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FROM PARTICLES TO PRECISION: MECHANISTIC PATHWAYS OF AIR POLLUTION-INDUCED CANCER AND THE AI FRONTIER

Community Medicine

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ABSTRACT

Background: Air pollution, particularly fine particulate matter ($PM_{2·5}$), is a recognized Group 1 carcinogen, yet the full spectrum of its mechanistic contributions to carcinogenesis—including tumor promotion—remains underexplored for AI-driven translational applications. Methods: Systematic narrative review of PubMed, Scopus, Web of Science, and Google Scholar (2010–March 2026) using PRISMA-informed search terms combining air pollution/$PM_{2·5}$ with carcinogenesis, oxidative stress, inflammation, epigenetics, immune surveillance, and tumor promotion. **Results:** $PM_{2·5}$ induces carcinogenesis via oxidative stress and DNA damage (initiation), chronic inflammation and epigenetic reprogramming, impaired immune surveillance, and tumor promotion through clonal expansion of preexisting mutated cells (e.g., EGFR-driven) in a pro-proliferative microenvironment. Meta-analyses confirm elevated lung cancer risk (HR 1.08–1.16 per 10 μg/m³ $PM_{2·5}$) with emerging signals for extrapulmonary malignancies. **Conclusion:** These pathways position air pollution as a modifiable driver of cancer. A targeted AI roadmap can overcome current technical barriers to deliver precision risk stratification and prevention.

KEYWORDS

Air Pollution, $Pm_{2·5}$, Carcinogenesis, Tumor Promotion, Oxidative Stress, Epigenetics, Artificial Intelligence, Precision Oncology, Environmental Health Informatics

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, with environmental factors playing an increasingly recognized role alongside genetic predisposition and lifestyle behaviors. Among environmental exposures, ambient air pollution stands out as a major public health threat. Comprising fine particulate matter ($PM_{2·5}$), nitrogen oxides, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds, and other toxicants generated by traffic, industrial activities, energy production, and biomass combustion, outdoor air pollution was classified by the International Agency for Research on Cancer (IARC) as a Group 1 human carcinogen in 2013.[1,2] This classification was based on sufficient evidence of carcinogenicity, particularly for lung cancer, with a positive association also noted for bladder cancer.[1,2]

While the association between long-term exposure to air pollutants and lung cancer is well established,[3,4,5,6,7] emerging evidence indicates that the effects are not confined to the respiratory tract. Inhaled pollutants can translocate into systemic circulation, triggering biological responses that influence carcinogenesis across multiple organ systems.[8,9,10] Importantly, air pollution not only initiates DNA damage but also promotes the progression of preexisting mutated cells through sustained inflammatory signaling.[11,12]

Meta-analyses and large prospective cohorts have consistently demonstrated dose-response relationships between $PM_{2·5}$ exposure and lung cancer incidence and mortality, with relative risks ranging from 1.08 to 1.16 per 10 μg/m³ increment.[7,13,14,15,16] Associations with extrapulmonary malignancies, including bladder, breast, and hematological cancers, are also increasingly recognized.[8,9]

This review provides a comprehensive synthesis of the key physiological mechanisms linking air pollution exposure to cancer development, with particular emphasis on the critical but often underappreciated role of tumor promotion. In addition, it outlines a forward-looking roadmap for leveraging artificial intelligence (AI) and machine learning to translate these mechanistic insights into precision environmental oncology and public health strategies.[19,20]

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for reporting. A systematic narrative review was conducted to synthesize the mechanistic and epidemiological evidence on air pollution and carcinogenesis. Four major databases—PubMed, Scopus, Web of Science, and Google Scholar—were searched from 1 January 2010 to 31 March 2026. The search strategy combined MeSH terms and free-text keywords using Boolean operators: ("air pollution" OR "$PM_{2·5}$" OR "particulate matter" OR "ambient pollution") AND ("cancer" OR "carcinogenesis" OR "carcinoma" OR "tumor promotion" OR "tumor progression") AND ("oxidative stress" OR "inflammation" OR "epigenetic" OR "DNA damage" OR "immune surveillance" OR "immune evasion" OR "EGFR" OR "mechanis*" OR "AhR" OR "IL-1β" OR "IL-18").

Two independent reviewers screened titles and abstracts, followed by full-text assessment of potentially eligible records. Inclusion criteria were: (1) peer-reviewed original research, systematic reviews, or meta-analyses published in English; (2) studies reporting mechanistic data (in vitro, in vivo, or human) or epidemiological associations with clear exposure assessment ($PM_{2·5}$ or equivalent); and (3) focus on carcinogenesis pathways or tumor promotion. Exclusion criteria included: studies limited exclusively to indoor/household air pollution, non-peer-reviewed sources (preprints, conference abstracts, editorials), articles without biological or clinical endpoints related to cancer, or those lacking quantitative exposure metrics.

Data extraction focused on study design, exposure metrics, key

mechanistic findings (oxidative stress, inflammation, epigenetics, immune effects, tumor promotion), epidemiological risk estimates (hazard ratios, relative risks, confidence intervals), and AI-related applications. Owing to the mechanistic heterogeneity and narrative nature of the topic, a qualitative synthesis was performed. Priority was given to high-impact publications from 2020–2026 and studies providing robust causal or mechanistic evidence. Quantitative estimates from meta-analyses were extracted verbatim where available to support epidemiological sections. No formal risk-of-bias assessment tool was applied to individual studies because of the broad scope; however, only peer-reviewed, high-quality sources were included.

RESULTS

Air pollution, particularly fine particulate matter ($PM_{2·5}$), drives carcinogenesis through multiple interconnected physiological pathways. These include oxidative stress and DNA damage (initiation), chronic inflammation, epigenetic reprogramming, immune surveillance impairment, and tumor promotion.

Oxidative Stress and DNA Damage

$PM_{2·5}$ and its associated metals (e.g., iron, copper) and organic compounds generate reactive oxygen species (ROS) primarily through Fenton-like reactions and direct surface reactivity.[3-5] When ROS production overwhelms cellular antioxidant systems (e.g., glutathione, superoxide dismutase), oxidative stress ensues, leading to direct genotoxic effects including DNA single- and double-strand breaks, base modifications (notably 8-oxoguanine), and chromosomal instability.[3-5] These lesions preferentially affect oncogenes (e.g., *KRAS*, *EGFR*) and tumor suppressor genes (e.g., *TP53*), initiating malignant transformation. In vitro and animal studies confirm that $PM_{2·5}$-induced ROS also activates redox-sensitive signaling pathways such as Nrf2 and p53, further amplifying genomic instability.[3]

Chronic Inflammation

Inhaled $PM_{2·5}$ particles are phagocytosed by alveolar macrophages and epithelial cells, triggering the release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-18) and activation of central transcription factors NF-κB and MAPK.[3,4,11] Sustained inflammation promotes cellular proliferation, inhibits apoptosis, stimulates angiogenesis via VEGF upregulation, and induces secondary DNA damage through reactive nitrogen species.[3] This creates a tumor-permissive microenvironment that synergizes with oxidative stress to accelerate carcinogenesis.

Epigenetic Alterations

$PM_{2·5}$ exposure induces genome-wide and locus-specific epigenetic changes, including altered DNA methylation (hypomethylation of LINE-1 and hypermethylation of tumor-suppressor promoters), histone modifications (increased HAT activity, decreased HDAC2), and dysregulation of non-coding RNAs (miRNAs targeting inflammatory and cell-cycle pathways).[18] These modifications persist long after exposure and can be transgenerational, disrupting genes involved in inflammation, DNA repair, and cell-cycle control, thereby amplifying cancer susceptibility.[18]

Impairment of Immune Surveillance

Pollutant-driven systemic and local inflammation suppresses effector immune functions, including reduced activity of natural killer (NK) cells and $CD8^+$ T-cells, while promoting regulatory T-cell phenotypes.[3] This immune evasion allows mutated cells to escape detection and elimination, facilitating tumor initiation and progression.

Tumor Promotion

Beyond initiation, air pollution acts as a potent tumor promoter by selectively expanding preexisting "sleepy" clones harboring driver mutations in otherwise normal tissue.[6,11,12] Landmark work by Hill et al. (Nature, 2023) demonstrated that $PM_{2·5}$ promotes EGFR-mutant lung adenocarcinoma through macrophage-derived IL-1β.[6] Ultra-deep mutational profiling of histologically normal lung tissue from 295 individuals revealed oncogenic EGFR and KRAS mutations in 18% and 53% of samples, respectively.[6] In inducible EGFR ^{858} mouse models, short-term $PM_{2·5}$ exposure caused macrophage infiltration, IL-1β release, and reprogramming of mutant alveolar type II cells into a progenitor-like state with enhanced self-renewal and proliferation.[6] Neutralization of IL-1β with monoclonal antibodies significantly attenuated tumor burden.[6] Complementary mechanistic studies show that $PM_{2·5}$ further drives progression via the AhR–TMPRSS2–IL-18 axis, enhancing epithelial–mesenchymal transition, angiogenesis, and immune evasion in established lesions.[11] This promotion phase explains the stronger associations with EGFR-mutant lung adenocarcinoma—even in never-smokers—and at exposure levels below many regulatory thresholds.[6,12]

Table 1. Summary of Biological Mechanisms Linking $PM_{2·5}$ to Carcinogenesis

Mechanism	Key Pathways / Mediators	Cellular Effects	Representative References
Oxidative Stress & DNA Damage	ROS via Fenton reactions; 8-oxoguanine	DNA breaks, chromosomal instability, oncogene activation	3, 5
Chronic Inflammation	NF-κB/MAPK; IL-6, TNF-α, IL-1β, IL-18	Proliferation, angiogenesis, apoptosis resistance	3, 4, 11
Epigenetic Alterations	DNA methylation (LINE-1 hypomethylation), histone mods, miRNA dysregulation	Persistent gene silencing/reactivation	18
Immune Surveillance Impairment	Suppression of NK/$CD8^+$ T-cells	Immune evasion of mutated clones	3
Tumor Promotion	Macrophage-derived IL-1β; AhR–TMPRSS2–IL-18 axis; progenitor-like reprogramming of EGFR/KRAS-mutant cells	Clonal expansion of preexisting mutations	6, 11, 12

Epidemiological Evidence

Large-scale meta-analyses and prospective cohorts consistently demonstrate a robust dose–response relationship between long-term $PM_{2·5}$ exposure and lung cancer.[7,13,15,16] Meta-estimates indicate an 8–16% increased risk per 10 μg/m³ increment in $PM_{2·5}$ (HR/RR 1.08–1.16), with the strongest associations observed for adenocarcinoma histology and never-smokers.[7,15] Recent high-quality cohorts further confirm these findings across diverse populations.[9,13] Associations extend beyond the lung to bladder, breast, and selected hematological malignancies.[8,9] Urban populations experience amplified risk due to higher traffic- and industry-related emissions.[8,10]

Table 2. Selected Epidemiological Associations Between $PM_{2·5}$ Exposure and Cancer Risk

Study / Meta-Analysis	Cancer Type	Risk Estimate (HR/RR, 95% CI)	Key Notes	Reference
Huang et al. (2017) meta-analysis	Lung (incidence)	1.08 (1.03–1.12)	17 studies	15
Ciabattini et al. (2021)	Lung	1.08–1.16	High-quality recent cohorts	7
Fisher et al. (2025) US cohort	Lung (adenocarcinoma)	1.05 (1.01–1.09) per 4.4 μg/m³	Large prospective cohort	13
Feng et al. (2025) Medicare cohort	Multiple (lung, bladder, breast)	Significant positive associations	$PM_{2·5}$ constituents analyzed	9
Kayyal-Tarabeia et al. (2024)	Bladder, breast	Elevated risk	Systematic review	8

Hill et al. (2023)	EGFR-mutant lung adenocarcinoma	Strong geographic correlation with $PM_{2·5}$	Tumor promotion focus	6

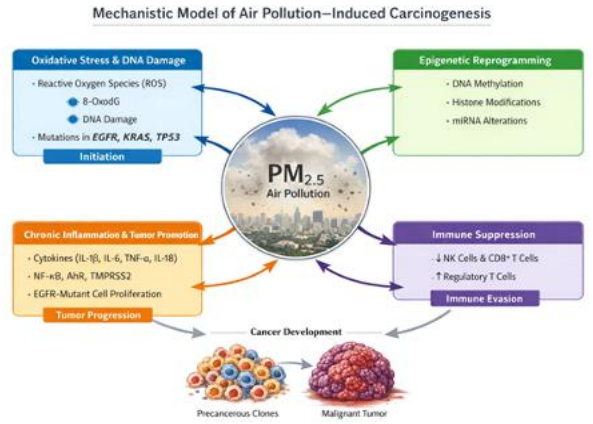

Figure 1: Mechanistic model of air pollution-induced carcinogenesis.

A schematic diagram illustrating the sequential and synergistic pathways: (1) oxidative stress and DNA damage (initiation), (2) chronic inflammation leading to tumor promotion via IL-1β and AhR signaling, (3) epigenetic reprogramming, and (4) immune evasion. Arrows depict crosstalk between mechanisms, with EGFR-mutant clonal expansion highlighted in the tumor-promotion panel.

DISCUSSION

The integrated mechanisms—oxidative initiation, inflammatory promotion, epigenetic reprogramming, and immune evasion—provide a coherent framework for air pollution as a modifiable carcinogen. Tumor promotion highlights how pollutants not only damage DNA but actively drive outgrowth of preexisting mutated cells, underscoring urgency for intervention even in low-exposure settings. Epidemiological consistency supports causality, though residual exposure misclassification and confounding remain challenges.

Roadmap for AI Implementation in Precision Environmental Oncology

To move from mechanistic understanding to actionable prevention, we propose a three-pronged AI roadmap addressing core technical hurdles:

1. Data Heterogeneity and Multimodal Integration: Exposure (satellite, ground sensors, personal monitors), genomics, epigenomics, electronic health records, and geospatial data vary in resolution, format, and quality. Federated learning and graph neural networks can harmonize these sources while preserving privacy, enabling robust risk models across diverse populations.

2. Accurate Personal Exposure Assessment and Sensor Calibration: Traditional models suffer from spatial/temporal uncertainty and calibration drift. AI-driven fusion of low-cost sensor networks with satellite data and uncertainty quantification (e.g., Bayesian deep learning) can generate high-resolution, individualized exposure profiles, reducing misclassification bias in risk prediction.

3. Model Interpretability and Causal Inference for Clinical Trust: Black-box predictions limit adoption. Explainable AI (XAI) techniques—SHAP values, counterfactual modeling, and causal discovery algorithms—can elucidate feature contributions (e.g., $PM_{2·5}$ × EGFR variant interactions) and support counterfactual "what-if" scenarios for pollution reduction, facilitating regulatory acceptance and personalized screening recommendations.

These advances would enable real-time risk dashboards, precision prevention trials, and equitable policy targeting of high-burden communities.

Limitations include observational data reliance and pollutant mixture complexity; future work should leverage AI for causal pathway discovery and prospective validation.

CONCLUSION

Air pollution drives cancer through initiation, promotion, and progression pathways that are now mechanistically clear. Reducing exposure via clean energy transitions and urban planning is a core prevention strategy. The proposed AI roadmap overcomes key technical barriers, positioning environmental health informatics at the forefront of precision oncology. Protecting air quality is both an environmental imperative and a transformative public health intervention.

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