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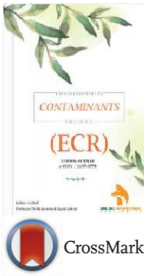

REVIEW ARTICLE

BIOCHEMICAL MECHANISMS OF CARCINOGENESIS: THE ROLE OF ENVIRONMENTAL POLLUTANTS IN CANCER DEVELOPMENT AND THERAPY

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ABSTRACT

Cancer remains one of the leading causes of death around the world. Its development is deeply rooted in a web of complex biochemical processes influenced by both inherited genetic traits and the environment we live in. Among the environmental influences, pollutants such as airborne toxins, heavy metals, pesticides, and industrial chemicals play a major role—not just in starting the disease, but also in making it worse over time. These harmful agents can trigger cancer by causing genetic mutations, changing the way genes function (without altering the DNA sequence itself), and setting off inflammatory reactions that create the perfect environment for tumors to grow. They don't just stop there. These pollutants interfere with critical processes inside our cells—like DNA repair, how cells grow and divide, how they die off naturally (a process called apoptosis), and even how tumors create their own blood supply (angiogenesis). The direct damage of DNA, forming harmful structures called DNA adducts or breaking the DNA strands entirely. This leads to mutations in important genes that either drive cancer (oncogenes) or normally suppress it (tumor suppressor genes). Environmental toxins can trigger mutations that make standard treatments less effective, either by altering the drug's target or by switching on the cell's defense mechanisms, like enhanced DNA repair or epigenetic adaptation. This makes treatment less successful and increases side effects, especially in healthy tissues already compromised by pollutants. There's also a growing interest in creating therapies that are more precisely targeted to the kinds of damage caused by environmental carcinogens. Promising strategies include therapies that can reverse epigenetic changes (epigenetic reprogramming), treatments based on antioxidants to counter oxidative stress, and small molecules that block harmful DNA repair or mutation pathways triggered by pollutants. Ultimately, beating environmentally driven cancer calls for an interdisciplinary approach—bringing together biochemical research, pharmacology, and environmental science. This broader, more connected view can help us better understand how pollutants contribute to cancer and guide us toward more personalized and effective treatments. The future of cancer care lies in therapies that are not only tailored to the patient's genetic makeup but also take into account their environmental exposures. By addressing the unique molecular impacts of environmental carcinogens, we can improve survival rates, enhance quality of life, and develop better prevention strategies.

KEYWORDS

Cancer, biochemical processes, genetic mutations, epigenetic changes, environmental pollutants, airborne toxins, heavy metals, pesticides, industrial chemicals, DNA repair

1. INTRODUCTION

Cancer is a heterogeneous and multifactorial disease characterized by uncontrolled cell growth, mutation accumulation, and evasion of normal cellular regulation. It arises from a complex interplay between genetic predispositions and environmental exposures, with environmental factors playing a particularly significant role in its initiation, progression, and therapeutic resistance (Brown et al., 2023). Understanding the biochemical mechanisms of carcinogenesis, especially those influenced by environmental pollutants, is crucial for developing targeted therapeutic strategies and effective prevention methods (Ullah et al., 2024). At the molecular level, cancer begins when genetic mutations occur in specific genes that regulate cell growth and death. These mutations can be spontaneous or induced by external agents, including environmental pollutants (Zhang et al., 2024). Carcinogenesis is a multi-step process, with pollutants acting as both initiators and promoters. Initial genetic mutations often activate proto-oncogenes or inactivate tumor suppressor genes, leading to abnormal cell behavior. These early molecular changes are then further driven by the continued presence of carcinogenic environmental agents, exacerbating genetic instability, promoting inflammation, and altering cellular metabolic pathways (Stojchevski et al., 2025).

Environmental pollutants, including airborne toxins, industrial chemicals, and contaminated water sources, significantly contribute to carcinogenesis through their direct effects on cellular DNA and cellular functions. Exposure to these pollutants can result in a variety of molecular changes, such as DNA adduct formation, mutations in key tumor

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suppressor genes, and activation of inflammatory pathways. Notably, carcinogens such as benzene, arsenic, and formaldehyde are involved in causing DNA strand breaks and inducing oxidative stress, both of which facilitate the accumulation of mutations and promote the growth of tumor cells. These pollutants can also alter the microenvironment, favoring chronic inflammation and immune system dysfunction, further exacerbating tumor progression. One of the most pervasive environmental carcinogens is radiation, which has been shown to cause direct DNA damage through ionization, leading to double-strand breaks and mutations that increase the risk of cancer (Turner et al., 2020). Air pollution, particularly fine particulate matter (PM2.5), benzene, and polycyclic aromatic hydrocarbons (PAHs), have long been recognized as a leading contributor to cancers such as lung, bladder, and skin cancers (Holme et al., 2023). Similarly, wastewater contamination, laden with heavy metals, pharmaceutical residues, and pesticides, poses a significant risk for the initiation of cancers, particularly those associated with gastrointestinal and kidney cancers. The biochemical mechanisms through which environmental pollutants contribute to cancer are varied. The most well-known mechanisms include the induction of genetic mutations, but environmental factors also influence the regulation of the cell cycle, apoptosis, and angiogenesis. Environmental toxins have been shown to dysregulate cellular signaling pathways involved in these processes, allowing cancer cells to proliferate uncontrollably, evade cell death, and develop the ability to spread and metastasize (Oladimeji et al., 2024). Furthermore, these pollutants induce chronic oxidative stress and inflammation, which are critical drivers of tumorigenesis. The molecular impact of pollutants extends to changes in cellular metabolism, such as the reprogramming of metabolic pathways to support uncontrolled cell growth, often referred to as the Warburg effect (Li et al., 2025).

In terms of therapy, cancers induced by environmental exposures often present unique challenges. Traditional chemotherapy and radiation therapies may be less effective for these cancers, as environmental carcinogens can contribute to drug resistance through the development of genetic mutations and alterations in DNA repair mechanisms (Talib et al., 2021). As a result, therapeutic strategies targeting specific mutations and biochemical pathways induced by environmental pollutants are becoming increasingly important. Targeted therapies, such as those targeting epidermal growth factor receptors (EGFR) or BRAF mutations, are demonstrating promising results in cancers associated with environmental exposure. Additionally, immunotherapy has emerged as a potential treatment, exploiting the immune system's ability to target tumor cells that have been modified by environmental factors (Lim et al., 2025). The scope of this review is to explore the biochemical mechanisms by which environmental pollutants contribute to carcinogenesis and to examine current and emerging therapeutic approaches aimed at combating these environment-induced cancers. The review will focus on the role of specific pollutants in DNA damage, inflammation, and metabolic reprogramming, and will highlight how these processes facilitate cancer progression. By investigating the molecular pathways activated by environmental exposures, we aim to provide a comprehensive overview of current research and identify potential areas for future therapeutic intervention. Furthermore, we will discuss the need for greater integration of environmental factors into cancer prevention and treatment strategies, emphasizing the importance of considering both genetic and environmental contributions to cancer risk.

2. Biochemical Mechanisms Of Carcinogenesis

Carcinogenesis is a complicated, step-by-step process in which healthy cells gradually develop characteristics typical of cancer, eventually becoming malignant. This change happens due to a mix of genetic mutations, changes in gene expression, and imbalances in cellular pathways that give the cells an edge in growth and survival(Feitelson et al., 2015). The first stage of carcinogenesis, known as initiation, starts when genetic mutations or epigenetic changes interfere with normal cellular processes. These changes may be triggered by external carcinogens like tobacco smoke, UV radiation, or specific chemicals, as well as internal sources such as reactive oxygen species (ROS) produced during routine metabolic activities. These mutations commonly impact proto-oncogenes and tumor suppressor genes, promoting unchecked cell growth and the ability to avoid programmed cell death (apoptosis)(Tanaka et al., 2013). Epigenetic modifications, like DNA methylation and changes to histone proteins, can turn off tumor suppressor genes or switch on oncogenes without changing the DNA itself, which helps cancer develop. After the initiation phase, the promotion phase involves the growth and multiplication of the affected cells. During this stage, more mutations build up, and the tumor's environment can encourage growth and help the cells avoid the immune system. Ongoing inflammation, driven by reactive oxygen species (ROS) and inflammatory cytokines, plays a big part by making the surroundings favorable for tumor development and spread. Also, when certain cell signaling pathways, such as those involving cyclin D1 and c-Jun, become unbalanced, they can speed up cell division and survival, making it easier for tumors to become malignant (Kanwal and Gupta, 2012).

The progression phase is marked by the acquisition of invasive and metastatic capabilities, enabling cancer cells to spread to distant organs. This stage involves further genetic and epigenetic alterations that enhance cell motility, angiogenesis, and immune evasion. Notably, the tumor suppressor protein p53, often referred to as the "guardian of the genome," plays a crucial role in maintaining genomic stability and preventing tumor progression. Mutations in p53 can lead to loss of function, allowing cells to accumulate additional genetic alterations that promote malignancy (Castaneda et al., 2022). Emerging research highlights the role of metabolic reprogramming in carcinogenesis. Oncometabolites, such as D-2-hydroxyglutarate, succinate, and fumarate, can accumulate due to mutations in metabolic enzymes like isocitrate dehydrogenase (IDH). These metabolites inhibit α-ketoglutarate–dependent dioxygenases, leading to epigenetic changes that affect gene expression and contribute to tumorigenesis. This concept, known as "oncometabolism," underscores the interplay between metabolism and gene regulation in cancer development. Understanding the biochemical mechanisms underlying carcinogenesis is essential for developing targeted therapies and preventive strategies (Yang and Chao, 2022). Continued research into the genetic, epigenetic, and metabolic alterations that drive cancer will provide deeper insights into tumor biology and inform the design of more effective interventions (Figure 1).

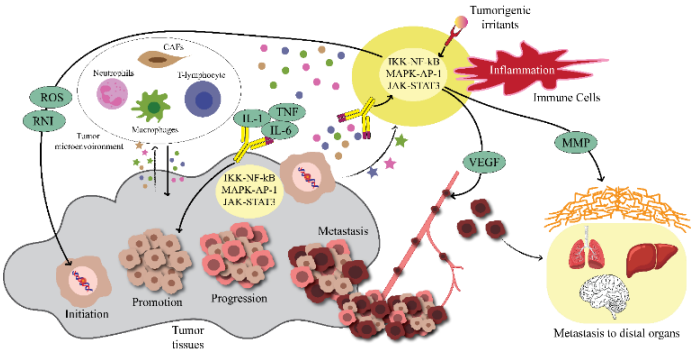

Figure 1: Inflammatory signaling pathways involved in cancer metastasis (Present Study)

Figure-1 illustrates the role of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) in the initiation, promotion, and progression of cancer. The activation of inflammatory cytokines such as IL-1, TNF, and IL-6 triggers key signaling pathways, including IKK-NF-kB, MAPK-AP-1, and JAK-STAT3, which drive inflammation and metastasis. The figure highlights the involvement of VEGF and MMP in promoting tumor vascularization and tissue remodeling, contributing to cancer spread to distant organs, such as the liver, lungs, and brain (Yang and Cao, 2022).

Environmental toxins play a pivotal role in the initiation and progression of cancer by inducing genetic mutations in proto-oncogenes and tumor suppressor genes. These mutations can lead to the activation of oncogenes and the inactivation of tumor suppressor genes, disrupting normal cellular functions and promoting uncontrolled cell proliferation. Exposure to environmental toxins such as benzene and asbestos has been linked to specific genetic alterations. Benzene, a known human carcinogen, is metabolized in the body to reactive intermediates that can form DNA adducts, leading to mutations (Singh et al., 2025)). These mutations often occur in genes involved in hematopoiesis, contributing to the development of hematologic malignancies like leukemia. Asbestos fibers, when inhaled, can cause chronic inflammation and direct DNA damage, leading to mutations in tumor suppressor genes like p53, which are critical for maintaining genomic stability. The accumulation of such mutations can result in the transformation of normal cells into cancerous ones. Proto-oncogenes are normal genes that, when mutated or abnormally expressed, become oncogenes capable of driving cancer development (Kay et al., 2019). Environmental carcinogens can activate proto-oncogenes through various mechanisms; A single nucleotide change can lead to a constitutively active protein that promotes cell proliferation. Increased copies of a proto-oncogene can lead to overexpression of its protein product, driving uncontrolled cell division. Rearrangements can place proto-oncogenes under the control of highly active promoters, leading to overexpression (Singh et al., 2025).

For instance, exposure to tobacco smoke, which contains carcinogens like benzo[a]pyrene, can induce mutations in the KRAS gene, a proto-oncogene. Mutations in KRAS lead to a constitutively active protein that drives cell proliferation, contributing to the development of lung cancer (Glauert et al., 2017).

Tumor suppressor genes are critical for regulating cell growth and ensuring the fidelity of cell division. Inactivation of these genes can remove critical control points, allowing cells to proliferate uncontrollably. Environmental carcinogens can inactivate tumor suppressor genes through several mechanisms; Alterations in the DNA sequence can disrupt the function of tumor suppressor proteins. Loss of entire genes can eliminate their tumor-suppressing activities. Changes such as DNA methylation can silence gene expression without altering the DNA sequence (Velez and Howard, 2015).

A well-known example is the p53 gene, often referred to as the "guardian of the genome." Environmental factors like UV radiation and tobacco smoke can induce mutations in p53, leading to its inactivation. This loss of function impairs the cell's ability to undergo apoptosis in response to DNA damage, facilitating the accumulation of additional mutations and the progression to cancer. Environmental toxins contribute to cancer development by inducing genetic mutations that activate oncogenes and inactivate tumor suppressor genes. Understanding these mechanisms is crucial for developing targeted therapies and preventive strategies to mitigate the impact of environmental carcinogens on public health (Min and Lee, 2022).

3. Pharmaceutical Interventions And Targeted Therapies

Cancers caused by or affected by environmental carcinogens can reduce chemotherapy's efficacy, despite its widespread usage in cancer treatment. Cancer cells' behaviour can be changed and chemoresistance can develop as a result of DNA mutations and changes in gene expression caused by environmental contaminants as asbestos, benzene, tobacco smoke, and polycyclic aromatic hydrocarbons (PAHs) (Min and Lee, 2022).

Specifically, tumours that develop as a result of prolonged contact with these contaminants typically have a greater mutational load, which makes treatment response more difficult and increases the risk of chemotherapy resistance. Furthermore, these environmental carcinogens have the ability to change DNA repair processes through epigenetic modifications and disrupt pathways that cells use to respond to stress, which in turn makes standard chemotherapy treatments less effective.Furthermore, environmental exposures exacerbate chemotherapeutic reactions by adding to oxidative stress, which in turn leads to the buildup of cancer-promoting genetic alterations (Alhmoud et al., 2020). To combat the molecular alterations brought about by environmental carcinogens, targeted medicines have been created. These therapies centre on blocking certain mutations that fuel cancer. Environmental exposures frequently impact genes like EGFR and BRAF, and these medicines target these alterations. Lung cancer, especially non-small-cell lung cancer (NSCLC), which is often associated with exposure to radon and tobacco smoking, can be treated with EGFR inhibitors like Erlotinib or Gefitinib. Vemurafenib and other BRAF inhibitors are also used to treat melanoma, particularly when the disease was caused by UV radiation (Min and Lee, 2022).

A key component of these targeted treatments is their ability to inhibit the growth and survival of cancer cells by inhibiting certain proteins that are essential in cancer cell signalling. Targeted treatments are essential for the successful treatment of malignancies induced by environmental factors including cigarette smoke and UV radiation, which are known to trigger mutations in the EGFR and BRAF genes. Immunotherapy, particularly CAR-T treatments and immune checkpoint inhibitors, has demonstrated encouraging results in the treatment of tumours associated with environmental exposures (Shuel, 2022). The large mutational loads seen in tumours caused by environmental carcinogens may render them more vulnerable to assaults by the immune system. To enable T-cells to assault cancer cells, immune checkpoint drugs like Pembrolizumab disrupt the PD-1/PD-L1 relationship. The effectiveness of immunotherapy can be enhanced when environmental toxins such as benzene, asbestos, and PAHs cause DNA damage and chronic inflammation. These factors can lead to immune suppression, but they can also make tumours more immunogenic(Ahmed et al., 2022).

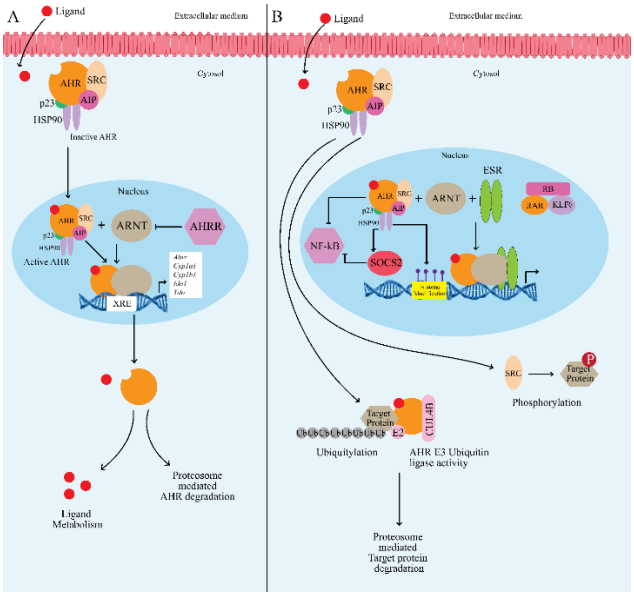

Figure 2: Illustration of the signaling pathways and degradation processes involving the Aryl Hydrocarbon Receptor (AHR) (Present Study)

From the Figure-2, activation of AHR involves its binding to ligand molecules and interaction with core proteins like HSP90, p23, SRC, and AIP, which leads to the translocation of the AHR-ARNT complex into the nucleus. This complex binds to XRE regions on the DNA to regulate gene expressions involved in metabolism. The pathway also includes proteasomal degradation of AHR through specific interactions. On the right, the figure shows the involvement of AHR in protein degradation and modulation through phosphorylation, ubiquitylation, and the activation of other transcription factors like NF-kB, ESR, and SOCS2, which further modify the target proteins involved in gene regulation.

Environmental contaminants such as dioxins and PAHs stimulate the aryl hydrocarbon receptor (AhR) signalling pathway, which is involved in the complicated course of cancer. This pathway has a role in controlling the migration, invasion, and metastasis of tumour cells. Although the precise function of this route in many cancer types is still up for discussion, environmental substances that activate AhR can either improve immune surveillance or accelerate tumour growth.Because endocrine-disrupting chemicals (EDCs) in the environment might affect the development of malignancies including breast and prostate, hormonal medicines play an essential role in their treatment (Sweeney et al., 2022). Commonly found in plastics, insecticides, and industrial chemicals are compounds like bisphenol A (BPA) and polychlorinated biphenyls (PCBs). These chemicals mimic oestrogen and disturb the body's hormonal balance, raising the risk of hormone-sensitive malignancies. Research has demonstrated that exposure to bisphenol A (BPA) in breast cancer can modify gene expression and enhance tumour development through interactions with oestrogen receptors.Breast tumours that test positive for oestrogen

receptors are treated with drugs that inhibit these receptors, such as Tamoxifen. Cancer cell proliferation is stifled by these treatments because oestrogen is unable to attach to its receptor. Just as environmental contaminants can change testosterone levels, Flutamide prevents their impact in prostate cancer (Ullah et al., 2024). When cancer patients' hormone levels have dropped below normal due to environmental factors, these hormonal medicines become life-saving tools (Figure 2).

4. The Impact Of Environmental Pollutants On Carcinogenesis

Cancer is a complex disease characterized by the unregulated growth and proliferation of cells. Although genetic mutations are known to be a major factor, environmental influences and chemicals are increasingly acknowledged as important contributors to the onset and progression of cancer(Ullah et al., 2024).

Pollution is a widely acknowledged risk factor for cancer, with a particular emphasis on lung cancer. The risk of developing respiratory and other malignancies is increased by exposure to particulate matter (PM 2.5 and PM 10), nitrogen oxides, and volatile organic compounds, as evidenced by previous research. Furthermore, urban areas with substantial traffic congestion frequently experience elevated pollution levels, which increases the health hazards of their residents. Another substantial concern is water pollution, as bladder and skin malignancies have been associated with contaminants such as arsenic, lead, and nitrates. Skin lesions, internal cancers, and developmental issues have been linked to chronic exposure to arsenic in potable water(Shehata et al., 2023). The accumulation of DNA damage and mutations can result from prolonged exposure to outdoor air pollution, particularly fine particulate matter (PM 2.5) and nitrogen dioxide (NO2). For example, research has demonstrated that a 6% increase in the risk of developing overall urological cancer is associated with a 5 µg/m3 increase in PM 2.5 exposure, while a 3% increase in risk is associated with a 10 µg/m3 increase in NO2. DNA damage can also be induced by indoor pollutants, such as second-hand smoke and culinary fumes. Biological evidence of these substances in the lungs was discovered in a study that examined pleural fluid for prevalent air pollutants, suggesting their potential involvement in the development of lung cancer(Gavito-Covarrubias et al., 2024). Environmental contaminants can produce epigenetic alterations, such as DNA methylation, histone modifications, and the control of non-coding RNAs, which influence gene expression without altering the DNA sequence. These alterations can have a role in the onset and progression of lung cancer. Pollutants can also promote chronic inflammation, a proven cancer

risk factor. This inflammation can lead to the formation of reactive oxygen species (ROS), leading in oxidative stress and further DNA damage(Miguel et al., 2020). Particulate matter and other pollutants can cause reactive oxygen species (ROS), resulting in oxidative stress and cellular damage, which may trigger and accelerate the development of cancer (Figure 3). Polycyclic aromatic hydrocarbons (PAHs), prevalent in automobile exhaust and industrial pollutants, are highly potent carcinogens. They can connect to DNA and produce adducts, leading to mutations and the start of cancer. Additionally, arsenic and other heavy metals found in drinking water and air are also carcinogenic, with arsenic particularly connected with skin, lung, and bladder cancers(Santibáñez-Andrade et al., 2023).

According to data from the World Health Organization (WHO), in 2020, there were 19.3 million new cancer diagnoses, and the number of cancer-related fatalities rose to 10 million. Presently, it is estimated that one in five people worldwide will be diagnosed with cancer at some point in their life. The types and levels of carcinogens found in drinking water can differ depending on their origin, which may include contamination at the water source, the processes used in water treatment, or issues arising during the distribution of water to consumers (Lin et al., 2022).

From the point of view of water sources, cancer is strongly linked to pollutants like arsenic, nitrate, and chromium. Drinking water that contains arsenic has been linked to a higher risk of skin cancer, kidney cancer, and bladder cancer (Lin et al., 2022). A well-designed study conducted in northern Chile from 1994 to 1996 found a strong association between arsenic in drinking water and lung cancer, involving lung cancer patients and a control group matched by frequency at a local hospital. In addition, research has shown that smoking and exposure to arsenic through drinking water together increase the risk of developing lung cancer (Lin et al., 2022). Exposure to elevated levels of arsenic in drinking water has also been linked to the development of liver cancer. However, this association was not found to be significant at exposure levels below 0.64 mg/L (Lin et al., 2022).

Nitrates are widespread pollutants that have been closely connected to several types of cancer in humans, particularly colorectal cancer. Research from East Azerbaijan found a significant relationship between nitrate levels in drinking water and colorectal cancer in men, but not in women. The cancer risk from nitrates depends on how much is present, with the danger rising steeply when concentrations exceed 3.87 mg/L—much lower than the current safety limit of 50 mg/L for drinking water. This means that even nitrate levels considered safe under current guidelines may still raise the risk of developing colorectal cancer (Schullehner et al., 2018). Drinking water with elevated chromium levels poses a considerable carcinogenic risk due to the presence of hexavalent chromium. Studies on the consumption of hexavalent chromium in drinking water have shown its potential to induce respiratory cancer in humans (Schullehner et al., 2018) (Figure-3). From the point of view of the water treatment process, carcinogens could be added during the stage where chlorine is used. Because of this, drinking water has been linked to a number of cancers, such as cancers of the urinary system and the digestive system (Schullehner et al., 2018).

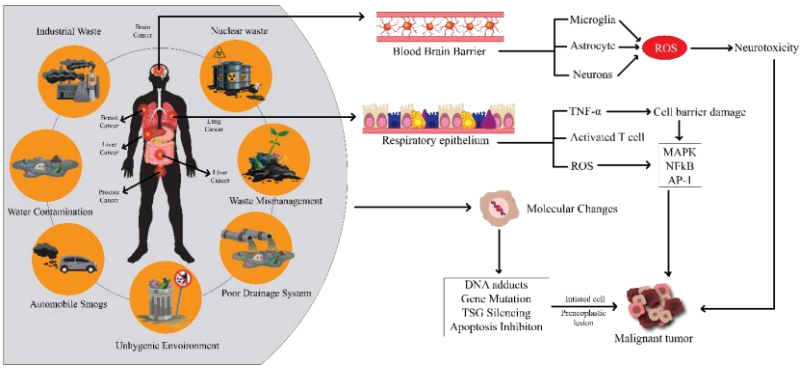

Figure 3: This diagram illustrates the major environmental pollutants that contribute to cancer development through their impact on various biochemical processes (Present Study).

Figure-3 highlights how exposure to industrial waste, nuclear waste, and water contamination can lead to the onset of several types of cancers, such as lung, liver, breast, and prostate cancer. Additionally, environmental factors like automobile smogs, waste mismanagement, and poor drainage systems exacerbate the risk of developing cancers, promoting pathways associated with oxidative stress and DNA damage, represented by the production of Reactive Oxygen Species (ROS). These environmental exposures cause cellular mutations, leading to genetic instability and triggering the development of malignancies. The diagram also shows how ROS interacts at the molecular level with cell structures, contributing to tumor progression.

The relationship between pollutants in drinking water and cancer is complicated. Studies have found that different contaminants in drinking water—like chlorinated by-products, nitrates, arsenic, and radionuclides—are linked to a higher risk of cancer in people. Important groundwater contaminants such as lead, uranium, fluoride, and nitrates are also seen as major possible cancer-causing agents. Additionally, other pollutants from sources like herbicides, pesticides, and fertilizers that add nitrates to water are also considered carcinogenic. For example, a case study from Hebei, China, showed that contamination from nitrogen compounds in well water was closely related to the use of nitrogen-based fertilizers in farming, and higher levels of three different nitrogen

compounds in the water were strongly tied to more deaths from esophageal cancer(Lin et al., 2022). A study looking at water quality changes in a watershed found that when water quality dropped by six grades, deaths from digestive cancers went up by 9.3%(Ebenstein, 2012). Heavy metals contaminate the environment and entire ecosystem—including the air, water, and soil—through both natural events and human activities. People come into contact with these metals in different ways, such as by breathing them in, eating or drinking contaminated food and water, or absorbing them through the skins (Rahman and Singh, 2019).

Metal carcinogen interactions with bio-systems prove quite intricate, thus preventing speculation that there exists a universal applicability of an equivalent mechanism of action for all metals. Arsenic (As), lead (Pb), mercury (Hg), cadmium (Cd), as well as chromium (Cr), prove toxic heavy metal pollutants of major environment with high capacities for posing hazards to ecosystems as well as human beings. Exposure to human beings can be realized through various exposure pathways with corresponding adverse effects that include a broad specter of toxic effects (Table 1). Behind a superficial glance, however, exists three general mechanisms common to a vast majority of metal compounds capable of instigating cancer: (1) disruption of cellular redox balance with corresponding DNA damage; (2) inhibition of an important DNA repair mechanism with corresponding genomic instability accompanied with crucial mutations buildup; as well as (3) induction of oncogenic pathways with corresponding inhibition of tumor suppressor gene functions with a resultant disruption of cell proliferation equilibrium vis-a-vis cell death equilibrium. Oxidative stress occupies a place in metal toxicity as well as its carcinogenicity explanation. According to dosage as well as time of free radical buildup, oxidative stress can instigate tumor formation with corresponding induction of mutagenesis, uncontrolled cell proliferation, as well as compromised repairing mechanism(Beyersmann and Hartwig, 2008). Low doses of cancer-initiating metal compounds were shown to inhibit DNA repair machinery primarily through forming toxic intermediates. Metal ions can alter gene expression, mitogenic signal pathway induction, as well as activating proto-oncogene expression of cells. Such gene expression modifications are often mediated by epigenetic pathways ignited by metal ions, which can lead to silencing of tumor suppressor gene activity. Consequently, they establish genomic instability as well as initiate uncontrollable cell proliferation(Parida and Patel, 2023).

Table 1: Permissible Limits and Health Impacts of Heavy Metals

Metal	Permissible Limits (ppm, WHO)	Portal of Entry	Associated Diseases	Reference
Lead	0.01	Enters the body via inhalation, ingestion, and dermal absorption, affecting the lungs, kidneys, liver, and soft tissues	Causes anemia, kidney dysfunction, elevated blood pressure, cerebrovascular events, neurotoxicity, and infertility	(Wani et al., 2015)
Chromium	0.05	Absorbed through the respiratory tract, gastrointestinal system, and skin	Responsible for allergic skin reactions, respiratory conditions like asthma, nasal tissue damage, anemia, and skin inflammation	(Chatterjee, 2015)
Cadmium	0.003	Taken up through ingestion and inhalation, impacting the gastrointestinal tract, liver, kidneys, and lungs	Linked to Itai-itai disease, formation of kidney stones, protein loss through urine, and reduction in bone density	(Bernard, 2008; Nishijo et al., 2017)
Arsenic	0.01	Penetrates via ingestion, inhalation, and skin contact, targeting the liver, kidneys, lungs, and skin	Leads to arsenicosis, dermatological damage, cardiovascular complications, metabolic disorders like diabetes, and neurological impairment	(Parida and Patel, 2023)
Mercury	0.001	Absorbed predominantly through inhalation and ingestion, affecting the lungs, kidneys, and brain	Associated with Minamata disease, cognitive decline, carcinogenic outcomes, headaches, alopecia, and chronic fatigue	(Parida and Patel, 2023)

Cell division and organismal development are intricately coordinated and tightly regulated processes. Disruption of the molecular mechanisms governing these processes may result in cancer, arising from events intrinsic and/or extrinsic to the cell. Cellular DNA can sustain damage from spontaneous hydrolysis, reactive oxygen species, abnormal cellular metabolism, or other perturbations capable of inducing DNA lesions. Furthermore, various environmental factors may cause DNA damage, modify cellular metabolism, or impair cellular interactions within their microenvironment (Carbone et al., 2020). Numerous human cancers are linked to exposure to genotoxic chemicals. There is often a prolonged latency period (spanning years) between the initial exposure to carcinogens, the onset of DNA damage and mutation fixation, and the eventual development of a tumor. The progression to a malignant phenotype necessitates repeated changes in gene expression (Table 2), which ultimately enable the expansion of tumor subpopulations that have lost growth-control mechanisms, thereby gaining a proliferative advantage over normal cells (Wang et al., 2025).

Table 2: Chemical Agents and Their Mechanisms of DNA Damage Leading to Tumor Suppressor and Oncogene Mutations

Chemical Agent	Type of DNA Damage	Target Site	Mutation in Tumor Suppressor / Oncogene	Citation
Aflatoxin B1 (AFB1)	Bulky DNA adducts	Guanine (forms AFB1–DNA adducts)	**TP53**: G→T transversion at codon 249 (exon 7)	(Dianov and Parsons, 2007; Yun et al., 2020)
Cisplatin	Cross-linking (intra- and inter-strand)	N7 or N2 of guanine	Linked to mutations/deletions in **TP53**, **BRCA1**, **RB1**	(Dianov and Parsons, 2007; Yun et al., 2020)
Malondialdehyde	DNA cross-links	Guanine bases	Contributes to mutagenic pressure on **tumor suppressor genes**	(Huang and Li, 2013; Wang et al., 2025)

Table 2 (Cont): Chemical Agents and Their Mechanisms of DNA Damage Leading to Tumor Suppressor and Oncogene Mutations

Chemical Agent	Type of DNA Damage	Target Site	Mutation in Tumor Suppressor / Oncogene	Citation
Acetaldehyde	DNA cross-links	Guanine bases	Can induce chromosomal aberrations affecting **tumor suppressor genes**	(Huang and Li, 2013; Wang et al., 2025)
Benzo[a]pyrene (B[a]P)	Strand breaks, oxidative damage	Phosphodiester backbone, base mispairing	Associated with mutations in **TP53**, **KRAS**	(Dianov and Parsons, 2007; Yun et al., 2020)
Hydroxyl radical (OH·) (generated via Fenton reaction or ROS)	Oxidative lesions, SSBs, DSBs	Guanine (C8), phosphodiester bonds	Mutations in **TP53**, oxidative stress-linked oncogene activation	(Achanta and Huang, 2004; Cadet and Davies, 2017; Dianov and Parsons, 2007; Dianov and Parsons, 2007; Yun et al., 2020)

5. The Influence Of Inflammation On Tumor Progression And Metastasis

As cancers advance, tumor cells get more aggressive, with a capability of metastasis, which can be severe as well as life-threatening. Characteristic of this progression is the epithelial-to-mesenchymal transition (EMT), where epithelial tumor cells convert into mesenchymal cells with a concomitant rise in mobility as well as an improved capability of migration(Derynck and Weinberg, 2019; Pastushenko et al., 2018). EMT not only occurs during wound repairing and tissue fibrosis following injury but is also involved in cancer progression as well as metastasis. Certain inflammatory mediators, such as TNF, IL-1β, IL-6, IL-11, and IL-8, were shown to be strong inducers of EMT. Tumor stroma remodeling plays a significant role in cancer cell migration and invasion, with inflammation as a core element. For example, tumor-associated macrophages (TAMs) stimulate metastasis of cancer cells by secreting matrix metalloproteinases (MMPs), which break down cell–cell adhesions as well as the extracellular matrix (Shang et al., 2019). Tumor cell migration and metastasis to specific distant organs is directed by tumor microenvironmental (TME) gradients of chemokines, which are detected by chemokine receptors as in leukocyte movement. Certain of the pro-inflammatory cytokines, such as TNF and IL-1β, which are commonly found in the TME, elicit the expression of chemokines such as CXCL1 (keratinocyte-derived chemokine), CXCL5, CXCL8 (IL-8), CCL2 (MCP-1), and CCL5 (RANTES). Metastatic cancer cells spread through both lymphatic as well as blood vessels(Hibino et al., 2021). Activated macrophages secrete proangiogenic and lymphangiogenic molecules, such as members of the VEGF family. Once entering the bloodstream as metastatic tumor cells, inflammatory mediators from immune cells help them survive and provide for their colonization of the target organ. Albrengues and colleagues showed that chronic experimental inflammation of lungs, induced with smoke from tobacco or exposure to lipopolysaccharide (LPS), with NET formation, activated dormant tumor cells, which were transformed into actively growing metastases in mice(Albrengues et al., 2018).

Environmental toxicants, for instance, persistent organic compounds as well as endocrine disruptors, accelerate progression of breast cancer through activation of an assortment of signal pathways, for instance, c-Src, ERK1/2, PI3K/AKT, as well as JNK. Such pathways stimulate cell migration, invasion, as well as tumor progression as well as induce metastasis. Certain chemicals, for instance, dioxins as well as polychlorinated biphenyls (PCBs), control motility-associated proteins, therefore enhancing cancer dissemination(Koual et al., 2020). Protein kinase C (PKC) is a family of structurally similar serine/threonine kinases that function as signal transmitters for a multitude of molecules, including hormones (like adrenaline and angiotensin), growth factors (e.g., insulin and epidermal growth factor), cytokines (e.g., Tumor Necrosis Factor α (TNF-α), IL-1β, and IL-6), and neurotransmitters (e.g., dopamine and endorphins). These kinases are crucial for controlling a variety of cell functions, some of which encompass survival, growth, differentiation, apoptosis, adhesion, as well as malignant conversion (Garg et al., 2014). Binding of its ligand to its receptor can activate phospholipase C leading to an increase in cytosolic contents of diacylglycerol (DAG) and Ca++, which are significant activators of PKC signaling (Sadeghi et al., 2021). PKC activation can stimulate multiple molecular pathways, for instance, Akt, signal transducer and activator of transcription 3 (STAT3), nuclear factor-κB (NF-κB), as well as apoptotic pathways, thus impacting on tumorigenesis as well as metastasis. Antitumor activity is demonstrated by PKC alpha, a specific PKC isoform, due to tumor-associated macrophages polarization induction within the tumor microenvironment. Conversely, protein levels of PKC alpha, beta, as well as epsilon are decreased in cancers like colon cancer. PKC theta shows tumor-suppressing activity due to induction of immunosuppression within the tumor microenvironment, primarily with reference to regulation of CTLA4-mediated function of regulatory T-cells. Nevertheless, natural PKC activators, phorbol esters, exhibit tumor-promotion activity, suggesting that PKC can function as an oncogene. Furthermore, PKC beta plays a significant role for VEGF signaling within the tumor microenvironment, with reference to promoting angiogenesis as well as tumor invasiveness in diverse cancers, including pancreatic cancer(Goenka et al., 2023).

Kinases play a crucial role in cancer development by enabling the transduction of signals that lead to uncontrolled cell proliferation and survival. Oncogenic kinases, such as tyrosine and serine/threonine kinases, are often mutated or activated in many cancers, initiating signaling cascades that disrupt the regulation of gene expression. These kinases activate critical pathways, including MAPK, PI3K, and Akt, which drive tumorigenesis by promoting cell cycle progression, preventing apoptosis, and activating transcription factors(Tsatsanis and Spandidos, 2000).

In addition to their role in tumor initiation, kinases are essential for the survival and proliferation of tumor cells and can function as downstream components of oncogenic kinase pathways. One such kinase is EGFR, a receptor tyrosine kinase, which has been shown to prevent autophagic cell death by maintaining intracellular glucose levels through its interaction with and stabilization of the sodium/glucose cotransporter 1 (SGLT1)(Weihua et al., 2008). Oncogenic mutations in EGFR account for approximately 45% of alterations in the tyrosine kinase domain, leading to the loss of regulatory domains that prevent dimerization. This loss promotes the hyper-proliferation of cancer cells by advancing the G1/S phase of the cell cycle. Aurora kinases (A-C), particularly Aurora A, are crucial for spindle pole organization and oncogenic activities, with amplification seen in 10-25% of ovarian cancers. Aurora A, initially known as BTAK, is overexpressed in breast cancer, where it inhibits p53-DNA binding and disrupts cell cycle checkpoints (Figure 4). Additionally, Aurora A activates NF-κB, enhancing cancer cell survival by providing resistance to apoptosis. Other kinases, such as MEK1, MEK2, mTOR, and S6 kinase, which are downstream components of the MAPK, PI3K-Akt, and EGFR pathways, also play significant roles in promoting tumor cell survival and metastasis(Bhullar et al., 2018).

From the Figure-4, It shows how cytokines and reactive oxygen species (ROS) activate the Ras-GTP pathway, which then triggers downstream signaling through Raf, MEK, and ERK, ultimately leading to the activation of transcription factors (TF) that regulate gene expression. Additionally, the figure depicts the role of PGE2, TXA, and COX2 in activating PI3K, which further regulates PDK1, AKT, and mTOR, contributing to cancer cell survival and growth. The negative regulation of pTEN is also highlighted, which enhances the signaling cascade and supports tumor progression.

Since 2001, over 10,000 patent applications for kinase inhibitors have been filed in the United States. Along with small-molecule kinase inhibitors, kinase-targeted antibodies have shown effectiveness in treating various cancers, such as cetuximab in colorectal and head and neck cancers, and trastuzumab in breast cancer(Fabbro et al., 2015).

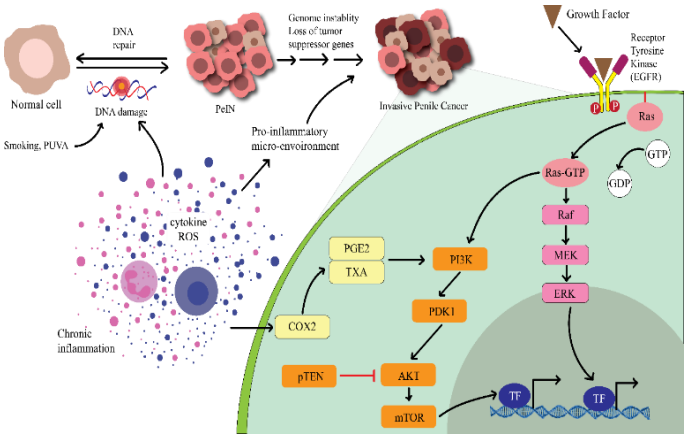

Figure 4: The figure illustrates the signaling pathway involved in the progression of invasive penile cancer, highlighting key molecular interactions (Present Study)

Trastuzumab and cetuximab bind to the extracellular domains of HER2 and EGFR, respectively. This stops their natural ligands from binding and stops the conformational changes that are needed for kinase activation and the signaling pathways that follow. The FDA has approved 35 drugs so far, 31 of which are for cancer treatment. These drugs are orally effective direct protein kinase inhibitors that target a small number of enzymes. But even with these promising developments, drug resistance, toxicity, and lower effectiveness are still major problems in both clinical and experimental oncology(Fabbro et al., 2015).

6. Challenges And Opportunities In Cancer Therapy

Cancer therapy often faces the significant challenge of drug resistance, which can be attributed to both genetic and environmental factors. When cancer cells are exposed to chemotherapy or targeted therapies, they undergo a variety of adaptive changes that allow them to survive and continue proliferating despite treatment. These adaptive mechanisms are often driven by mutations in specific genes related to drug metabolism, DNA repair, and cellular signaling pathways. Environmental factors play a crucial role in inducing these mutations, particularly in the presence of carcinogenic agents (Wang et al., 2025).

Carcinogens, such as those found in tobacco smoke, industrial chemicals, and environmental pollutants, contribute to the accumulation of mutations in cancer cells. These mutations may occur in genes that are directly involved in drug resistance. For example, mutations in the gene encoding for the drug-targeted protein can lead to a structural change that renders the drug ineffective. Furthermore, environmental toxins like benzene, formaldehyde, and arsenic can induce mutations that affect DNA repair pathways, such as those involving the tumor suppressor gene p53, which is pivotal in responding to DNA damage (Zhou, 2019).

In addition to direct mutagenic effects, environmental exposures can also promote chronic inflammation and oxidative stress, both of which contribute to the development of drug resistance. Chronic inflammation in the tumor microenvironment can activate pro-survival pathways that allow cancer cells to resist apoptosis (programmed cell death). For instance, the persistent activation of nuclear factor-kappa B (NF-κB) signaling can result in the upregulation of anti-apoptotic proteins that protect tumor cells from the cytotoxic effects of chemotherapy. Similarly, oxidative stress induced by environmental toxins can damage cellular structures, further promoting the survival of mutated cells that are resistant to treatment (Wang et al., 2025).

As a result of these adaptive mechanisms, cancer cells can evade the intended effects of chemotherapy, leading to drug resistance. This resistance significantly reduces the efficacy of cancer treatments, making it harder to achieve complete remission. The presence of drug-resistant cancer cells necessitates the development of new therapeutic strategies, such as combination therapies, which aim to target multiple pathways involved in resistance (Khan et al., 2024).

6.1 Toxicity and Side Effects of Cancer Treatments

Cancer treatments, such as chemotherapy and radiation, are designed to target and eliminate rapidly dividing cancer cells. However, these treatments also have significant side effects, as they do not exclusively differentiate between cancerous and healthy cells. The inherent toxicity of these treatments arises from their mechanisms of action, which often involve inducing DNA damage, disrupting cell division, or altering metabolic processes. This can cause harm to healthy, non-cancerous tissues, resulting in a variety of toxic side effects. When combined with environmental carcinogen exposure, these side effects can be exacerbated, making the management of cancer therapy even more challenging (Anand et al., 2022).

6.1.2 Biochemical Basis of Side Effects

The toxicity of chemotherapy drugs is primarily linked to their ability to induce DNA damage, disrupt cellular replication, and trigger apoptosis in rapidly dividing cells. Chemotherapeutic agents like alkylating agents, topoisomerase inhibitors, and antimetabolites work by interfering with DNA replication and transcription, leading to errors in cellular division and programmed cell death. While this mechanism is effective in killing cancer cells, it can also affect other fast-growing healthy tissues, such as those in the gastrointestinal tract, bone marrow, and hair follicles. This accounts for common chemotherapy side effects like nausea, vomiting, hair loss, and bone marrow suppression (Bai et al., 2024).

Radiation therapy, on the other hand, causes DNA damage through the generation of free radicals, which induce single- and double-strand breaks in the DNA. The highly localized but potent radiation can affect not only the tumor but also surrounding normal tissues. While the targeted delivery of radiation is designed to minimize collateral damage, side effects such as skin burns, fatigue, and organ dysfunction can still occur. Additionally, radiation therapy can cause long-term damage to tissues, leading to secondary cancers or fibrosis, particularly when combined with other therapies (Wang et al., 2025).

6.1.3 Environmental Carcinogen Exposure and Increased Toxicity

Patients with a history of environmental carcinogen exposure, such as those living in areas with high air pollution, heavy metals in drinking water, or those who have been exposed to asbestos or pesticides, face additional challenges during cancer treatment. These individuals are more likely to experience heightened sensitivity to the toxicity of cancer therapies due to pre-existing damage in their cells (Cani et al., 2023).

For instance, exposure to environmental carcinogens like arsenic or benzene can alter the function of DNA repair mechanisms, increasing the likelihood of DNA damage during chemotherapy or radiation. The genetic mutations caused by these pollutants can impair the ability of cells to repair the damage induced by cancer treatments, leading to further mutations and toxicity. This can cause cumulative DNA damage, which may not be easily repaired, increasing the risk of both short-term side effects and long-term complications such as secondary cancers. Moreover, environmental pollutants often induce chronic inflammation, which can further exacerbate the toxic effects of cancer treatments. Inflammatory cells, such as macrophages and neutrophils, release pro-inflammatory cytokines and reactive oxygen species (ROS) that not only contribute to cancer progression but also sensitize normal tissues to the toxic effects of chemotherapy and radiation. This combination of environmental exposure and cancer treatment-induced toxicity can lead to a vicious cycle of enhanced tissue damage, reduced immune response, and prolonged recovery times for patients (Yu et al., 2022).

6.1.4 Strategies for Minimizing Toxicity

To mitigate the side effects of cancer treatments, several strategies are employed. One approach is to use targeted therapies that specifically aim at cancer cells while sparing healthy tissues. For example, therapies targeting specific mutations or overexpressed proteins in tumors, such as monoclonal antibodies or tyrosine kinase inhibitors, offer a more selective approach compared to traditional chemotherapy (Garg et al., 2024).

In addition, strategies such as dose reduction, scheduling adjustments, and the use of adjunctive drugs like growth factors (e.g., erythropoietin for anemia or granulocyte-colony stimulating factor for neutropenia) help to manage the toxicity of cancer therapies. These supportive measures are designed to minimize side effects while maintaining the efficacy of treatment. However, the challenge is to optimize these strategies, especially for patients with environmental exposures that may already compromise their ability to recover from therapy (Dale, 2002).

Furthermore, ongoing research into chemoprotective agents aims to protect normal cells from the cytotoxic effects of cancer treatments. For example, amifostine is a radioprotective agent that has been shown to reduce the risk of radiation-induced toxicity in normal tissues. The goal is to enhance the therapeutic window of cancer treatments, improving their efficacy while reducing harm to healthy tissues (Dale, 2002).

6.2 Personalized Medicine and Biomarkers in Environmental Cancers

The concept of personalized medicine in cancer therapy becomes more intricate when we consider cancers influenced by environmental factors. These cancers often exhibit unique molecular alterations that may not be found in genetic-based cancers. Environmental carcinogens, like pollutants, heavy metals, and chemicals, introduce specific mutations that target critical proteins and cellular pathways (Verma, 2012).

6.2.1 p53 Pathway in Environmental Cancers

p53, often referred to as the "guardian of the genome," is one of the most frequently mutated tumor suppressor genes in various cancers. p53 plays a key role in regulating cell cycle checkpoints and initiating apoptosis in response to DNA damage. Environmental exposures, such as those to benzene, arsenic, or tobacco smoke, can directly induce mutations in the TP53 gene, rendering it inactive. When p53 is mutated, cells with damaged DNA are allowed to proliferate, which can lead to cancer formation. Benzene exposure has been associated with mutations in p53, particularly in hematologic cancers, like leukemia, where G→T transversions at codon 249 are common. Tobacco smoke introduces multiple mutagens, including benzo[a]pyrene, which can induce mutations in the TP53 gene. Biomarker for Environmental Exposure: The presence of specific p53 mutations in the tumor tissue can help identify cancers that are likely caused by environmental carcinogens, and provide insights into which therapies (such as p53 reactivation therapies or checkpoint inhibitors) might be more effective (Capuozzo et al., 2022)

6.2.2 DNA Repair Pathways: BRCA1/2 and Environmental Exposures

The BRCA1/2 genes are vital in repairing double-strand breaks (DSBs) through homologous recombination (HR), a precise DNA repair mechanism. Mutations in these genes are strongly associated with breast and ovarian cancers. Environmental factors can contribute to the dysfunction of the BRCA repair system, especially when heavy metals (e.g., cadmium and arsenic) or radiation are involved (Chen et al., 2018).

BRCA1/2 Mutations and Environmental Exposures, Arsenic exposure has been shown to compromise BRCA1-mediated DNA repair, increasing the risk of genomic instability and facilitating tumorigenesis. Cadmium impairs the DNA repair function of BRCA1 by promoting oxidative stress, which hampers its role in DSB repair and increases mutation accumulation in DNA. For patients with BRCA mutations, particularly those influenced by environmental exposures, PARP inhibitors (e.g., Olaparib and Rucaparib) are an excellent therapeutic option. These inhibitors target cells with defective DNA repair mechanisms, selectively killing cancer cells while sparing normal cells. This strategy is referred to as synthetic lethality, where the combination of defective BRCA repair and PARP inhibition leads to tumor cell death (Huang and Zhou, 2021).

6.2.3 Epidermal Growth Factor Receptor (EGFR) Mutations and Environmental Pollutants

EGFR is a receptor tyrosine kinase involved in the MAPK and PI3K/AKT signaling pathways that regulate cell growth, survival, and differentiation. In lung cancers, particularly those associated with environmental exposures such as air pollution, asbestos, and tobacco smoke, mutations in EGFR (e.g., EGFR L858R and exon 19 deletions) are common. These mutations lead to constant activation of the EGFR pathway, driving uncontrolled cell proliferation. Tobacco smoke and air pollution are known to cause EGFR mutations in non-small cell lung cancer (NSCLC). These mutations make the tumor cells more susceptible to targeted EGFR inhibitors (e.g., Erlotinib, Gefitinib) (Huang and Fu, 2015).

EGFR inhibitors are particularly effective for NSCLC patients with EGFR mutations. These targeted therapies can inhibit the aberrant signaling pathways and prevent cancer cell growth. However, acquired resistance to EGFR inhibitors can develop over time, often due to a secondary mutation (T790M), leading to the need for third-generation EGFR inhibitors (e.g., Osimertinib) (Huang and Fu, 2015).

6.2.4 Novel Biomarkers for Environmental Mutations

Cancers induced by environmental pollutants often exhibit mutations that are distinct from those found in genetically driven cancers. Therefore, identifying novel biomarkers for environmental mutations is critical for both diagnosis and treatment. Here are some potential biomarkers and their relevance:

6.2.5 DNA Adducts and Carcinogen-Induced Mutations

DNA adducts are formed when environmental carcinogens bind to DNA, causing mutations. The presence of specific DNA adducts can serve as a biomarker for environmental exposure. For example, benzo[a]pyrene, a polycyclic aromatic hydrocarbon found in tobacco smoke and air pollution, forms adduct with guanine bases in DNA, leading to G→T transversions commonly observed in lung cancers. DNA adduct analysis using liquid biopsy or tissue samples can help detect environmental exposure to specific carcinogens, guiding treatment decisions based on the patient's exposure history (Yun et al., 2020).

6.2.6 Inflammation-Associated Biomarkers

Chronic inflammation is a hallmark of many cancers, particularly those influenced by environmental exposures. Pollutants like particulate matter (PM2.5), arsenic, and cigarette smoke induce reactive oxygen species (ROS), leading to DNA damage and chronic inflammation. Key biomarkers of inflammation, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), can provide insight into the inflammatory status of tumors, particularly those arising from environmental carcinogens. The presence of elevated CRP or IL-6 levels could indicate an environment-driven cancer and might be used to monitor the efficacy of anti-inflammatory therapies (e.g., IL-6 inhibitors) (Valavanidis et al., 2013).

6.2.7 Epigenetic Modifications and Environmental Exposures

Environmental factors can also induce epigenetic modification, such as DNA methylation and histone modification, which alter gene expression without changing the underlying DNA sequence. For example, arsenic exposure has been linked to DNA hypermethylation, which silences tumor suppressor genes like p16INK4a and MGMT, promoting tumorigenesis. The detection of hypermethylation of tumor suppressor genes in liquid biopsies or tumor samples could be used as biomarkers for diagnosing and monitoring environmentally induced cancers (Li et al., 2021).

6.2.8 Clinical Implications and Future Directions

As research progresses, the integration of environmental exposures into personalized cancer therapy will lead to more targeted treatments, minimizing side effects and improving outcomes. The identification of novel biomarkers related to environmental carcinogen exposure will enable earlier detection, more accurate diagnosis, and better-targeted therapies. For instance, knowing a patient's specific environmental exposure history (e.g., arsenic, benzene) can guide decisions on the best treatment options, such as targeted therapies, immunotherapies, or PARP inhibitors for patients with BRCA1/2 mutations.

In the future, multi-omics approaches, combining genomic, transcriptomic, proteomic, and metabolomic data, will play a crucial role in identifying complex interactions between genetic predispositions and environmental exposures, enabling truly personalized therapies for cancer patients (Passaro et al., 2024).

7. Emerging Trends And Future Directions

The landscape of cancer research and treatment is constantly evolving. With recent advancements in technology and a deeper understanding of cancer's molecular underpinnings, the scientific community is increasingly focused on the interplay between cancer biochemistry and environmental exposures. As we look toward the future, several key trends and strategies are shaping the way we approach cancer therapy and prevention.

7.1 Advancements in Biochemical Research on Cancer

The field of cancer biochemistry has witnessed remarkable progress in recent years, driven by cutting-edge technologies and the integration of multiple research disciplines. One of the most exciting areas of study is the role of cancer stem cells (CSCs) and epigenetic changes in tumor progression and therapy resistance (Afkhami et al., 2024).

7.1.1 Cancer Stem Cells (CSCs) and Their Role in Treatment Resistance

Cancer stem cells (CSCs) are a subpopulation of cells within a tumor that possess self-renewal capabilities, enabling them to initiate tumor growth and contribute to metastasis. These cells are also responsible for therapy resistance, as they are often more resistant to conventional cancer treatments like chemotherapy and radiation. Recent biochemical studies have revealed that CSCs harbor unique metabolic profiles and exhibit altered signaling pathways compared to bulk tumor cells, making them difficult to target with existing therapies (Chu et al., 2024).

Environmental pollutants, such as tobacco smoke, arsenic, and pollutants found in air and water, have been shown to influence CSC behavior. These carcinogens can lead to the activation of pathways that promote the survival and proliferation of CSCs. For example, benzo[a]pyrene, a component of air pollution, has been linked to the activation of the Wnt/β-catenin signaling pathway, which plays a crucial role in maintaining CSC properties (Zhou, 2019).

Understanding how environmental factors affect CSC survival and drug resistance is critical for developing more effective treatments. New research is focusing on targeting CSC-specific pathways, such as Notch, Hedgehog, and Wnt, to eradicate these cells and prevent recurrence. Furthermore, therapies that target the epigenetic changes driving CSCs could lead to more effective strategies for overcoming resistance (Zhou, 2019).

7.1.2 Epigenetic Modifications in Cancer Development

Epigenetic changes, including DNA methylation, histone modification, and non-coding RNA regulation, are key players in the development and progression of cancer. Unlike genetic mutations, epigenetic changes do not alter the underlying DNA sequence but instead affect gene expression, allowing cancer cells to evade normal regulatory mechanisms.

Environmental exposures to pollutants and toxic chemicals can induce epigenetic modifications that contribute to carcinogenesis. For example, arsenic exposure has been shown to induce DNA hypermethylation of tumor suppressor genes, thereby silencing their expression and promoting tumor growth. Similarly, tobacco smoke and airborne pollutants can cause histone modifications, which alter the expression of genes involved in cell cycle regulation, apoptosis, and DNA repair. The emerging field of epigenetic reprogramming holds promise for cancer therapy. By reversing the epigenetic changes induced by environmental exposures, it may be possible to restore normal gene expression and re-sensitize cancer cells to treatment. Researchers are also exploring small molecule inhibitors that target specific epigenetic regulators, providing new avenues for treatment development (Sadida et al., 2023).

7.2 Therapeutic Strategies Targeting Environmental Exposures

Given the significant role that environmental pollutants play in cancer development and progression, novel therapeutic strategies are being developed to specifically address the molecular effects of these toxins on cancer cells. These approaches aim to mitigate the impact of environmental exposures, reduce cancer risk, and improve treatment outcomes.

7.2.1 New Therapeutic Approaches for Environmental Pollutants

Environmental pollutants, such as heavy metals, pesticides, and airborne toxins, can directly influence cancer progression by inducing mutations, altering cellular metabolism, and promoting inflammation. As our understanding of these processes grows, targeted therapies are being designed to counteract the harmful effects of these pollutants. A promising therapeutic approach involves developing drugs that specifically target the molecular pathways altered by environmental toxins. For example, antioxidant-based therapies are being explored to counteract oxidative stress caused by pollutants like PM2.5 and ozone. These antioxidants could help protect cancer cells from the DNA damage induced by environmental exposures and reduce the risk of mutation accumulation. Another emerging strategy is activating detoxifying enzymes, such as glutathione-S-transferases (GSTs), which play a crucial role in neutralizing environmental toxins. By enhancing the expression or activity of these enzymes, researchers aim to reduce the toxicity of carcinogens and improve patient outcomes in environmental cancer types ((Saintilnord and Fondufe-Mittendorf, 2021).

7.2.2 Development of Targeted Drugs for Environmental Carcinogens

As our understanding of the molecular mechanisms of environmental carcinogenesis advances, the development of targeted therapies aimed at specific environmental toxins becomes more feasible.

Both arsenic and cadmium have been linked to cancer through their ability to disrupt DNA repair and induce epigenetic changes. Researchers are exploring small molecules and biologic agents that can target the specific molecular effects of these pollutants, such as inhibiting DNA methylation or modulating metal detoxification pathways. PAHs, found in tobacco smoke and vehicle emissions, are potent carcinogens that form DNA adducts and cause mutations. Therapeutic strategies are being developed to inhibit the formation of DNA adducts or reverse the mutations caused by PAHs, thereby preventing tumorigenesis (Saintilnord and Fondufe-Mittendorf, 2021).

7.3 Collaborative Research Approaches

The complex nature of cancer, especially cancer influenced by environmental factors, requires an integrated, interdisciplinary approach. Collaborative research between biochemists, pharmacologists, and environmental scientists is crucial for advancing our understanding of how environmental exposures contribute to cancer development and how we can develop more effective treatments.

7.3.1 Interdisciplinary Collaboration

The interaction between genetics, biochemistry, and environmental science is key to understanding the full impact of carcinogens on cancer cells. Biochemists can provide insights into the molecular mechanisms through which environmental toxins affect DNA repair, gene expression, and protein function, while pharmacologists can focus on designing targeted therapies that specifically address these changes. Environmental scientists bring essential knowledge about how pollutants and toxins interact with human biology and influence cancer risk.

Collaborative research efforts are increasingly utilizing multi-omics approaches, combining genomics, proteomics, metabolomics, and epigenomics to develop more comprehensive models of cancer caused by environmental exposures. This approach allows for the identification of novel biomarkers and therapeutic targets that account for both genetic and environmental factors.

7.3.2 Advancing Cancer Prevention and Treatment Strategies

An interdisciplinary approach to cancer research has the potential to lead to novel cancer prevention strategies, especially for cancers induced by environmental exposures. By understanding how environmental factors alter cancer cell behavior at the molecular level, researchers can develop preventative therapies that target these molecular changes before cancer develops. Additionally, combining targeted treatments with environmental interventions, such as reducing pollutant exposure in high-risk populations, can offer a more comprehensive strategy for cancer prevention.

Collaboration between scientists and public health experts is essential for translating research into preventive public health measures. Reducing environmental exposures, such as through air quality regulations, safer industrial practices, and public awareness campaigns, can lower the incidence of environmentally induced cancers.

As biochemical research continues to unravel the molecular effects of environmental pollutants on cancer, we are entering an era where personalized therapies, epigenetic reprogramming, and collaborative research approaches hold the potential to revolutionize cancer treatment. By targeting specific environmental toxins and identifying novel biomarkers, researchers can develop more precise treatments that not only target genetic mutations but also mitigate the effects of harmful environmental exposures. With interdisciplinary collaboration, we are moving toward a future where cancer prevention, early detection, and treatment are better aligned with each individual's unique environmental and genetic profile.

8. Conclusion

Cancer development is a complex process driven by intricate biochemical mechanisms, where genetic mutations, epigenetic changes, and environmental pollutants play pivotal roles. Environmental carcinogens, such as airborne toxins, heavy metals, and industrial chemicals, induce mutations and dysregulate essential cellular processes, including DNA repair, cell cycle regulation, and apoptosis. These pollutants not only contribute to tumor initiation but also exacerbate tumor progression and drug resistance, making cancer more difficult to treat. Understanding these biochemical processes is crucial for developing targeted strategies that address both genetic and environmental factors in cancer therapy.

Current pharmaceutical approaches, such as chemotherapy, radiation, and targeted therapies, have made significant strides in treating cancer. However, their limitations in treating cancers linked to environmental exposures are evident, especially in cases where drug resistance, toxicity, and treatment efficacy are compromised by environmental carcinogen-induced mutations. Despite advances in personalized medicine, many therapies fail to specifically target the unique molecular alterations induced by environmental factors. As such, biomarker identification and novel drug development remain essential for improving outcomes for

patients with environmentally influenced cancers. There is an urgent need for continued research that focuses on the biochemical impact of environmental exposures on cancer cells, as well as the development of therapies that can specifically target the molecular effects of these exposures. This research should emphasize innovative therapeutic strategies, such as epigenetic reprogramming and environmental toxin-targeted drugs, to overcome the current limitations in cancer treatment. By integrating genetic, biochemical, and environmental research, the future of cancer therapy can be more effective, personalized, and capable of addressing the root causes of environmentally induced cancer.

Declaration Of Interest

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The authors declare that all the data will be available without any restrictions.

9. References

Achanta, G., Huang, P., 2004. Role of p53 in sensing oxidative DNA damage in response to reactive oxygen species-generating agents. Cancer Res 64, 6233–6239. https://doi.org/10.1158/0008-5472.CAN-04-0494

Afkhami, H., Yarahmadi, A., Bostani, S., Yarian, N., Haddad, M.S., Lesani, S.S., Aghaei, S.S., Zolfaghari, M.R., 2024. Converging frontiers in cancer treatment: the role of nanomaterials, mesenchymal stem cells, and microbial agents—challenges and limitations. Discov Onc 15, 818. https://doi.org/10.1007/s12672-024-01590-0

Ahmed, H., Mahmud, A.R., Siddiquee, Mohd.F.-R.-, Shahriar, A., Biswas, P., Shimul, Md.E.K., Ahmed, S.Z., Ema, T.I., Rahman, N., Khan, Md.A., Mizan, Md.F.R., Emran, T.B., 2022. Role of T cells in cancer immunotherapy: Opportunities and challenges. Cancer Pathog Ther 1, 116–126. https://doi.org/10.1016/j.cpt.2022.12.002

Albrengues, J., Shields, M., Ng, D., Park, C.G., Ambrico, A., Poindexter, M., Upadhyay, P., Uyeminami, D., Pommier, A., Küttner, V., Bružas, E., Maiorino, L., Bautista, C., Carmona, E.M., Gimotty, P.A., Fearon, D.T., Chang, K., Lyons, S.K., Pinkerton, K., Trotman, L.C., Goldberg, M.S., Yeh, J.T.-H., Egeblad, M., 2018. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. Science 361, eaao4227. https://doi.org/10.1126/science.aao4227

Alhmoud, J.F., Woolley, J.F., Al Moustafa, A.-E., Malki, M.I., 2020. DNA Damage/Repair Management in Cancers. Cancers (Basel) 12, 1050. https://doi.org/10.3390/cancers12041050

Anand, U., Dey, A., Chandel, A.K.S., Sanyal, R., Mishra, A., Pandey, D.K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J.K., Dewanjee, S., Vallamkondu, J., Pérez de la Lastra, J.M., 2022. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. Genes Dis 10, 1367–1401. https://doi.org/10.1016/j.gendis.2022.02.007

Bai, B., Ma, Y., Liu, D., Zhang, Y., Zhang, W., Shi, R., Zhou, Q., 2024. DNA damage caused by chemotherapy has duality, and traditional Chinese medicine may be a better choice to reduce its toxicity. Front Pharmacol 15, 1483160. https://doi.org/10.3389/fphar.2024.1483160

Bernard, A., 2008. Cadmium & its adverse effects on human health. Indian J Med Res 128, 557–564.

Beyersmann, D., Hartwig, A., 2008. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol 82, 493–512. https://doi.org/10.1007/s00204-008-0313-y

Bhullar, K.S., Lagarón, N.O., McGowan, E.M., Parmar, I., Jha, A., Hubbard, B.P., Rupasinghe, H.P.V., 2018. Kinase-targeted cancer therapies: progress, challenges and future directions. Journal of Molecular Cancer, 17 (1), 48-58. https://doi.org/10.1186/s12943-018-0804-2

Brown, J.S., Amend, S.R., Austin, R.H., Gatenby, R.A., Hammarlund, E.U., Pienta, K.J., 2023. Updating the Definition of Cancer. Mol Cancer Res 21, 1142–1147. https://doi.org/10.1158/1541-7786.MCR-23-0411

Cadet, J., Davies, K.J.A., 2017. Oxidative DNA damage & repair: An introduction. Free Radical Biology and Medicine, Oxidative DNA Damage & Repair 107, 2–12. https://doi.org/10.1016/j.freeradbiomed.2017.03.030

Cani, M., Turco, F., Butticè, S., Vogl, U.M., Buttigliero, C., Novello, S., Capelletto, E., 2023. How Does Environmental and Occupational Exposure Contribute to Carcinogenesis in Genitourinary and Lung Cancers? Cancers (Basel) 15, 2836. https://doi.org/10.3390/cancers15102836

Capuozzo, M., Santorsola, M., Bocchetti, M., Perri, F., Cascella, M., Granata, V., Celotto, V., Gualillo, O., Cossu, A.M., Nasti, G., Caraglia, M., Ottaiano, A., 2022. p53: From Fundamental Biology to Clinical Applications in Cancer. Biology (Basel) 11, 1325. https://doi.org/10.3390/biology11091325

Carbone, M., Arron, S.T., Beutler, B., Bononi, A., Cavenee, W., Cleaver, J.E., Croce, C.M., D'Andrea, A., Foulkes, W.D., Gaudino, G., Groden, J.L., Henske, E.P., Hickson, I.D., Hwang, P.M., Kolodner, R.D., Mak, T.W., Malkin, D., Monnat, R.J., Novelli, F., Pass, H.I., Petrini, J.H., Schmidt, L.S., Yang, H., 2020. Tumour predisposition and cancer syndromes as models to study gene–environment interactions. Nat Rev Cancer 20, 533–549. https://doi.org/10.1038/s41568-020-0265-y

Castaneda, M., den Hollander, P., Kuburich, N.A., Rosen, J.M., Mani, S.A., 2022. Mechanisms of cancer metastasis. Seminars in Cancer Biology 87, 17–31. https://doi.org/10.1016/j.semcancer.2022.10.006

Chatterjee, S., 2015. Chromium Toxicity and its Health Hazards. International Journal of Advanced Research Volume 3, 167–172.

Chen, C.-C., Feng, W., Lim, P.X., Kass, E.M., Jasin, M., 2018. Homology-Directed Repair and the Role of BRCA1, BRCA2, and Related Proteins in Genome Integrity and Cancer. Annu Rev Cancer Biol 2, 313–336. https://doi.org/10.1146/annurev-cancerbio-030617-050502

Chu, X., Tian, W., Ning, J., Xiao, G., Zhou, Y., Wang, Z., Zhai, Z., Tanzhu, G., Yang, J., Zhou, R., 2024. Cancer stem cells: advances in knowledge and implications for cancer therapy. Sig Transduct Target Ther 9, 170. https://doi.org/10.1038/s41392-024-01851-y

Dale, D.C., 2002. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs 62 Suppl 1, 1–15. https://doi.org/10.2165/00003495-200262001-00001

Derynck, R., Weinberg, R.A., 2019. EMT and Cancer: More Than Meets the Eye. Developmental Cell 49, 313–316. https://doi.org/10.1016/j.devcel.2019.04.026

Dianov, G.L., Parsons, J.L., 2007. Co-ordination of DNA single strand break repair. DNA Repair, Repair of small base lesions in DNA—from molecular biology to phenotype 6, 454–460. https://doi.org/10.1016/j.dnarep.2006.10.009

Ebenstein, A., 2012. The Consequences of Industrialization: Evidence from Water Pollution and Digestive Cancers in China. The Review of Economics and Statistics 94, 186–201. https://doi.org/10.1162/REST_a_00150

Fabbro, D., Cowan-Jacob, S.W., Moebitz, H., 2015. Ten things you should know about protein kinases: IUPHAR Review 14. Br J Pharmacol 172, 2675–2700. https://doi.org/10.1111/bph.13096

Feitelson, M.A., Arzumanyan, A., Kulathinal, R.J., Blain, S.W., Holcombe, R.F., Mahajna, J., Marino, M., Martinez-Chantar, M.L., Nawroth, R., Sanchez-Garcia, I., Sharma, D., Saxena, N.K., Singh, N., Vlachostergios, P.J., Guo, S., Honoki, K., Fujii, H., Georgakilas, A.G., Bilsland, A., Amedei, A., Niccolai, E., Amin, A., Ashraf, S.S., Boosani, C.S., Guha, G., Ciriolo, M.R., Aquilano, K., Chen, S., Mohammed, S.I., Azmi, A.S., Bhakta, D., Halicka,

D., Keith, W.N., Nowsheen, S., 2015. Sustained proliferation in cancer: Mechanisms and novel therapeutic targets. Seminars in Cancer Biology, A broad-spectrum integrative design for cancer prevention and therapy 35, S25–S54. https://doi.org/10.1016/j.semcancer.2015.02.006

Garg, P., Malhotra, J., Kulkarni, P., Horne, D., Salgia, R., Singhal, S.S., 2024. Emerging Therapeutic Strategies to Overcome Drug Resistance in Cancer Cells. Cancers (Basel) 16, 2478. https://doi.org/10.3390/cancers16132478

Garg, R., Benedetti, L.G., Abera, M.B., Wang, H., Abba, M., Kazanietz, M.G., 2014. Protein kinase C and cancer: what we know and what we do not. Oncogene 33, 5225–5237. https://doi.org/10.1038/onc.2013.524

Gavito-Covarrubias, D., Ramírez-Díaz, I., Guzmán-Linares, J., Limón, I.D., Manuel-Sánchez, D.M., Molina-Herrera, A., Coral-García, M.Á., Anastasio, E., Anaya-Hernández, A., López-Salazar, P., Juárez-Díaz, G., Martínez-Juárez, J., Torres-Jácome, J., Albarado-Ibáñez, A., Martínez-Laguna, Y., Morán, C., Rubio, K., 2024. Epigenetic mechanisms of particulate matter exposure: air pollution and hazards on human health. Front. Genet. 14. https://doi.org/10.3389/fgene.2023.1306600

Glauert, H.P., Elliott, R.S., Han, S.G., Athey, M., Lee, E.Y., Gairola, C.G., 2017. Effect of cigarette smoke exposure and mutant Kras overexpression on pancreatic cell proliferation. Oncol Lett 13, 1939–1943. https://doi.org/10.3892/ol.2017.5606

Goenka, A., Khan, F., Verma, B., Sinha, P., Dmello, C.C., Jogalekar, M.P., Gangadaran, P., Ahn, B.-C., 2023. Tumor microenvironment signaling and therapeutics in cancer progression. Cancer Communications 43, 525–561. https://doi.org/10.1002/cac2.12416

Hibino, S., Kawazoe, T., Kasahara, H., Itoh, S., Ishimoto, T., Sakata-Yanagimoto, M., Taniguchi, K., 2021. Inflammation-Induced Tumorigenesis and Metastasis. International Journal of Molecular Sciences 22, 5421. https://doi.org/10.3390/ijms22115421

Holme, J.A., Vondráček, J., Machala, M., Lagadic-Gossmann, D., Vogel, C.F.A., Le Ferrec, E., Sparfel, L., Øvrevik, J., 2023. Lung cancer associated with combustion particles and fine particulate matter (PM2.5) - The roles of polycyclic aromatic hydrocarbons (PAHs) and the aryl hydrocarbon receptor (AhR). Biochem Pharmacol 216, 115801. https://doi.org/10.1016/j.bcp.2023.115801

Huang, L., Fu, L., 2015. Mechanisms of resistance to EGFR tyrosine kinase inhibitors. Acta Pharm Sin B 5, 390–401. https://doi.org/10.1016/j.apsb.2015.07.001

Huang, R., Zhou, P.-K., 2021. DNA damage repair: historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy. Signal Transduct Target Ther 6, 254. https://doi.org/10.1038/s41392-021-00648-7

Huang, Y., Li, L., 2013. DNA crosslinking damage and cancer - a tale of friend and foe. Transl Cancer Res 2, 144–154. https://doi.org/10.3978/j.issn.2218-676X.2013.03.01

Kay, J., Thadhani, E., Samson, L., Engelward, B., 2019. Inflammation-Induced DNA Damage, Mutations and Cancer. DNA Repair (Amst) 83, 102673. https://doi.org/10.1016/j.dnarep.2019.102673

Khan, S.U., Fatima, K., Aisha, S., Malik, F., 2024. Unveiling the mechanisms and challenges of cancer drug resistance. Cell Communities Signal, 22 (2), 109-125. https://doi.org/10.1186/s12964-023-01302-1

Koual, M., Tomkiewicz, C., Cano-Sancho, G., Antignac, J.-P., Bats, A.-S., Coumoul, X., 2020. Environmental chemicals, breast cancer progression and drug resistance. Environmental Health, 19 (2), 117-125. https://doi.org/10.1186/s12940-020-00670-2

Li, D., Yang, Y., Li, Y., Zhu, X., Li, Z., 2021. Epigenetic regulation of gene expression in response to environmental exposures: From bench to model. Science of The Total Environment, 776, 145998. https://doi.org/10.1016/j.scitotenv.2021.145998

Li, S., Yuan, H., Li, L., Li, Q., Lin, P., Li, K., 2025. Oxidative Stress and Reprogramming of Lipid Metabolism in Cancers. Antioxidants (Basel) 14, 201. https://doi.org/10.3390/antiox14020201

Lim, J.U., Jung, J., Kim, Y.W., Kim, C.Y., Lee, Sang Hoon, Park, D.W., Choi, S.I., Ji, W., Yeo, C.D., Lee, Seung Hyeun, 2025. Targeting the Tumor Microenvironment in EGFR-Mutant Lung Cancer: Opportunities and Challenges. Biomedicines 13, 470. https://doi.org/10.3390/biomedicines13020470

Lin, L., Yang, H., Xu, X., 2022. Effects of Water Pollution on Human Health and Disease Heterogeneity: A Review. Front. Environ. Sci. 10. https://doi.org/10.3389/fenvs.2022.880246

Miguel, V., Lamas, S., Espinosa-Diez, C., 2020. Role of non-coding-RNAs in response to environmental stressors and consequences on human health. Redox Biology 37, 101580. https://doi.org/10.1016/j.redox.2020.101580

Min, H.-Y., Lee, H.-Y., 2022. Molecular targeted therapy for anticancer treatment. Exp Mol Med 54, 1670–1694. https://doi.org/10.1038/s12276-022-00864-3

Nishijo, M., Nakagawa, H., Suwazono, Y., Nogawa, K., Kido, T., 2017. Causes of death in patients with Itai-itai disease suffering from severe chronic cadmium poisoning: a nested case-control analysis of a follow-up study in Japan. BMJ Open 7, e015694. https://doi.org/10.1136/bmjopen-2016-015694

Oladimeji, T.E., Oyedemi, M., Emetere, M.E., Agboola, O., Adeoye, J.B., Odunlami, O.A., 2024. Review on the impact of heavy metals from industrial wastewater effluent and removal technologies. Heliyon 10, e40370. https://doi.org/10.1016/j.heliyon.2024.e40370

Parida, L., Patel, T.N., 2023. Systemic impact of heavy metals and their role in cancer development: a review. Environmental Monitoring and Assessment, 195 (2), 766-786. https://doi.org/10.1007/s10661-023-11399-z

Passaro, A., Al Bakir, M., Hamilton, E.G., Diehn, M., André, F., Roy-Chowdhuri, S., Mountzios, G., Wistuba, I.I., Swanton, C., Peters, S., 2024. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell 187, 1617–1635. https://doi.org/10.1016/j.cell.2024.02.041

Rahman, Z., Singh, V.P., 2019. The relative impact of toxic heavy metals (THMs) (arsenic (As), cadmium (Cd), chromium (Cr)(VI), mercury (Hg), and lead (Pb)) on the total environment: an overview. Environ Monit Assess 191, 419. https://doi.org/10.1007/s10661-019-7528-7

Sadeghi, M.M., Salama, M.F., Hannun, Y.A., 2021. Protein Kinase C as a Therapeutic Target in Non-Small Cell Lung Cancer. International Journal of Molecular Sciences 22, 5527. https://doi.org/10.3390/ijms22115527

Sadida, H.Q., Abdulla, A., Marzooqi, S.A., Hashem, S., Macha, M.A., Akil, A.S.A.-S., Bhat, A.A., 2023. Epigenetic modifications: Key players in cancer heterogeneity and drug resistance. Translational Oncology, 39 (2), 101-120. https://doi.org/10.1016/j.tranon.2023.101821

Saintilnord, W.N., Fondufe-Mittendorf, Y., 2021. Arsenic-Induced Epigenetic Changes in Cancer Development. Seminars in Cancer Biology. 76 (2), 195–205. https://doi.org/10.1016/j.semcancer.2021.03.019

Santibáñez-Andrade, M., Quezada-Maldonado, E.M., Rivera-Pineda, A., Chirino, Y.I., García-Cuellar, C.M., Sánchez-Pérez, Y., 2023. The Road to Malignant Cell Transformation after Particulate Matter Exposure: From Oxidative Stress to Genotoxicity. International Journal of Molecular Sciences 24, 1782. https://doi.org/10.3390/ijms24021782

Schullehner, J., Hansen, B., Thygesen, M., Pedersen, C.B., Sigsgaard, T., 2018. Nitrate in drinking water and colorectal cancer risk: A nationwide population-based cohort study. International Journal of Cancer, 143, 73–79. https://doi.org/10.1002/ijc.31306

Shang, S., Ji, X., Zhang, L., Chen, J., Li, C., Shi, R., Xiang, W., Kang, X., Zhang, D., Yang, F., Dai, R., Chen, P., Chen, S., Chen, Y., Li, Y., Miao, H., 2019. Macrophage ABHD5 Suppresses NFκB-Dependent Matrix Metalloproteinase Expression and Cancer Metastasis. Cancer Res 79, 5513–5526. https://doi.org/10.1158/0008-5472.CAN-19-1059

Shehata, S.A., Toraih, E.A., Ismail, E.A., Hagras, A.M., Elmorsy, E., Fawzy, M.S., 2023. Vaping, Environmental Toxicants Exposure, and Lung Cancer Risk. Cancers, 15, 4525. https://doi.org/10.3390/cancers15184525

Shuel, S.L., 2022. Targeted cancer therapies. Canadian Journal of Faming Physician, 68, 515–518. https://doi.org/10.46747/cfp.6807515

Singh, S.R., Bhaskar, R., Ghosh, S., Yarlagadda, B., Singh, K.K., Verma, P., Sengupta, S., Mladenov, M., Hadzi-Petrushev, N., Stojchevski, R., Sinha, J.K., Avtanski, D., 2025. Exploring the Genetic Orchestra of Cancer: The Interplay Between Oncogenes and Tumor-Suppressor Genes. Cancers 17, 1082. https://doi.org/10.3390/cancers17071082

Stojchevski, R., Sutanto, E.A., Sutanto, R., Hadzi-Petrushev, N., Mladenov, M., Singh, S.R., Sinha, J.K., Ghosh, S., Yarlagadda, B., Singh, K.K., Verma, P., Sengupta, S., Bhaskar, R., Avtanski, D., 2025. Translational Advances in Oncogene and Tumor-Suppressor Gene Research. Cancers, 17 (2), 100-128. https://doi.org/10.3390/cancers17061008

Sweeney, C., Lazennec, G., Vogel, C.F.A., 2022. Environmental exposure and the role of AhR in the tumor microenvironment of breast cancer. Frontiers in Pharmacology, 13 (2), 109-121 . https://doi.org/10.3389/fphar.2022.1095289

Talib, W.H., Alsayed, A.R., Barakat, M., Abu-Taha, M.I., Mahmod, A.I., 2021. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. Biomedicines 9 (2), 135-150. https://doi.org/10.3390/biomedicines9101353

Tanaka, T., Shimizu, M., Kochi, T., Moriwaki, H., 2013. Chemical-induced Carcinogenesis. Journal of Experimental & Clinical Medicine 5, 203–209. https://doi.org/10.1016/j.jecm.2013.10.009

Tsatsanis, C., Spandidos, D.A., 2000. The role of oncogenic kinases in human cancer (Review). International Journal of Molecular Medicine, 20(2), 34-45. https://doi.org/10.3892/ijmm.5.6.583

Turner, M.C., Andersen, Z.J., Baccarelli, A., Diver, W.R., Gapstur, S.M., Pope, C.A., Prada, D., Samet, J., Thurston, G., Cohen, A., 2020. Outdoor Air Pollution and Cancer: An Overview of the Current Evidence and Public Health Recommendations. CA Cancer Journal of Clinical Medicine, 10 (2), .332-352. https://doi.org/10.3322/caac.21632

Ullah, A., Arif, M., Waqas, M., Hasnain, M., Saira, A., Tariq, R., Shahzad, F., Khaliq, H., 2024. Exploring the Role of Chemicals and Environmental Factors for Cancer Proliferation. Open Access Library Journal 11, 1–19. https://doi.org/10.4236/oalib.1112607

Valavanidis, A., Vlachogianni, T., Fiotakis, K., Loridas, S., 2013. Pulmonary Oxidative Stress, Inflammation and Cancer: Respirable Particulate Matter, Fibrous Dusts and Ozone as Major Causes of Lung Carcinogenesis through Reactive Oxygen Species Mechanisms. International Journal of Environmental Research in Public Health, 10 (2), 3886–3907. https://doi.org/10.3390/ijerph10093886

Velez, A.M.A., Howard, M.S., 2015. Tumor-suppressor Genes, Cell Cycle Regulatory Checkpoints, and the Skin. North American Journal of Medicine and Science, 7 (2), 176–188. https://doi.org/10.4103/1947-2714.157476

Verma, M., 2012. Personalized Medicine and Cancer. Journal of Persian Medicine, 2 (2), 1–14. https://doi.org/10.3390/jpm2010001

Wang, M., Xiao, Y., Miao, J., Zhang, X., Liu, M., Zhu, L., Liu, H., Shen, X., Wang, J., Xie, B., Wang, D., 2025. Oxidative Stress and Inflammation: Drivers of Tumorigenesis and Therapeutic Opportunities. Antioxidants , 14 (2), 735-755. https://doi.org/10.3390/antiox14060735

Wani, A.L., Ara, A., Usmani, J.A., 2015. Lead toxicity: a review. Interdisciplinary Toxicology, 8 (2), 55–64. https://doi.org/10.1515/intox-2015-0009

Weihua, Z., Tsan, R., Huang, W.-C., Wu, Q., Chiu, C.-H., Fidler, I.J., Hung, M.-C., 2008. Survival of cancer cells is maintained by EGFR independent of its kinase activity. Cancer Cell 13, 385–393. https://doi.org/10.1016/j.ccr.2008.03.015

Yang, Y., Cao, Y., 2022. The impact of VEGF on cancer metastasis and systemic disease. Seminars in Cancer Biology 86, 251–261. https://doi.org/10.1016/j.semcancer.2022.03.011

Yu, W., Tu, Y., Long, Z., Liu, J., Kong, D., Peng, J., Wu, H., Zheng, G., Zhao, J., Chen, Y., Liu, R., Li, W., Hai, C., 2022. Reactive Oxygen Species Bridge the Gap between Chronic Inflammation and Tumor Development. Oxidative Medicine and Cellular Longevity, 26(2), 25-45. https://doi.org/10.1155/2022/2606928

Yun, B.H., Guo, J., Bellamri, M., Turesky, R.J., 2020. DNA Adducts: formation, biological effects, and new biospecimens for mass spectrometric measurements in humans. Mass Spectrometer Reviews, 39 (2), 55–82. https://doi.org/10.1002/mas.21570

Zhou, G., 2019a. Tobacco, air pollution, environmental carcinogenesis, and thoughts on conquering strategies of lung cancer. Cancer Biology & Medicine 16, 700–713. https://doi.org/10.20892/j.issn.2095-3941.2019.0180