SCHOLARLY REVIEW

The ubiquitous silent killer: Exploring the link between air pollution and brain cancer

By Saket Singh

Author Biography

Saket Singh is a high school student at Skyline High School in Sammamish, Washington, where he is pursuing an IB Diploma. Driven by his passion for understanding complex systems, Saket has delved into research at the intersection of air pollution and brain cancer, inspired by a deep interest in environmental science and public health. A published author, he has explored the cognitive benefits of chess in his journal article 'Chess and the Human Brain – Demystifying the Therapeutic Value of a Board Game'. Beyond academics, Saket leads as a chess instructor and webmaster, running Connect Chess to make learning fun and accessible. He also actively participates in Skyline's band, playing the clarinet, and represents his school on the Varsity Tennis Team. In his free time, he develops Python-based applications, tutors students, and volunteers at community initiatives, showcasing his commitment to making a positive impact.

Abstract

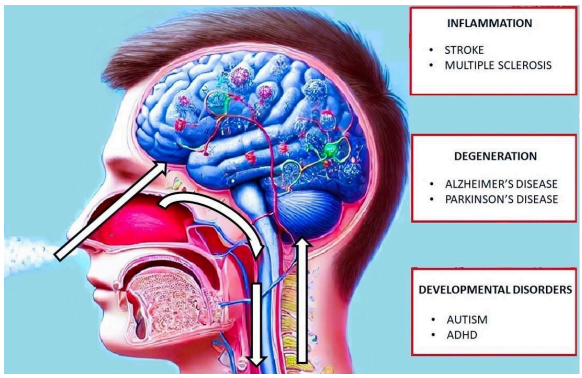
Air pollution has been associated with various diseases including respiratory, cardiovascular, and neurodegenerative disorders. Recent evidence suggests a potential link between air pollution and the development of brain cancer. This narrative review discusses epidemiological evidence on the topic, reviews biological pathways, and identifies directions for future research. From a total of 334 records screened from a PUBMED search, 30 articles focusing on pollutants such as particulate matter (PM), ultrafine particles (UFPs), black carbon, and nitrogen dioxide were included. While the findings of some studies were used to review underlying biological mechanisms, the results of epidemiological studies, a meta-analysis, and a systematic review were used to interpret existing evidence. The results indicated that air pollutants affect the central nervous system both directly and indirectly. Mechanisms of tumorigenesis include oxidative stress, inflammation, and DNA damage. UFPs pose a heightened risk due to the ease by which they penetrate the brain. Epidemiological studies indicate a higher incidence of brain cancer among individuals exposed to elevated levels of various pollutants. Synthesized results suggest that black carbon, $PM_{2.5}$, NO_2, and NO_x are amongst the pollutants with significant risks. Despite evidence suggesting a correlation between air pollution and brain cancer, the association remains complex and requires further investigation, especially with data on long-term exposure. Artificial intelligence models, particularly those incorporating gene-environment interactions, should be used to comprehensively predict brain cancer risk. Collaborative efforts between environmental scientists, oncologists, and policymakers are necessary to address the lethal threat posed by the ubiquitous 'silent killer'.

Keywords: air pollution; brain cancer; brain tumors; tumorigenesis; environmental carcinogens; long-term exposure; particulate matter; ultrafine particles; black carbon; nitrogen dioxide.

Introduction

Air pollution is a global environmental issue that affects millions of people daily (Lelieveld et al., 2015). It is primarily caused by the burning of fossil fuels, industrial emissions, and vehicular exhaust, leading to the release of harmful particles and gases into the atmosphere (Guerreiro et al., 2014). These pollutants, including particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3), have been extensively studied for their impact on human health (Cohen et al., 2017). Air pollution has been linked to a range of adverse health outcomes, including respiratory diseases, cardiovascular conditions, and even premature death (Dockery et al., 1993). In the central nervous system (CNS), air pollution has been associated with stroke, neurodevelopmental disorders, and neurodegenerative conditions like Parkinson's disease and Alzheimer's disease (see Figure 1) (Costa et al., 2020). However, its potential connection with brain cancer is a relatively underexplored area of research (Raaschou-Nielsen et al., 2013).

Figure 1
CNS Disorders Associated with Chronic Exposure to Air Pollutants. (ADHD = Attention Deficit Hyperactivity Disorder)

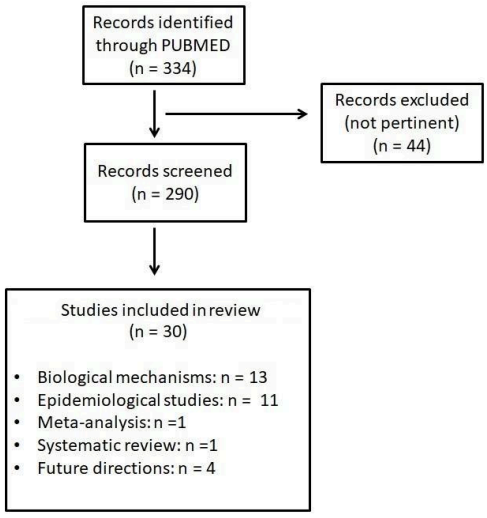


Brain cancer, although less common than other types of cancer, is particularly devastating due to the complexity of treatment and its poor prognosis despite decades of research (Ostrom et al., 2016). The exact causes of brain cancer are not well understood, but it is believed that genetic mutations and environmental factors play significant roles (Schwartzbaum et al., 2006). Recent studies have begun to investigate whether air pollution might be one of these environmental factors, given the ability of certain pollutants to penetrate the body's defenses and potentially cause damage to the brain (Genc et al., 2012). This study aims to explore the possible relationship between air pollution and brain cancer by reviewing the existing scientific literature, examining underlying biological mechanisms, and highlighting areas where further research is needed.

Methodology

The methodology for this study involved a comprehensive review of articles focusing on the links between air pollution and brain cancer. The PubMed database was searched for relevant studies using keywords such as "air pollution," "brain cancer," "brain tumors," "particulate matter," and "environmental carcinogens." Studies published between 2000 and 2024 were considered. After screening a total of 334 PubMed records (see Figure 2), a total of 30 articles were included in the final review. Both, experimental studies that investigated the biological mechanisms underlying the link between air pollution and brain cancer and epidemiological studies that evaluated this relationship were reviewed. Additionally, a meta-analyses and a systematic review were included for obtaining better evidence on the topic.

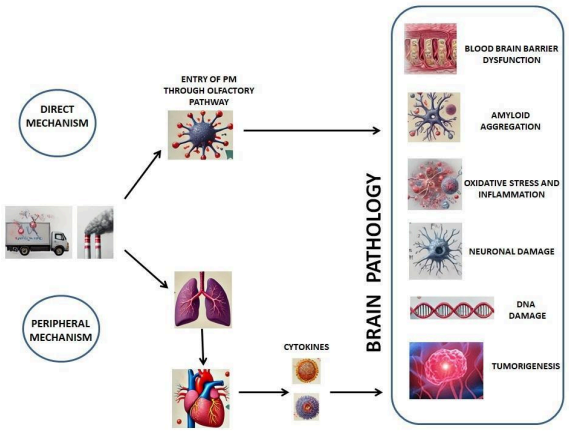
Figure 2
Flow-Diagram Showing the Inclusion of Articles in the Review



Underlying Biological Mechanisms

The potential link between air pollution and pathologies in the central nervous system has been explained by several biological mechanisms (Genc et al., 2012, Calderón-Garcidueñas et al., 2002). The effects of pollutants on the brain occur by both, direct and indirect methods (see Figure 3).

Figure 3
Mechanisms by which Air Pollution Affects the Brain



Ultrafine particles (UFPs), for example, enter the nervous system directly, through the olfactory mucosa in the nose- a neuronal epithelium that is directly exposed to environmental air (Genc et al., 2012). Fine particles and UFPs access the brain via olfactory receptor neurons or the trigeminal nerve. These olfactory receptor neurons are bipolar sensory cells responsible for mediating the sense of smell by transmitting sensory information from the nose to the central nervous system (CNS). Pollutants inhaled through the nose can reach the olfactory mucosa and enter the cilia of these neurons via pinocytosis, simple diffusion, or receptor-mediated endocytosis. Once inside the sensory neurons, the pollutants may be transported to the olfactory bulb through slow axonal transport.

Once absorbed into the blood stream after reaching the alveoli in the lungs, certain air pollutants indirectly enter the brain by penetrating the blood-brain barrier (BBB), a protective membrane that shields the brain from harmful substances circulating in the bloodstream (Oberdörster et al., 2004). Particulate matter (PM), especially ultrafine particles (UFPs) less than 0.1 micrometers in diameter, can bypass this barrier and enter the brain directly (Peters et al., 2004).

Once inside the brain, these particles may induce oxidative stress, inflammation, and DNA damage, all of which are known to contribute to carcinogenesis (Liu et al., 2016). Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants (Block et al., 2009). Excessive ROS can damage cellular components, including DNA, proteins, and lipids, leading to mutations and potentially triggering the development of cancerous cells (Risom et al., 2005). Air pollutants such as PM, ozone, and nitrogen dioxide have been shown to increase ROS production, thereby elevating the risk of oxidative damage in brain cells (Genc et al., 2012).
Inflammation is another critical factor in the development of cancer (Hanahan et al., 2011). Chronic exposure to air pollution can lead to a persistent inflammatory response in the body, including the brain (Calderón-Garcidueñas et al., 2004). Inflammation in the brain is particularly harmful as it can create an environment conducive to tumor growth. Pro-inflammatory cytokines, which are signaling molecules released during inflammation, promote cell proliferation and inhibit apoptosis (programmed cell death), both of which are hallmarks of cancer (Mantovani et al., 2008).
Air pollutants are also postulated to directly damage DNA in brain cells (Rossner et al., 2011). Certain pollutants, such as polycyclic aromatic hydrocarbons (PAHs), are known to be mutagenic, meaning they can cause changes in the DNA sequence (Perera et al., 1997). These mutations can disrupt normal cell functions and lead to uncontrolled cell growth, a defining characteristic of cancer (Schwartzbaum et al., 2006). Additionally, 'epigenetic' changes (alterations in gene expression without changes to the DNA sequence) may also play a role (Feinberg et al., 2006). Air pollution has been linked to epigenetic modifications, such as DNA methylation, which can affect the regulation of genes involved in cell cycle control and tumor suppression.

Evidence from epidemiological studies

Recent epidemiological studies have increasingly revealed an association between specific air pollutants and the incidence of brain tumors. Nitrogen oxides (NO_x), particulate matter (PM), and UFPs are amongst some of the main pollutants identified to be risk factors for brain tumorigenesis. A nationwide cohort study in Denmark (Raaschou-Nielsen et al., 2011) found that a 100 µg/m³ increase in NO_x exposure was linked to a hazard ratio (HR) of 2.28 (95% CI: 1.24–4.17) for brain cancer incidence, emphasizing the heightened risk in high-pollution areas. Nitrogen dioxide (NO_2), another common traffic pollutant, has been similarly implicated in brain tumorigenesis. Research from other cohort studies (Andersen et al., 2018, Weichenthal et al., 2020) demonstrated an association between NO_2 exposure and gliomas, possibly through oxidative stress and neuro-inflammation pathways.

Particulate matter, particularly fine particles like $PM_{2.5}$ and PM_{10}, has been linked to an increased risk of brain cancer. In a Canadian cohort study, a rise in $PM_{2.5}$ levels was associated with higher brain tumor risks, especially in urban areas with higher traffic pollution. The hazard ratio in this study was 1.14 (95% CI: 1.01–1.28) per 10 µg/m³ of $PM_{2.5}$ exposure (Ghosh et al., 2013). Volatile organic compounds (VOCs), such as benzene and formaldehyde, are amongst other by-products of traffic emissions that have been shown to elevate brain tumor risk (Villeneuve et al., 2014).

Studies involving prenatal and early-life exposures to air pollution indicate that early exposure may contribute to the development of brain tumors later in life. A study examining traffic-related air pollution in China found that prenatal exposure to NO_2 and $PM_{2.5}$ was associated with an increased risk of childhood brain cancers (Huang et al., 2020). These findings imply that the timing of exposure may be another critical factor in determining the risk of developing brain cancer.

Insights from synthesized data

A meta-analysis of eight studies (Shen et al., 2023) evaluated the impact of six environmental air pollutants: black carbon (BC), nitrogen oxides (NO_x), fine particulate matter ($PM_{2.5}$), NO_2, coarse particulate matter (PM_{10}), and ozone (O_3). The combined effect size (ES) for a 10 µg/m³ increase in BC exposure was 1.67 (95% CI: 1.25, 2.22), p = 0.449. For each 10 µg/m³ rise in NO_2 levels, the ES was 1.03 (95% CI: 1.01, 1.05), p = 0.319. Additionally, there was a borderline association between NO_x and adult brain tumors (ES: 1.01; 95% CI: 1.00, 1.01/10 µg/m³; p = 0.716). No significant associations were observed for $PM_{2.5}$, PM_{10}, or O_3 ($PM_{2.5}$: ES 1.04; 95% CI: 0.99, 1.08/10 µg/m³; p = 0.834; PM_{10}: ES 1.01; 95% CI: 0.97, 1.04/10 µg/m³; p = 0.627; O_3: ES 0.97; 95% CI: 0.94, 1.00/10 µg/m³; p = 0.253). These findings suggested an association between BC, NO_2, and NO_x exposure and adult brain tumors.

A systematic review (Hassanipour et al., 2023) of 5 studies reviewed the relationship between short- and long-term exposure to various air pollutants, including SO_2, CO, NO_2, PM_{10}, O_3, $PM_{2.5}$, and others, and the incidence of brain tumors. Relative risk (RR) obtained for proximity to traffic ('Trafnear', $PM_{2.5}$, $PM_{2.5}$ absorbance, O_3 and NO_x were as follows: RR = 1.07, (95% CI 0.99–1.16), p = 0.079, for Trafnear; RR = 0.90, (95% CI 0.80–1.00), p = 0.064 for $PM_{2.5}$; RR = 1.63, (95% CI 1.04–2.55), p = 0.031 for $PM_{2.5}$ absorbance; RR = 1.3, (95% CI 1.03–1.6), p = 0.023 for O_3; and RR = 1.16, (95% CI 0.93–1.45), p = 0.173 for NO_x. A significant correlation between exposure to O_3 and $PM_{2.5}$ absorbance and brain tumors suggested a potential role of these pollutants in the development of brain tumors. However, these results were limited by high levels of heterogeneity between some of the cohorts.

UFPs and brain cancer- the growing evidence

Given that $PM_{2.5}$ and black carbon (elemental carbon, EC) are amongst the significant pollutants identified in the above meta-analyses, it

can be extrapolated that UFPs which are smaller particles than $PM_{2.5}$ and often contain EC, pose a greater risk for brain cancer. With their smaller size and higher surface-area to volume ratio compared to $PM_{2.5}$, it is much easier for UFPs to penetrate the blood-brain barrier and cause neurotoxicity. Once in the brain, EC- an important component of UFPs- has been established to promote neuro-degeneration by causing deleterious effects in the memory-related regions like the thalamus, prefrontal cortex and hippocampus (Vanbrabant et al., 2024). While some of these areas are probably affected by the direct entry of these particles through the olfactory pathway, it is likely that their potential for tumorigenesis is related more to their crossing the blood- brain barrier and affecting distant areas as well.

The association of UFPs with brain tumorigenesis has been borne out in large cohort studies (Weichenthal et al., 2020, Wu et al., 2021). A within-city epidemiological study found a positive association of ambient UFPs with brain tumors independent of $PM_{2.5}$ or NO_2. (Weichenthal et al., 2020). The hazard ratios remained elevated (>1) even after adjusting for socio-demographic factors, smoking, and body mass index. In absolute terms, the association suggested that a 10,000/cm^3 increase in 3-year mean ambient UFP-concentration would contribute to one new brain tumor for every population of 100,000 people.

Although the source of UFPs is mainly from the incomplete combustion of fossil fuels in motor vehicles, they can also be found in high ambient concentrations in urban fires (DeBono et al., 2023) and from aircraft exhaust. The latter was identified in a study that determined the composition of particles from jet engines during take-off and landing in real-world conditions (Fushimi et al., 2019). In a large epidemiological study (Wu et al., 2021), airport-related UFP and the risk of developing malignant brain cancer was studied in a multiethnic cohort of 75,936 men and women with a longitudinal follow-up of 16 years. UFP exposure from aircrafts was estimated within a fixed area around the Los Angeles International Airport. Malignant brain cancer risk in all subjects was found to have increased by 12% (95% CI 0.98–1.27) per interquartile range of UFP exposure (~6700 particles/cm^3).

Surrogate measurements and biomarker analysis

While existing literature provides insights into the potential link between air pollution and brain cancer, significant gaps in knowledge still remain. A significant limitation is with regard to the inaccuracies in the existing techniques of measuring exposure to air pollutants. Researchers should aim to improve exposure assessment methods by incorporating personal exposure monitoring, and the use of biomarkers to more accurately reflect individual exposures. Surrogate measurements, such as the concentration of EC in the bloodstream or cerebrospinal fluid, can serve as indicators of UFP exposure. Biomarkers of oxidative stress and DNA damage such as levels of 8-oxo-2'-deoxyguanosine in brain tissue (Valavanidis et al., 2009) can be used to establish a causal link between UFP exposure and brain cancer. Incorporation of these biomarkers into epidemiological models would help in accurate assessments of the long-term impact of low-level UFP exposure, reduce misclassification bias, and improve the reliability of study findings.

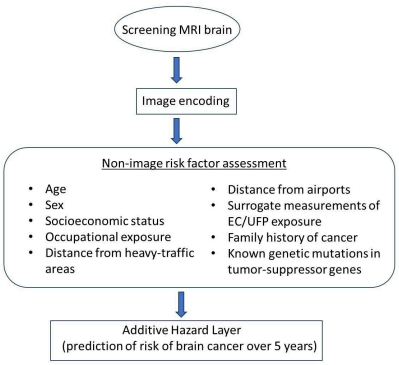
Future directions - need for AI models

In the healthcare domain, AI based ‘personalized care’ enables patients to benefit from more accurate diagnoses, prognoses, and more effective therapies. AI helps in analyzing complex, multi-factorial data and providing precise information on various disease-related aspects like risk stratification, disease prediction, survival, and overall prognosis (Zhang et al., 2023). With respect to cancer, agnostic AI algorithms can potentially enhance risk stratification criteria and influence cancer screening recommendations. This can be especially useful in the understanding of the air pollution–brain cancer association, given that the etiology of brain cancer is multifactorial, with a combination of genetic, environmental, and lifestyle factors being implicated (Schwartzbaum et al., 2006).

To better understand the links between UFP exposure and brain cancer risk, it would be useful to develop quantitative models that integrate multiple known risk factors for brain tumorigenesis (Pagano et al., 2023). Machine learning approaches, such as convolutional neural networks (CNNs), can be used to analyze large-scale epidemiological complex data sets from multiple cohorts. For instance, one of the meta-analyses (Hassanipour et al., 2023) identified significant variability in hazard ratios (HRs) while studying the association between $PM_{2.5}$ and brain tumors. Using CNNs, these patterns can be modeled across different demographic groups (age, sex, socio-economic status) and exposure levels to improve prediction and also to redefine exposure thresholds for policy action.

Since brain cancer is increasingly being associated with various genetic mutations, AI models should also incorporate data on gene-environment interactions and assess how genetic predispositions (such as mutations in tumor-suppressor genes) modulate the effects of UFP exposure. This information can help identify high-risk populations, such as children living in urban areas or individuals with a family history of cancer. These insights would help in preventative healthcare, and would help in mitigating the morbidity and mortality associated with brain cancer. A deep-learning tool for predicting the risk of developing air pollution-related brain cancer would include multilayers (see Figure 4), akin to the 'Mirai' algorithm developed at MIT for predicting breast cancer (Yala et al., 2022).

Figure 4
A Proposed Framework to Predict the Risk of Air Pollution-Related Brain Cancer using a Multilayer Non-Image Risk Assessment.



Implications for public health research and policy

A significant gap in knowledge is the lack of studies examining the effects of long-term, low-level exposure to air pollution. Most research has focused on high levels of exposure or short-term exposure events, but the cumulative effects of chronic, low-level exposure over many years are not well understood (Lelieveld et al., 2015). Conducting long-term, prospective cohort studies with large, diverse populations, along with detailed spatial analyses of pollutant exposure, and cumulative effects of multiple pollutants will provide more robust data on the relationship between air pollution and brain cancer.

Healthcare policies must adopt an interdisciplinary approach that integrates environmental science, oncology, and public health to effectively address the potential link between air pollution and brain cancer. Given the growing evidence of the role of UFP carbon and other pollutants in brain cancer, stricter air quality regulations are necessary, particularly in urban areas and near major transportation hubs. Currently, UFPs remain non-regulated, despite evidence of their adverse health effects. Public health initiatives should establish limits on UFP and EC emissions, and also focus on targeted interventions for vulnerable groups, such as firefighters, children, and urban populations living near high-traffic areas or airports. These groups are disproportionately affected by unregulated UFP emissions, and policies that reduce their exposure could significantly mitigate long-term health risks. Pollution research should also look at developing superior technologies for controlling aircraft emissions (e.g., through breather vents) to decrease UFPs (Fushimi et al., 2019). A detailed knowledge of aircraft emissions would improve our understanding of the fate of UFPs in the upper troposphere. This would help in potentially affecting the 'radiative' balance of the atmosphere[34] and mitigating its tumorigenic threat.
Collaboration with oncologists is essential to understand the biological mechanisms through which pollutants may contribute to brain cancer, guiding the development of targeted prevention strategies and

early detection methods. Public health initiatives should focus on education and outreach, informing the public about the risks of air pollution and promoting behavior that reduces exposure, such as using public transportation, supporting green spaces, and advocating for cleaner energy sources. Interdisciplinary research should be prioritized, with funding directed towards studies that explore the complex interactions between environmental factors and cancer development.

Conclusion

The potential link between air pollution and brain cancer is an emerging area of research with significant public health implications. Although evidence is still evolving, several studies have suggested that exposure to air pollution, particularly ultrafine particles, may increase the risk of developing brain cancer. The biological basis underlying this association includes mechanisms like oxidative stress, inflammation, and DNA damage. Significant gaps in knowledge still remain, and further research is needed to clarify these links. Future studies should focus on effects of long-term exposure to air pollutants, and use AI-models to predict the risk of brain cancer by studying interactions between air pollution and established risk factors. An interdisciplinary approach combining environmental science, oncology, and public health might help in mitigating the health threat posed by the ubiquitous ‘silent killer’.

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