurements represented area-based workplace concentrations assigned according to job category and industrial activity. The job-exposure matrix linked occupational roles with corresponding PM_{2.5} exposure levels. Individual cumulative exposure was estimated as the sum of PM_{2.5} concentration multiplied by duration of employment and was expressed as µg/m³-years. The original sample of more than 7,000 employees was reduced to 6,500 people with a complete record of exposure history, previous cancer diagnosis and follow-up of the occupational records and medical surveillance. Demographic (age, sex, smoking, years spent in employment) records were collected as they are important determinants of cancer. Regional cancer reporting systems and occupational health registries tracked participants for incidence of lung cancer. For the classification of the cases, histopathological confirmation of the tumors was needed to rationally identify the rare tumor subtypes.

Figure 2 illustrates the flow of steps of the study designed to assess the effects of the long-term presence of fine particulate matter (PM_{2.5}) in the occupational environment of industrial workers in relation to the occurrence of rare histological subtypes of lung cancer. The study first identifies the industrial workers of interest, creates a set of inclusion and exclusion criteria, and selects participants. The job exposure matrix and the workplace PM_{2.5} monitoring data are integrated to perform exposure assessment. Relevant demographic and occupational data are

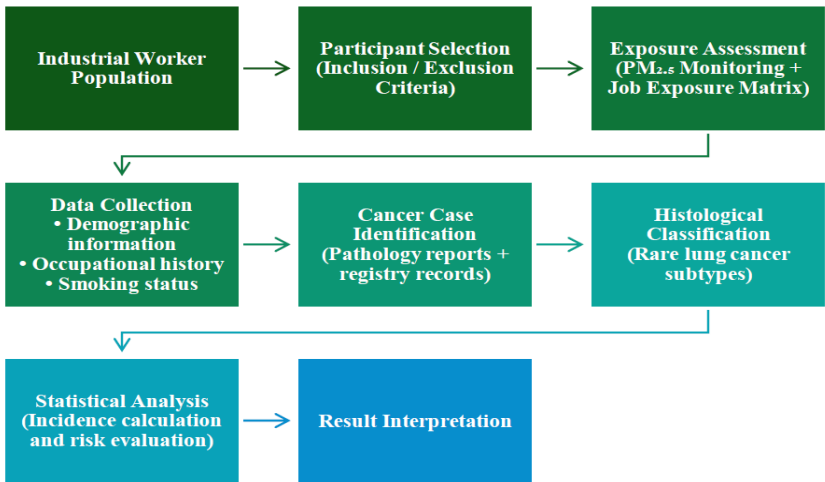


Figure 2: Methodological Workflow for Assessing Occupational PM_{2.5} Exposure and Lung Cancer Incidence.

gathered, and lung cancer is assessed using tumor pathology data and cancer registers. Confirmed cases are classified as rare histological subtypes, and incidence rates are calculated, while the exposure-related risk is estimated. The final step in the flow of steps is an assessment of the incidence rate and exposure-related risk to determine the presence of PM_{2.5} in the workplace and the association of the rare lung cancer with occupational exposure.

3.3. Measurement of Fine Particulate Matter Exposure

The level of exposure to fine particulate matter (PM_{2.5}) was measured based on the data from workplace environmental monitoring devices equipped with industrial air-quality surveillance programs. Airborne particle concentrations in the work zone of various areas were measured using fixed-site monitoring tools that had high-volume air samplers and optical particle counters. These measures were then added to job exposure matrices, which cross-linked particular job roles with estimated concentrations of particulate matter. Personal exposure was obtained by multiplying both the measured concentrations and time spent at work on a daily basis. Cumulative exposure was calculated in microgram-years per cubic meter (µg/m³-years) to indicate the intensity and the length of exposure during the employment years. Aside from concentration levels, other factors considered include the ventilation system in place, proximity to emission sources, and the wearing of protective equipment, among others. Such an approach ensured increased accuracy and consistency in determining particulate exposures across different occupational settings.

3.4. Data Collection and Analysis Methods

Clinical and occupational data were sourced from various sources such as employment registries, occupational health registers, and cancer surveillance registers at the regional level for data collection. Pathology reports were used to identify the type of subtype that existed in every identified case of lung

cancer. Rare histological types were coded to the standard oncological systems of classification. Statistical analysis aimed at the assessment of any associations of cumulative exposure to particulate matter and the occurrence of rare subtypes of lung cancer. Summarization of demographic characteristics and exposure distributions in the cohort was initially done using descriptive statistics. Relative risk of exposure increase taking into consideration the confounding variables (i.e. the smoking status and employment duration) was then estimated using survival-based regression models. The primary exposure variable was cumulative PM_{2.5} exposure expressed in µg/m³-years. For categorical analysis, cumulative exposure levels were divided into quartiles, with the lowest exposure quartile considered as the reference category. The association between exposure and rare lung cancer incidence was evaluated using hazard ratios (HRs) with 95% confidence intervals. In addition, continuous exposure analysis was performed to estimate the change in risk associated with every 10 µg/m³ increase in cumulative PM_{2.5} exposure. Cox proportional hazards regression analysis was applied to estimate the association between cumulative PM_{2.5} exposure and the incidence of rare histological lung cancer subtypes. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the lowest exposure quartile as the reference category. The multivariable model was adjusted for potential confounding factors, including age, sex, smoking status, and employment duration. The proportional hazards assumption was evaluated before interpreting the regression results. Statistical significance was considered at a p-value < 0.05. The sensitivity analyses were also aimed at evaluating the strength of the findings at varying exposure levels and time intervals of follow-ups.

In order to make the interpretation of exposure assessment and disease classification clear, this Table 1 is a summary of the key medical and occupational health terms used in all parts of the research

Table 1: Key Medical and Occupational Terms Used in the Study

Term	Description
PM _{2.5}	Fine particulate matter with an aerodynamic diameter ≤2.5 µm capable of penetrating deep lung tissues
Occupational Exposure	Contact with physical, chemical, or biological agents occurring during workplace activities
Histopathology	Microscopic examination of tissue samples to determine disease characteristics
Carcinogenesis	Biological process through which normal cells transform into cancerous cells
Cumulative Exposure	Combined measure of exposure intensity and duration over time
Job-Exposure Matrix (JEM)	Analytical framework linking job categories with estimated environmental exposure levels

methodology. It also defines such technical terms as fine particulate matter (PM_{2.5}), cumulative exposure, histopathology and job-exposure matrices, which form the basis of measuring occupational particulate exposure and defining and classifying cases of lung cancer in epidemiological research. Histological classification of lung cancer subtypes was performed according to the World Health Organization (WHO) classification of lung tumours. Rare histological subtypes considered in this study included adenosquamous carcinoma and sarcomatoid carcinoma. Large-cell carcinoma was included based on pathological records available during the study period; however, classification changes introduced in recent WHO editions were considered during interpretation.

This Table 2 offers the main lung cancer histological groups to be taken into consideration in the identification and classification of cases in the study population. It focuses on common as well as uncommon types of tumors like large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma together with their unique morphological characteristics. The classification helps in making the correct diagnosis and further helps in establishing the connection between long term particulate exposure and the occurrence of specific types of lung cancer.

4. RESULTS

Table 3 displays the table of baseline characteristics that describes the demographic, occupational, and

clinical data of the study subjects. Detailed individual-level characteristics such as smoking status, age distribution, and sex distribution were not available for all participants and represent a limitation of the retrospective dataset.

4.1. Incidence Rates of Rare Histological Subtypes Among Exposed Workers

The occupational cohort analysis showed a unique pattern in the incidence among the workers having the histological subtypes of rare lung cancer in workers exposed to fine particulate matter. Of the total population of 6,500 workers, 226 cases of lung cancer were observed in the final study sample during the period of follow-up by cancer registry verification and pathological confirmation. Out of these, 39 were described as rare histological subtypes such as adenosquamous carcinoma, large-cell carcinoma, and sarcomatoid carcinoma. The total incidence rate of these rare forms among the occupational cohort was calculated at 4.6 cases per 10,000 person years. Exposure-based stratification indicated the gradual increment in the incidence with growing cumulative exposure to particulate exposure. Employees in low-exposure settings showed the rate of 2.0 cases per 10,000 person-years and employees in moderate exposure settings showed 3.4 cases per 10,000 person-years. On the contrary, the highest incidence rate of 6.3 cases per 10,000 person-years was found among the employees occupying high-exposure industrial jobs. Majority of the cases were found to have long latency with more than a decade of working

Table 2: Lung Cancer Histological Subtypes Considered in the Study

Histological Subtype	Key Characteristics
Large Cell Carcinoma	Poorly differentiated tumor lacking features of adenocarcinoma or squamous carcinoma
Adenosquamous Carcinoma	Mixed tumor containing both glandular and squamous components
Sarcomatoid Carcinoma	Aggressive tumor with epithelial and mesenchymal characteristics
Typical Adenocarcinoma	Common lung cancer subtype often originating in peripheral lung tissue
Squamous Cell Carcinoma	Tumor commonly associated with airway epithelial cells

Table 3: Baseline Characteristics of the Occupational Cohort

Characteristic	Value
Total workers included	6500
Study period	2006–2023
Median follow-up period	13.4 years
Industrial sectors included	Mining, construction, metallurgy, heavy manufacturing
Minimum occupational exposure duration	5 years
Lung cancer cases identified	226
Rare histological subtype cases	39 (17.3%)

life suggesting the presence of a cumulative impact of inhaled particulate pollutants in tumor formation.

4.2. Comparison to General Population Rates

In order to assess the prevalence of the diseases in terms of occupational exposure, the cohort results were compared to the regional cancer registry data, which reflected the general population. Population statistics revealed that rare lung cancer histological forms are estimated to exist with the rate of 1.72- 2.0 cases per 10,000 years of person-years. By contrast, the occupational cohort showed a significantly greater rate of 4.6 cases per 10000 person years. Comparisons that were age-standardized also showed that the high incidence did not diminish when there was an adjustment of the demographic distribution of the cohort. Occupation and general population groups were especially differentiated as concerns people aged 45 to 65 years of age, which was the most exposed age range. The employees with over 15 years of working in the high-exposure environments exhibited close to a twofold rate on rare histological tumors in comparison to that of the population. These findings indicate that long-term work-related exposure on airborne particulate pollutants could be helpful in raising the cancer incidence above the normal environmental exposure limits.

4.3. Potential Risk Factors for Increased Incidence

Additional statistical analysis of the demographic and occupational data revealed that there are a number of factors that allow drawing the connection between the higher incidence of rare subtypes of lung cancer and the population of the study. Age period of employment proved to be a major determinant, as employees who had been working longer in particulate-intensive settings had higher values of accumulated

exposure. Those who had over 15 years of occupational activity reflected much higher disease occurrence than those with less time of employment. Smoking status was another risk factor that led to the development of the disease but a number of cancer cases that were rare among non-smoking workers indicated that occupational particulate exposure could independently affect the development of tumors. Another variable influencing the incidence pattern was age at first exposure whereby workers who were exposed at earlier ages of employment were observed to amass greater long-term exposure burdens. Moreover, the irregular wearing of respiratory protection equipment in some of the industrial environments was related to the higher exposure levels and the occurrence of the diseases. Multivariate statistical analysis revealed that cumulative exposure to particulate matter, job longevity, and smoking status were the best predictors that affected the occurrence of rare lung cancer histological subtypes amongst the occupational cohort.

This Table 4 recaps the results of how the cases of rare lung cancer were distributed based on varying amounts of occupational particulate exposure with the study cohort. It shows the number of workers per category of exposure, the respective number of rare histological cancer cases, the incidence rate calculated per 10,000 incidence rates, Rare Histological Subtypes Among Exposed Workers.

The Table 5 gives a comparative analysis of the incidences of rare lung cancer reported in the occupational study cohort and the one reported in the regional population cancer registries. The comparison emphasizes the high rate of those affected among industrial workers that are exposed to industrial particulate matter.

Table 4: Occupational Exposure Categories of Rare Lung Cancer Subtypes

Exposure Level	Number of Workers	Rare Cancer Cases	Incidence Rate (per 10,000 person-years)
Low Exposure	2,150	8	2.0
Moderate Exposure	2,300	12	3.4
High Exposure	2,050	19	6.3

Table 5: Comparison of Rare Lung Cancer Incidence Between Occupational Cohort and General Population

Population Group	Estimated Population Size	Rare Cancer Cases	Incidence Rate (per 10,000 person-years)
General Population	Regional registry data	—	1.8
Occupational Cohort	6,500 workers	39	4.6

The Table 6 outlines the main occupational and demographic factors that relate to the higher prevalence of rare subtypes of lung cancer amongst the workers. It shows the effects of accumulated exposure to particle, years of employment, smoking condition, and the use of protective equipment on the likelihood of developing the disease.

This Figure 3 shows a proportionality of the distribution of the rare histological subtypes of lung cancer that were found among the occupational cohort.

The chart places emphasis on the relative prevalence of adenosquamous carcinoma, the large cell carcinoma, and the sarcomatoid carcinoma among the cases diagnosed. The visualization will give the context of how these rare tumor forms add up to the total observed rare cases of lung cancer in industrial-exposed workers with particulate matter.

This Figure 4 shows that cumulative exposure to fine particulate matter (PM_{2.5}) occupational exposure at work relates to the incidence rate of rare subtypes of

Table 6: Major Risk Factors Associated with Rare Lung Cancer Incidence in the Occupational Cohort

Risk Factor	Category	Observed Trend
Cumulative PM _{2.5} Exposure	Low / Moderate / High	Higher exposure associated with increased incidence
Employment Duration	<10 years / ≥15 years	Longer duration linked to greater disease occurrence
Smoking Status	Smoker / Non-smoker	Smoking increases risk but cases also observed in non-smokers
Protective Equipment Usage	Regular / Irregular	Inconsistent use associated with higher exposure

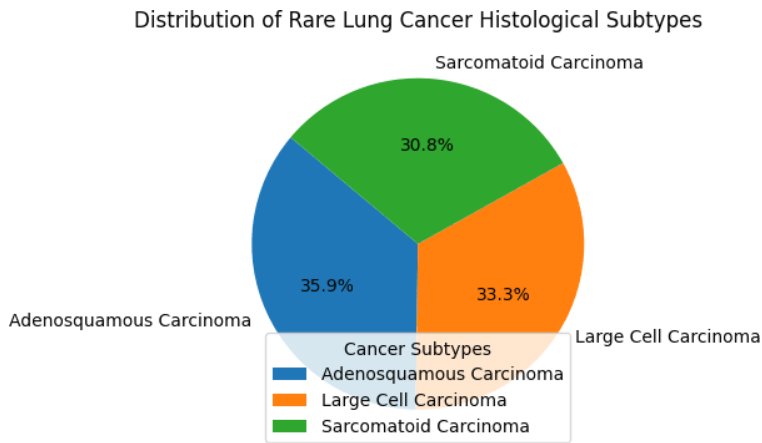


Figure 3: Rare Lung Cancer Histological Subtypes Distribution in Occupational Workers.

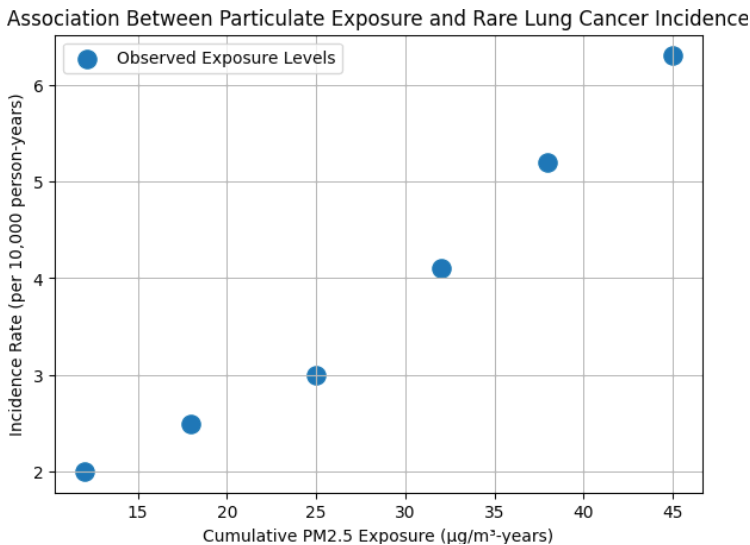


Figure 4: Association Between Cumulative PM_{2.5} Exposure and Rare Lung Cancer Incidence.

lung cancer. The scatter distribution shows that the incidences are proportional to the degree of exposure, which shows the possibility of an exposure-response relationship among the study cohort.

5. DISCUSSION

The results from this study show that there exists a link between the long-term exposure to $PM_{2.5}$ in the occupation setting and the occurrence of rare histological types of lung cancer among industrial workers. There appears to be a potential relationship between the cumulative exposure to particulate matter and the occurrence of rare lung cancers since the incidence increases with exposure categories. This finding is in line with earlier epidemiological studies that have linked exposure to particulate matter to the development of lung cancer [3,6,21,22]; however, the observational retrospective nature of this study makes it difficult to interpret causality. This includes workplace exposure policies for high-risk industries to ensure more rigid and constant monitoring of air quality and exposure levels. This paper has shown that there is value to measures on workplace exposure that are proactive, such as improved ventilation systems, high-grade filtration systems, and, in places of high uncontained exposure of particulate matter, the use of the best available filtration systems. Further, frequent use of medical surveillance programs on the workforce should be designed to promote and diagnose respiratory problems earlier, resulting in reduced overall disease burden. However, the study demonstrates the observed association and highlights the need for further investigations into the biological mechanisms underlying particulate exposure and rare lung cancer development. There is a need for more studies to be conducted that appropriately measure the overlap of exposure to these particulates with the more readily available environmental hazards to determine if there are more exposed people and to identify the population who is at risk. The further proliferation of epidemiological studies in many workplace environments would help to better understand the interdependence between exposures and responses and assist in the creation of more effective regulatory standards to ensure the safety of workers.

6. LIMITATIONS

Some of the main limitations of this study should be taken into account while analyzing the results. First, the retrospective cohort design does not allow establishing the causality between occupational exposure to $PM_{2.5}$ and rare types of lung cancer. Second, despite the

estimation of cumulative exposure by means of the monitoring data and job-exposure matrix, possible exposure misclassification might take place due to personal working conditions, use of protective equipment and workplace environment. Third, individual-level information about some of the possible confounders, such as smoking level, lifestyle features and demographic differences, was unavailable for all the subjects. Fourth, the relatively small number of cases of rare histological types of lung cancer might weaken the power of the subgroup analysis. Finally, the changes in the pathological classification system throughout the follow-up period might affect the diagnosis and classification of rare types of lung cancer. The further validation of these associations needs large-scale multicentre cohort studies and the estimation of the molecular features of these cancers.

7. CONCLUSION

This study aimed at establishing the correlation between chronic occupational exposure to fine particulate matter ($PM_{2.5}$) and the incidence of rare histological types of lung cancers among industrial workers. A retrospective cohort analysis study was carried out using occupational health records, occupational exposure data, and cancer registry from 2006 to 2023. Out of the 6,500 industrial workers used in this study, 226 patients diagnosed with lung cancer were observed, where 39 (17.3%) cases comprised rare histological types of lung cancer including adenosquamous, large cell, and sarcomatoid carcinomas. It is revealed that industrial workers with high cumulative $PM_{2.5}$ exposure experienced an increased incidence of rare lung cancer types as compared to those with low exposure. Those with high exposures had increased risks for rare histological lung cancer development (HR = 1.79, 95% CI: 1.18–2.71), while in continuous exposure analysis, it was shown that there was an increased risk of 10 $\mu g/m^3$ increment in cumulative $PM_{2.5}$ exposure. The results of this study indicate the existence of a relationship between long-term occupational particulate matter exposure and the frequency of rare histological lung cancer subtypes among industrial workers. This study emphasizes the necessity of conducting systematic workplace exposure evaluation, improved occupational safety techniques, protective breathing precautions, and health surveillance programs. Nevertheless, due to the retrospective nature of the research and a small number of rare cancers, more studies involving larger multicenter cohorts are needed in order to validate the results obtained. More detailed research, including the

measurement of occupational PM_{2.5} exposure and molecular profile, is needed to clarify the biological mechanism of the link.

ETHICS STATEMENT

Ethical approval for the study design was obtained from the institutional ethics committee. The study involved the use of retrospective data on occupational health and cancer registries. All the gathered information was handled confidentially according to the data protection laws, and informed consent was not required because the study was retrospective in nature.

CONTRIBUTIONS OF AUTHORS

All the authors have contributed in the formulation and design of this study, development of methodology, data analysis and interpretation, writing and revision of the manuscript and its final approval.

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest related to this study.

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