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Review Article

Environmental Epimutagens and Molecular Mechanisms Linking Pollution to Cancer

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ABSTRACT

Background: Environmental pollution is an increasingly important contributor to cancer risk, yet its carcinogenic effects cannot be explained solely by direct DNA damage. Emerging evidence indicates that many pollutants act as environmental epimutagens, inducing persistent changes in gene regulation without altering the underlying DNA sequence. These epigenetic alterations may influence cancer susceptibility by disrupting molecular pathways involved in genomic stability, inflammation, apoptosis, cell-cycle control, and tissue-specific developmental programming. **Objective:** This narrative review synthesizes current evidence on the molecular mechanisms through which environmental epimutagens link pollution exposure to cancer development, with emphasis on DNA methylation, histone modifications, chromatin remodeling, non-coding RNA dysregulation, developmental vulnerability, and public health implications. **Methods:** A narrative literature synthesis was conducted using peer-reviewed studies retrieved from PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The main search period covered 2014–2024, with older landmark studies included when they provided foundational mechanistic evidence. Eligible studies addressed environmental pollutants, epigenetic alterations, and cancer-related molecular pathways. Evidence was organized thematically by pollutant class and epigenetic mechanism rather than statistically pooled. **Results:** The synthesized evidence indicates that particulate matter, heavy metals, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, pesticides, and industrial contaminants converge on four major epigenetic regulatory systems: DNA methylation, histone modification, chromatin remodeling, and non-coding RNA expression. Global DNA hypomethylation, promoter-specific hypermethylation of tumor suppressor and DNA repair genes, altered histone acetylation or methylation, and dysregulated microRNAs were repeatedly linked with genomic instability, impaired DNA repair, apoptosis resistance, chronic inflammation, and proliferative signaling. Developmental exposures during embryonic, fetal, childhood, pubertal, and germline-sensitive periods may produce durable epigenetic programming that increases later-life cancer susceptibility. **Conclusion:** Environmental epimutagens provide a biologically plausible framework for understanding pollution-associated carcinogenesis through mechanisms that complement classical genotoxic pathways. Incorporating epigenetic biomarkers, developmental exposure prevention, and non-genotoxic endpoints into environmental health policy may strengthen cancer prevention strategies. **Keywords:** Environmental epimutagens; Cancer; Epigenetics; DNA methylation; Histone modification; Non-coding RNA; Environmental pollution; Carcinogenesis.

INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide, and its rising incidence has intensified interest in preventable environmental determinants of malignant disease. Classical models of carcinogenesis have emphasized irreversible genetic mutations caused by endogenous replication errors or exogenous genotoxic agents; however, this model alone does not fully explain the long latency, tissue specificity, developmental sensitivity, and persistent biological effects observed after chronic environmental exposures. Increasing evidence indicates that carcinogenesis is also shaped by epigenetic dysregulation, a set of heritable but potentially reversible molecular changes that regulate gene expression without altering the underlying DNA sequence (1,2).

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Epigenetic regulation is essential for normal development, cellular differentiation, genomic stability, and tissue homeostasis. Core epigenetic mechanisms include DNA methylation, histone post-translational modifications, chromatin remodeling, and non-coding RNA-mediated gene regulation. These mechanisms function as a dynamic interface between environmental exposures and transcriptional control, allowing external chemical, physical, and nutritional signals to influence cellular phenotype over time. Because the epigenome is responsive to environmental stimuli, pollutants can induce persistent molecular changes that resemble early cancer-associated alterations, including global DNA hypomethylation, promoter-specific hypermethylation of tumor suppressor genes, altered histone marks, and dysregulated microRNA expression (3,4).

Environmental pollution has become one of the most pervasive and preventable contributors to human disease, particularly in rapidly industrializing and urbanizing regions. Airborne particulate matter, heavy metals, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, pesticides, and persistent industrial contaminants expose populations to complex mixtures across the life course. Many of these exposures occur at low doses over prolonged periods, making their biological consequences difficult to assess using toxicological models focused only on acute cytotoxicity or direct DNA damage. Epidemiological and experimental studies increasingly suggest that pollutants with weak or variable mutagenic activity may still contribute to carcinogenesis by disrupting epigenetic regulation, inflammatory signaling, oxidative stress responses, DNA repair, apoptosis, and cell-cycle control (5,6).

The concept of environmental epimutagens has emerged to describe agents capable of inducing stable epigenetic modifications that alter disease susceptibility without directly changing DNA sequence. Unlike classical mutagens, epimutagens may act through changes in DNA methyltransferase activity, histone-modifying enzymes, chromatin accessibility, or non-coding RNA networks. These alterations can silence tumor suppressor pathways, activate oncogenic or pro-inflammatory programs, impair genomic maintenance systems, and create a permissive cellular environment for malignant transformation. This framework is especially important for understanding pollution-associated cancers because environmentally induced epigenetic alterations may persist after exposure cessation and may interact with somatic mutations during tumor initiation and progression (7,8).

Among the best-characterized pollutant-related epigenetic effects are changes in DNA methylation. Exposure to traffic-related air pollution and fine particulate matter has been associated with altered methylation of repetitive elements and genes involved in inflammation, oxidative stress, and genomic stability. Heavy metals such as arsenic, cadmium, nickel, and chromium have also been implicated in aberrant methylation of tumor suppressor genes and disruption of DNA repair pathways. Polycyclic aromatic hydrocarbons, while traditionally recognized for DNA adduct formation, may additionally induce methylation and chromatin changes that influence immune regulation and carcinogenic susceptibility. Endocrine-disrupting chemicals such as bisphenol A and phthalates can modify developmental epigenetic programming, particularly in hormone-responsive tissues, thereby linking early-life exposure to later disease vulnerability (9–13).

Histone modifications and non-coding RNA dysregulation provide additional mechanistic pathways through which environmental contaminants may influence cancer risk. Pollutants can disrupt the balance between histone acetyltransferases, histone deacetylases, methyltransferases, and demethylases, producing chromatin states that favor inappropriate gene activation or repression. Similarly, altered microRNA expression after exposure to particulate matter, diesel exhaust, pesticides, or industrial chemicals may affect oncogenes, tumor suppressors, apoptotic pathways, and inflammatory mediators. These mechanisms are unlikely to operate in isolation; rather, DNA methylation, histone remodeling, and microRNA networks interact with oxidative stress, endocrine disruption, immune activation, and genomic instability to shape cancer-related phenotypes (14–16).

A further challenge is that susceptibility to epigenetic disruption varies across the life course. During embryogenesis, fetal development, early childhood, and puberty, the epigenome undergoes extensive

remodeling to establish tissue-specific gene expression programs. Environmental exposures during these windows may therefore produce durable biological effects that are not immediately apparent but become relevant later in life. Experimental studies also suggest that some environmentally induced epigenetic marks may persist across generations, although the extent and clinical relevance of transgenerational epigenetic inheritance in humans remain uncertain. This uncertainty highlights the need to distinguish established evidence from plausible mechanistic inference when evaluating pollution-related cancer risk (17,18).

Despite growing interest in environmental epimutagenesis, the evidence remains dispersed across epidemiology, toxicology, molecular oncology, developmental biology, and environmental health sciences. Existing studies vary widely in exposure assessment, biological sample type, epigenetic endpoint, cancer outcome, and strength of causal inference. As a result, there is a need for an integrative narrative synthesis that clarifies how major environmental pollutants converge on shared epigenetic mechanisms, where evidence is strongest, where findings remain preliminary, and how these mechanisms may inform prevention, biomarker discovery, and environmental regulation. This narrative review therefore aims to synthesize current evidence on the molecular epigenetic mechanisms by which environmental epimutagens link pollution exposure to cancer development, with specific emphasis on DNA methylation, histone modifications, non-coding RNA dysregulation, developmental windows of susceptibility, and translational implications for cancer prevention and public health policy.

MATERIALS AND METHODS

This narrative review was designed to synthesize current evidence on environmental epimutagens and their molecular contribution to pollution-associated carcinogenesis. A narrative approach was selected because the topic spans diverse pollutant classes, experimental systems, epidemiological designs, epigenetic mechanisms, and cancer-related biological pathways, making conceptual and mechanistic integration more appropriate than quantitative pooling. The review was structured to examine how environmental contaminants influence DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation, and how these alterations may contribute to tumor initiation, progression, developmental susceptibility, and long-term cancer risk.

A literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar to identify peer-reviewed studies relevant to environmental pollutants, epigenetic regulation, and carcinogenesis. The main search period covered studies published from 2014 to 2024, while older landmark studies were included when they provided foundational mechanistic or historical evidence directly relevant to environmental epimutagenesis. Search terms were applied alone and in combination using Boolean operators and included “environmental epimutagens,” “environmental pollution,” “cancer,” “carcinogenesis,” “epigenetics,” “DNA methylation,” “histone modification,” “chromatin remodeling,” “microRNA,” “non-coding RNA,” “particulate matter,” “PM2.5,” “heavy metals,” “arsenic,” “cadmium,” “lead,” “nickel,” “chromium,” “polycyclic aromatic hydrocarbons,” “PAHs,” “benzo[a]pyrene,” “bisphenol A,” “phthalates,” “endocrine-disrupting chemicals,” “pesticides,” “developmental exposure,” and “transgenerational epigenetic inheritance.”

Studies were considered eligible when they addressed environmental exposure to pollutants or toxicants and reported epigenetic alterations relevant to cancer biology, including DNA methylation changes, histone modification patterns, altered chromatin regulation, or dysregulation of microRNAs and other non-coding RNAs. Eligible evidence included human epidemiological studies, occupational or environmental exposure studies, birth cohort studies, experimental animal studies, in vitro mechanistic studies, and relevant reviews that contributed to conceptual interpretation. Priority was given to studies that linked pollutant exposure with cancer-related pathways such as tumor suppressor gene silencing, oncogene activation, impaired DNA repair, oxidative stress, inflammation, apoptosis evasion, proliferative signaling, genomic instability, or developmental reprogramming.

Studies were excluded when they did not address environmental pollutants, did not include an epigenetic endpoint, focused exclusively on non-cancer outcomes without mechanistic relevance to carcinogenesis, lacked sufficient molecular detail, or were not available as full-text peer-reviewed articles. Duplicate records, opinion pieces without evidentiary synthesis, and articles with limited relevance to the review objective were also excluded. Because this was a narrative review, no formal meta-analysis, pooled effect estimation, or statistical heterogeneity assessment was performed.

The selected literature was organized using a thematic synthesis framework. Evidence was first grouped by major pollutant class, including particulate matter, heavy metals, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, pesticides, and industrial contaminants. Within each pollutant class, findings were further categorized according to the principal epigenetic mechanism involved: DNA methylation, histone modification, chromatin remodeling, or non-coding RNA dysregulation. The synthesis then examined how these mechanisms intersect with recognized cancer-related processes, including loss of cell-cycle control, suppression of DNA repair, resistance to apoptosis, chronic inflammation, altered immune regulation, angiogenesis, cancer stemness, and tumor progression.

Evidence from human studies was interpreted separately from animal and in vitro findings to distinguish direct population-level associations from experimental mechanistic evidence. Particular attention was given to developmental windows of susceptibility, including embryonic, fetal, childhood, and pubertal exposure periods, because epigenetic programming during these stages may influence long-term disease vulnerability. Evidence concerning transgenerational epigenetic inheritance was interpreted cautiously and primarily as mechanistic or experimental support unless derived from human observational data.

No formal risk-of-bias tool was applied, consistent with the narrative-review design. However, the strength of evidence was considered according to study design, biological plausibility, consistency across studies, relevance of the exposure model, specificity of the epigenetic endpoint, and connection to cancer-related molecular pathways. Findings were synthesized descriptively to provide an integrated mechanistic account of how environmental epimutagens may contribute to pollution-associated cancer risk and to identify implications for biomarker development, prevention strategies, and environmental health policy.

RESULTS

The synthesized evidence indicates that environmental epimutagens act through multiple, overlapping epigenetic pathways rather than through a single molecular mechanism. Across pollutant classes, the most consistently described mechanisms include aberrant DNA methylation, disrupted histone modification patterns, chromatin remodeling abnormalities, and dysregulation of microRNAs and other non-coding RNAs. Particulate matter, heavy metals, PAHs, endocrine-disrupting chemicals, pesticides, and industrial contaminants differ in their sources and exposure contexts, but they converge biologically on pathways involved in oxidative stress, inflammation, DNA repair, apoptosis, cell-cycle regulation, and genomic stability.

Particulate matter and diesel exhaust particles are strongly represented in the environmental epigenetics literature. Their main epigenetic signatures include global DNA hypomethylation, altered methylation of repetitive elements, methylation changes in inflammatory genes, and dysregulation of microRNAs involved in apoptosis and proliferation. These changes are biologically relevant because global hypomethylation can destabilize the genome, while altered microRNA expression may reduce apoptotic control and support survival of damaged cells. Air-pollution-associated epigenetic changes therefore provide a plausible mechanistic bridge between chronic inhalational exposure, inflammatory airway injury, and cancer-related molecular remodelling.

Table 1. Major Environmental Epimutagens, Principal Sources, and Dominant Epigenetic Effects

Epimutagen Class	Representative Agents	Principal Environmental Sources	Dominant Epigenetic Effects	Cancer-Relevant Biological Consequences
Particulate matter	PM2.5, PM10, ultrafine particles, diesel exhaust particles	Vehicle emissions, industrial combustion, fossil fuel burning, urban air pollution	Global DNA hypomethylation, altered methylation of repetitive elements, dysregulated microRNA expression, histone acetylation changes	Genomic instability, oxidative stress activation, chronic inflammation, impaired apoptosis, increased proliferative signaling
Heavy metals	Arsenic, cadmium, lead, nickel, chromium	Contaminated water, mining, smelting, industrial discharge, cigarette smoke, occupational exposure	Tumor suppressor gene hypermethylation, DNMT dysregulation, altered histone methylation, DNA repair gene silencing	Loss of cell-cycle control, impaired DNA repair, genomic instability, malignant transformation
Polycyclic aromatic hydrocarbons	Benzo[a]pyrene and related PAHs	Vehicle exhaust, tobacco smoke, coal combustion, grilled or charred foods, industrial emissions	DNA methylation changes, histone acetylation disruption, chromatin remodeling abnormalities	Immune dysregulation, tumor suppressor silencing, persistent transcriptional reprogramming
Endocrine-disrupting chemicals	Bisphenol A, phthalates, organochlorine compounds	Plastics, food packaging, consumer products, pesticides, industrial residues	Developmental DNA methylation changes, altered histone marks, hormone-responsive epigenetic reprogramming	Increased susceptibility of hormone-sensitive tissues, altered developmental programming, later-life cancer vulnerability
Pesticides and herbicides	Organophosphates, organochlorines, glyphosate-related compounds	Agricultural runoff, occupational exposure, food residues, environmental persistence	Altered DNA methylation, microRNA dysregulation, epigenetic effects on apoptosis and cell-cycle pathways	Enhanced proliferation, apoptosis evasion, inflammatory activation
Industrial chemicals	Dioxins, PCBs, volatile organic compounds	Manufacturing, waste incineration, chemical spills, contaminated soil and water	Persistent chromatin and methylation changes, endocrine and immune-related epigenetic disruption	Long-term transcriptional dysregulation, immune modulation, tumor-promoting microenvironment

Table 2. Epigenetic Mechanisms Linking Environmental Pollutants to Cancer Hallmarks

Epigenetic Mechanism	Pollutant Examples	Molecular Event	Affected Genes or Pathways	Cancer Hallmark Influenced
DNA methylation	Arsenic, cadmium, PM2.5, PAHs	Global DNA hypomethylation	Repetitive elements, intergenic regions	Genomic instability
DNA methylation	Arsenic, cadmium, PAHs	Promoter hypermethylation	p16, RASSF1A, BRCA1, MLH1, MGMT	Loss of growth control, impaired DNA repair
Histone acetylation	PM2.5, diesel exhaust particles, PAHs	HAT/HDAC imbalance	Tumor suppressor and inflammatory genes	Sustained proliferation, chronic inflammation
Histone methylation	Nickel, chromium, arsenic	Increased repressive marks such as H3K9me2, H3K9me3, and H3K27me3	Tumor suppressor loci, DNA repair genes	Transcriptional silencing, genomic instability
Chromatin remodeling	PAHs, heavy metals, endocrine disruptors	Altered chromatin accessibility	Regulatory regions controlling differentiation, apoptosis, and proliferation	Abnormal cell fate, apoptosis resistance
MicroRNA dysregulation	PM2.5, diesel exhaust, pesticides	Downregulation of tumor-suppressive microRNAs	miR-34a, miR-16 and related apoptotic regulators	Apoptosis evasion, proliferation
MicroRNA dysregulation	PAHs, pesticides, industrial pollutants	Upregulation of oncogenic microRNAs	Inflammatory, proliferative, and survival pathways	Tumor promotion and progression

Table 3. Pollutant-Specific Evidence Pattern and Mechanistic Strength

Pollutant Class	Main Evidence Base	Most Consistent Epigenetic Findings	Cancer-Relevant Interpretation	Overall Mechanistic Strength
Particulate matter and diesel exhaust	Human exposure studies, occupational studies, in vitro airway models	DNA hypomethylation, altered methylation of inflammatory genes, microRNA dysregulation	Strongly supports a mechanistic link between air pollution, inflammatory signaling, oxidative stress, and cancer-related epigenetic disruption	Moderate to strong
Arsenic	Human epidemiological studies, exposed-population studies, animal and cellular models	Promoter hypermethylation of tumor suppressor genes, DNMT dysregulation, persistent methylation abnormalities	Provides one of the clearest examples of pollutant-driven epigenetic carcinogenesis, especially for skin, bladder, lung, and liver cancer risk	Strong
Cadmium	Cellular transformation studies, occupational/environmental studies, animal models	Global hypomethylation, promoter hypermethylation, DNA repair gene silencing	Supports interaction between epigenetic dysregulation and genomic instability in metal-associated carcinogenesis	Moderate to strong
Nickel and chromium	In vitro mechanistic studies, occupational carcinogenesis evidence	Histone methylation changes, chromatin condensation, tumor suppressor gene repression	Strong mechanistic evidence for histone-mediated transcriptional silencing, especially in respiratory carcinogenesis models	Moderate
PAHs	Birth cohort studies, in vitro studies, exposure biomarker studies	DNA methylation changes, histone acetylation changes, immune-regulatory gene effects	Supports dual genotoxic and epigenetic mechanisms, with particular relevance to prenatal exposure and long-latency cancer susceptibility	Moderate
BPA and phthalates	Animal developmental models, endocrine-related cancer models, human exposure studies	Developmental methylation changes, hormone-responsive chromatin effects	Supports early-life epigenetic reprogramming in hormone-sensitive tissues, although direct human cancer-causality evidence remains less consistent	Moderate
Pesticides	Agricultural exposure studies, cancer-cell models, toxicological studies	Altered DNA methylation and microRNA expression	Suggests epigenetic effects on cell-cycle control, apoptosis, and inflammatory regulation, with variable evidence across chemical classes	Emerging to moderate

Table 4. Developmental Windows of Epigenetic Vulnerability to Environmental Epimutagens

Developmental Period	Dominant Epigenetic Events	Pollutant Sensitivity	Likely Biological Consequence	Long-Term Cancer-Relevant Implication
Embryonic period	Establishment and resetting of early epigenetic marks	Extreme	Genome-wide epigenetic disruption	Broad developmental susceptibility and altered disease risk programming
Fetal development	Tissue-specific epigenetic programming and organogenesis	Very high	Organ-specific epigenetic remodeling	Increased vulnerability of developing tissues to later malignant transformation

Developmental Period	Dominant Epigenetic Events	Pollutant Sensitivity	Likely Biological Consequence	Long-Term Cancer-Relevant Implication
Early childhood	Consolidation of epigenetic patterns and immune maturation	High	Persistent changes in immune, inflammatory, and growth pathways	Increased susceptibility to chronic inflammation and altered cellular regulation
Puberty	Hormonal-epigenetic interaction and maturation of reproductive tissues	Moderate to high	Hormone-responsive epigenetic remodeling	Potentially increased risk in breast, prostate, and other hormone-sensitive cancers
Germline development	Epigenetic resetting in reproductive cells	High in experimental models	Transmission of altered epigenetic marks	Possible intergenerational or transgenerational susceptibility, strongest evidence from animal studies

Table 5. Integrated Mechanistic Pathway From Environmental Exposure to Cancer Development

Stage	Exposure or Molecular Trigger	Epigenetic Response	Intermediate Cellular Effect	Cancer-Related Outcome
1	Chronic exposure to pollutants such as PM2.5, arsenic, cadmium, PAHs, BPA, pesticides, or industrial chemicals	Initial disruption of DNA methylation, histone marks, and non-coding RNA expression	Altered transcriptional regulation	Early molecular reprogramming
2	Oxidative stress, inflammation, endocrine disruption, and xenobiotic metabolism	DNMT, HAT, HDAC, methyltransferase, demethylase, and microRNA network disruption	Persistent gene expression changes	Stable pro-oncogenic cellular state
3	Promoter hypermethylation and repressive chromatin formation	Tumor suppressor and DNA repair gene silencing	Reduced cell-cycle control and impaired DNA repair	Genomic instability and mutation accumulation
4	Global hypomethylation and chromatin relaxation	Activation of repetitive elements and oncogenic regions	Increased transcriptional instability	Enhanced malignant potential
5	MicroRNA dysregulation	Loss of tumor-suppressive microRNAs and activation of oncogenic microRNA patterns	Apoptosis resistance, proliferation, immune modulation	Tumor initiation and progression
6	Exposure during developmental windows	Persistent or possibly heritable epigenetic reprogramming	Long-term tissue-specific vulnerability	Increased later-life cancer susceptibility

Heavy metals show some of the strongest mechanistic evidence for environmental epimutagenesis. Arsenic is particularly important because it has been repeatedly associated with aberrant DNA methylation, including promoter hypermethylation of tumor suppressor genes and altered DNA methyltransferase activity. These molecular changes are relevant to cancers of the skin, bladder, lung, and liver. Cadmium also demonstrates a consistent pattern of global DNA hypomethylation combined with promoter-specific hypermethylation, particularly affecting genes involved in cell-cycle control and DNA repair. Nickel and chromium appear especially important in relation to histone methylation and chromatin condensation, supporting a model in which metal exposure can silence protective genes without directly changing the nucleotide sequence.

PAHs represent a mixed mechanistic category because they are well recognized for DNA adduct formation but also demonstrate important epigenetic effects. Evidence from prenatal and environmental exposure studies suggests that PAHs can alter DNA methylation patterns in immune-regulatory and tumor-suppressive pathways. Experimental findings further indicate that benzo[a]pyrene and related compounds can modify histone acetylation and chromatin organization, producing persistent transcriptional reprogramming. This suggests that PAH-related carcinogenesis is not exclusively genotoxic but may involve coordinated genetic and epigenetic disruption.

Endocrine-disrupting chemicals, particularly bisphenol A and phthalates, show strongest relevance in developmental and hormone-responsive contexts. Their epigenetic effects include altered DNA methylation, histone modifications, and disruption of hormone-sensitive regulatory regions. The evidence is especially important for tissues such as breast, prostate, and reproductive organs, where hormonal signaling and epigenetic regulation are closely linked. In this category, animal and

experimental developmental models provide stronger mechanistic evidence than direct human cancer-outcome studies, so the cancer relevance is best interpreted as biologically plausible and exposure-dependent.

Pesticides and industrial chemicals contribute additional evidence for pollutant-induced epigenetic dysregulation. Agricultural exposures have been associated with altered DNA methylation in genes involved in cell-cycle regulation and apoptosis, while experimental models suggest that pesticide exposure may modify microRNA expression in ways that enhance proliferation and reduce programmed cell death. Industrial contaminants such as dioxins, PCBs, and volatile organic compounds may also induce persistent epigenetic disruption through endocrine, immune, and inflammatory pathways. The evidence across these agents is heterogeneous because chemical structures, exposure levels, biological targets, and study designs vary substantially.

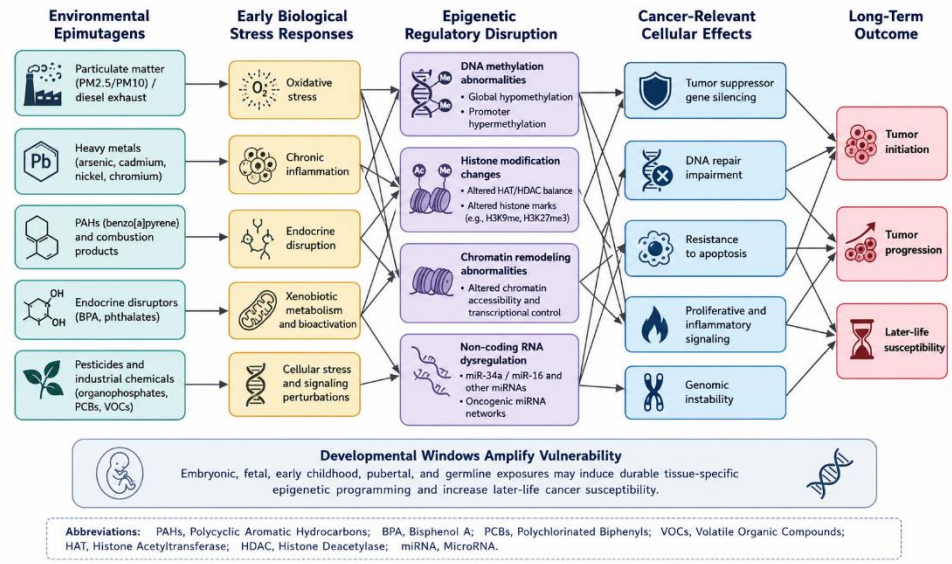

Figure 1. Integrated Pathway Linking Environmental Epimutagens to Cancer-Related Molecular Remodeling

The strongest cross-cutting pattern is that DNA methylation abnormalities appear across nearly all pollutant classes. Global hypomethylation is linked with genomic instability, while promoter-specific hypermethylation is linked with silencing of tumor suppressor and DNA repair genes such as p16, RASSF1A, BRCA1, MLH1, and MGMT. This dual methylation pattern is highly relevant to carcinogenesis because it simultaneously increases genomic vulnerability and suppresses protective cellular pathways. Histone modifications provide a second layer of regulation, especially through altered acetylation and methylation marks that influence chromatin accessibility. Together, methylation and histone changes create durable transcriptional states that may support malignant transformation.

Non-coding RNA dysregulation adds a further regulatory dimension. Pollutant-induced downregulation of tumor-suppressive microRNAs such as miR-34a and miR-16 may permit increased expression of anti-apoptotic and pro-proliferative factors. Conversely, upregulation of oncogenic microRNA networks can amplify inflammatory signaling, survival pathways, and cellular proliferation. Because microRNAs regulate multiple downstream targets simultaneously, their disruption may have broad effects on cancer-related cellular phenotypes. This makes microRNAs particularly useful as mechanistic links between environmental exposure and complex biological outcomes.

Developmental timing emerged as a major determinant of epigenetic vulnerability. Embryonic and fetal periods are characterized by extensive epigenetic remodeling, making them highly sensitive to pollutants that interfere with methylation, chromatin organization, or hormone-responsive gene regulation. Early childhood and puberty also represent sensitive periods because immune, endocrine, and tissue-specific transcriptional programs continue to mature. Exposures during these windows may

produce effects that persist long after the exposure has ended. Evidence for transgenerational inheritance is strongest in animal models, where germline epigenetic changes have been observed after toxicant exposure; in humans, the evidence remains more limited but supports the broader concept that early-life environments can leave durable epigenetic marks.

Figure 1 presents a conceptual synthesis of how major environmental epimutagens converge on cancer-related molecular remodeling. Particulate matter, heavy metals, PAHs, endocrine-disrupting chemicals, pesticides, and industrial contaminants initiate early biological stress responses, including oxidative stress, chronic inflammation, endocrine disruption, and xenobiotic metabolism. These upstream disturbances alter four major epigenetic regulatory systems: DNA methylation, histone modification, chromatin remodeling, and non-coding RNA expression. The resulting epigenetic disruption contributes to tumor suppressor gene silencing, impaired DNA repair, apoptosis resistance, proliferative and inflammatory signaling, and genomic instability, which collectively support cancer initiation, tumor progression, and later-life susceptibility. The lower developmental-window layer emphasizes that embryonic, fetal, childhood, pubertal, and germline exposures may amplify long-term vulnerability through durable tissue-specific epigenetic programming.

DISCUSSION

This narrative review synthesized evidence on the molecular mechanisms through which environmental epimutagens may contribute to pollution-associated carcinogenesis. The principal finding is that diverse environmental pollutants, including particulate matter, heavy metals, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, pesticides, and industrial contaminants, converge on a limited set of epigenetic regulatory systems that are central to cancer biology. Across the reviewed evidence, DNA methylation abnormalities, histone modification changes, chromatin remodeling disturbances, and non-coding RNA dysregulation emerged as recurring mechanisms through which environmental exposures may alter gene expression, impair DNA repair, disrupt apoptosis, promote inflammation, and create a cellular environment favorable to malignant transformation. This mechanistic convergence supports the concept that pollution-related cancer risk cannot be explained only by direct genotoxic injury, but also involves persistent epigenetic reprogramming that modifies cellular phenotype without changing the DNA sequence (16,18).

The strongest and most consistent evidence concerns DNA methylation changes induced by air pollution and heavy metals. Global DNA hypomethylation has been repeatedly associated with genomic instability, while promoter-specific hypermethylation can silence tumor suppressor and DNA repair genes, including pathways involved in cell-cycle regulation, apoptosis, and maintenance of genomic integrity. This dual methylation pattern is particularly important because it provides a biologically plausible route through which chronic low-dose exposures may increase cancer susceptibility over time. Arsenic and cadmium represent especially informative examples, as both have been linked to altered DNA methyltransferase activity, tumor suppressor gene methylation, and disruption of DNA repair processes. These findings are consistent with the broader cancer epigenetics literature, in which malignant cells commonly show simultaneous genome-wide hypomethylation and locus-specific hypermethylation of protective genes (19,20).

Histone modifications provide a second major mechanism connecting environmental exposures to cancer-related transcriptional dysregulation. Pollutants such as nickel, chromium, arsenic, PAHs, and particulate matter may influence histone acetylation, methylation, and chromatin accessibility by altering the activity of histone-modifying enzymes. These changes can shift chromatin toward either inappropriate activation of inflammatory and proliferative genes or repression of tumor suppressor and DNA repair genes. Unlike DNA sequence mutations, histone modifications are dynamic and context-dependent, but persistent exposure or repeated inflammatory stimulation may stabilize abnormal chromatin states (21). This suggests that environmental epimutagens may contribute not only to cancer

initiation but also to tumor progression by sustaining transcriptional programs that favor proliferation, immune evasion, and resistance to apoptosis.

Non-coding RNA dysregulation further expands the mechanistic landscape of environmental epimutagenesis. MicroRNAs are particularly relevant because each microRNA can regulate multiple gene targets, allowing pollutant exposure to influence broad cellular networks. Downregulation of tumor-suppressive microRNAs such as miR-34a and miR-16 may reduce apoptotic control and permit survival of damaged cells, while upregulation of oncogenic microRNA patterns may enhance inflammatory signaling, proliferation, and cellular survival. These findings support the view that pollutant-induced epigenetic disruption is network-based rather than gene-specific (22). MicroRNA signatures may also have translational value as minimally invasive biomarkers of exposure or early biological effect, although their clinical specificity remains limited because similar microRNA changes can occur in response to inflammation, smoking, aging, metabolic stress, and other non-pollution-related factors.

The reviewed evidence also indicates that environmental epimutagens interact closely with oxidative stress and inflammation. Many pollutants generate reactive oxygen species, activate inflammatory signaling, or disrupt mitochondrial and xenobiotic metabolism. These upstream stress responses can alter DNA methyltransferases, histone acetyltransferases, histone deacetylases, demethylases, and microRNA-processing pathways. In turn, epigenetic changes may reinforce inflammatory signaling and impair cellular repair mechanisms, creating a self-amplifying cycle. This interaction is highly relevant to cancer biology because chronic inflammation is a recognized tumor-promoting condition, and epigenetic remodeling can convert transient inflammatory responses into more durable transcriptional programs (23). Thus, environmental epimutagenesis should be understood as part of an integrated biological response involving oxidative injury, immune activation, endocrine disturbance, metabolic stress, and altered gene regulation.

Developmental timing emerged as a critical modifier of risk. The epigenome is most plastic during embryogenesis, fetal development, early childhood, puberty, and germline maturation, when tissue-specific gene expression programs are being established or remodeled. Exposure during these windows may produce epigenetic changes with long-lasting consequences, even when clinical disease appears decades later. This concept helps explain why early-life exposure to pollutants may influence adult cancer susceptibility and why hormone-responsive tissues may be especially vulnerable during pubertal or perinatal periods. Evidence for transgenerational epigenetic inheritance is compelling in several animal models, but the human evidence remains less definitive (24). Therefore, transgenerational effects should be interpreted as biologically plausible and experimentally supported, but not yet established as a major contributor to human cancer burden.

The synthesis also highlights an important conceptual advance over traditional carcinogenesis models. Classical environmental carcinogenesis has emphasized mutagenesis, DNA adduct formation, and irreversible genomic damage. The epimutagenesis framework does not replace this model; rather, it extends it. Several pollutants, including PAHs and certain heavy metals, may act through both genotoxic and epigenetic mechanisms. Epigenetic disruption can also indirectly increase mutation burden by silencing DNA repair pathways or destabilizing chromatin. In this way, genetic and epigenetic mechanisms may be mutually reinforcing rather than competing explanations (25). This integrated model is particularly useful for understanding chronic low-dose exposures, long latency periods, tissue-specific susceptibility, and persistent biological effects after exposure cessation.

The clinical and public health implications are substantial. Epigenetic changes may serve as early biomarkers of exposure, susceptibility, or biological effect before overt malignancy develops. DNA methylation signatures, histone modification profiles, and circulating microRNAs could help identify populations at increased risk from chronic environmental exposure. Such biomarkers may be especially useful in occupational settings, highly polluted urban areas, communities exposed to contaminated

water or soil, and vulnerable groups such as pregnant individuals and children (26). However, biomarker translation requires careful interpretation because epigenetic marks are tissue-specific, influenced by age and lifestyle, and may reflect both exposure and disease processes. Their strongest near-term role may be in population-level risk stratification and mechanistic research rather than immediate individual cancer prediction.

From a policy perspective, the findings support expanding environmental risk assessment beyond direct mutagenicity. Regulatory toxicology has historically prioritized DNA damage, cytotoxicity, and carcinogenicity endpoints, but epigenetic endpoints may detect biologically meaningful effects at lower exposure levels or earlier stages of disease development. Incorporating epigenotoxicity testing into environmental monitoring could improve assessment of pollutants whose carcinogenic potential is mediated partly through non-genotoxic mechanisms (27). This is especially important for complex mixtures such as urban air pollution, pesticide residues, industrial emissions, and persistent organic pollutants, where combined low-dose exposures may produce molecular effects that are difficult to capture using single-agent toxicity models.

Several limitations of this review should be acknowledged. As a narrative review, the synthesis was designed to integrate mechanistic and conceptual evidence rather than provide a reproducible systematic estimate of effect size. No formal risk-of-bias assessment, meta-analysis, or quantitative grading of certainty was performed. The included evidence also spans heterogeneous study designs, including human observational studies, occupational exposure studies, animal models, in vitro experiments, and prior reviews. These sources differ in exposure measurement, biological sample type, epigenetic endpoint, duration of follow-up, and cancer relevance. Consequently, the strength of inference varies across pollutant classes and mechanisms. Evidence is strongest where human exposure findings align with experimental mechanistic data, as seen with several heavy metals and air pollution-related methylation changes. Evidence is more preliminary where findings rely mainly on animal or cellular models, particularly for some endocrine-disrupting chemicals, pesticides, and transgenerational outcomes.

Another limitation is tissue specificity. Many human epigenetic studies use accessible samples such as blood, buccal cells, cord blood, or peripheral leukocytes, but cancer often develops in specific target tissues such as lung, bladder, liver, breast, prostate, or skin. Epigenetic changes measured in blood may reflect systemic exposure or immune response rather than direct molecular changes in the tissue of tumor origin. In addition, epigenetic marks are influenced by age, sex, smoking, diet, socioeconomic conditions, infection, medication use, and co-exposures. These factors complicate causal interpretation and may partly explain inconsistencies across studies. Future work should integrate tissue-specific epigenomics, exposure biomarkers, longitudinal sampling, and cancer outcome data to distinguish transient exposure responses from durable cancer-relevant epigenetic reprogramming.

Future research should prioritize prospective human cohort studies with repeated exposure assessment, longitudinal epigenomic profiling, and long-term cancer follow-up. Studies should integrate air, water, soil, dietary, occupational, and biological exposure measures to capture cumulative and mixture-based exposure more accurately. Multi-omics approaches combining DNA methylation, histone marks, chromatin accessibility, transcriptomics, microRNA profiling, metabolomics, and mutation analysis would clarify how epigenetic and genetic mechanisms interact over time. Developmental exposure studies should focus on pregnancy, early childhood, puberty, and germline-sensitive periods, while carefully distinguishing intergenerational from true transgenerational effects. Finally, translational research should evaluate whether pollutant-associated epigenetic signatures can be used for early detection, risk stratification, targeted prevention, or monitoring the impact of environmental interventions.

CONCLUSION

Environmental epimutagens represent an important mechanistic link between pollution exposure and cancer development by inducing persistent changes in gene regulation without altering the underlying DNA sequence. The evidence synthesized in this narrative review indicates that particulate matter, heavy metals, polycyclic aromatic hydrocarbons, endocrine-disrupting chemicals, pesticides, and industrial contaminants can disrupt DNA methylation, histone modifications, chromatin organization, and non-coding RNA expression, thereby influencing tumor suppressor gene silencing, impaired DNA repair, chronic inflammation, apoptosis resistance, proliferative signaling, and genomic instability. These epigenetic effects appear especially consequential during sensitive developmental windows, when environmental exposures may produce durable tissue-specific changes that influence later-life cancer susceptibility. Although the strength of evidence varies across pollutant classes and is strongest when human exposure findings align with experimental mechanistic data, the overall synthesis supports the view that epigenetic disruption complements classical genotoxic mechanisms in pollution-associated carcinogenesis. The most important implication is that cancer prevention strategies and environmental health policy should give greater attention to early-life exposure reduction, epigenetic biomarkers of risk, and regulatory approaches that account for non-genotoxic as well as genotoxic pathways of carcinogenesis.

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