

# Molecular Mechanisms of DNA Damage and Their Role in The Development of Carcinogenesis

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**Received:** 12 February 2026; **Accepted:** 08 March 2026; **Published:** 30 March 2026

**Abstract:** It is well-established that external factors inevitably exert an influence at the level of human molecular mechanisms. These factors induce mutations and trigger the activation of oncogenes. Proto-oncogenes (growth factors, apoptosis inhibitors) and oncogenes (nuclear and Ras genes) are considered the fundamental basis of carcinogenesis. Tumors lead to severe clinical outcomes, such as astrocytoma, glioblastoma, as well as gastric and lung cancers. This research was conducted based on clinical data and biochemical analysis methods from the past six years. In conclusion, the study of biomarkers serves as a critical foundation for the early detection and diagnosis of neoplastic and genetic diseases.

**Keywords:** DNA damage, Carcinogenesis, Molecular mechanisms, DNA repair, Mutation, Genomic stability, Oncogenesis.

**Introduction:** Next-Generation Sequencing (NGS) technologies enable high-precision analysis of mutational profiles in tumor cells. By 2025, expanded genomic panel testing has been integrated into the clinical practice of numerous medical centers. This facilitates the identification of a patient-specific molecular "signature" and the selection of personalized therapeutic strategies. According to recent scientific paradigms, oncogenesis is driven not only by alterations in DNA sequences but also by significant epigenetic reprogramming. Recent advances in cancer biology suggest that epigenetic alterations are not merely secondary consequences of genetic mutations but may act as primary drivers of oncogenesis. While classical models emphasize DNA mutations as the initiating events, emerging evidence indicates that epigenetic dysregulation alone can disrupt gene expression patterns, leading to malignant transformation. These findings challenge the traditional mutation-centered paradigm and highlight the importance of chromatin structure, DNA methylation, and histone modifications as key

determinants in tumor initiation and progression. DNA methylation, histone modifications, and non-coding RNA molecules exert profound control over gene expression. Research conducted between 2024 and 2025 demonstrates that epigenetic alterations manifest during the early stages of certain tumor types, thereby expanding the prospects of utilizing epigenetic markers as tools for early diagnostics. The development of single-cell sequencing and multi-omics technologies has significantly improved our understanding of early oncogenic processes. These approaches have revealed that epigenetic alterations, including changes in chromatin accessibility and transcriptional regulation, occur at very early stages of tumor development, often preceding detectable genetic mutations. Such findings emphasize the importance of epigenomic reprogramming in initiating and shaping tumor heterogeneity.

Mutations arise from alterations in the sequence of purine and pyrimidine bases within DNA caused by exogenous factors. These include apurination (loss of nitrogenous bases), cytosine deamination (conversion

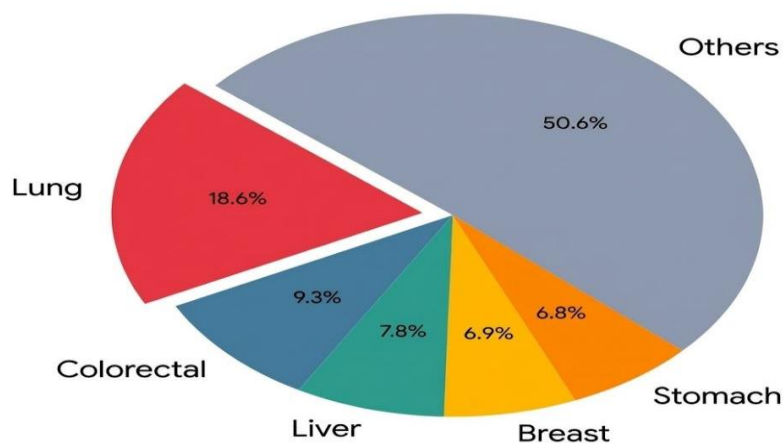
to uracil), alkylation (hypermethylation), thymine dimerization (induced by ultraviolet radiation), strand breaks (induced by ionizing radiation), as well as deletions and duplications. Under normal physiological conditions, these damages are rectified through DNA repair mechanisms. If repair fails and the damaged cell is not eliminated via apoptosis, carcinogenesis ensues. Carcinogens—the primary drivers of oncogenesis—include radiation-based factors such as ultraviolet rays, X-rays, and gamma rays. Chemical carcinogens encompass polycyclic aromatic hydrocarbons (e.g., benzopyrene), aromatic amines (e.g., 2-acetylaminofluorene), nitrosamines (e.g., dimethylnitrosamine), alkylating agents (e.g., cyclophosphamide, diethylstilbestrol), and inorganic substances (e.g., chromium, beryllium, asbestos, cadmium).

The failure of anti-carcinogenic mechanisms leads to:

- 1) Initiation—where chemical carcinogens damage DNA, giving rise to abnormal tumor-specific cells;
- 2) Promotion—where repeated exposure to additional carcinogens accelerates tumor progression.

Susceptibility to retinoblastoma in children is inherited as an autosomal dominant trait, with 40% of cases exhibiting a familial character. Similarly, a predisposition to intestinal polyposis is hereditary, almost invariably progressing to adenocarcinoma in patients of reproductive age. The World Health Organization (WHO) projects that the number of cancer cases will exceed 35 million by 2050, representing a 77% increase from the 20 million cases recorded in 2022. According to WHO data, the three most prevalent types of cancer in 2022 were lung cancer, breast cancer, and colorectal cancer.

Composition of cancer deaths in 2022 (Total 9.7 mln)



## RESULTS

Polycyclic Aromatic Hydrocarbons (PAHs) are considered the most hazardous chemical carcinogens. For instance, benzopyrene induces oncogenesis upon contact with any tissue. Upon entering the body, it is primarily converted into epoxides by liver enzymes, which subsequently bind to DNA purine bases, causing genomic damage. Specifically, benzopyrene is oxidized in the liver by monooxygenase (a cytochrome P450-containing enzyme) to form 7,8-epoxybenzopyrene. This intermediate is then converted by epoxide hydrolase into 7,8-dihydrodiol-benzopyrene, which undergoes further oxidation by monooxygenase to produce 7,8-dihydrodiol-9,10-epoxybenzopyrene. This final product binds to DNA purine bases, resulting in structural damage; the latter stage is characterized as a spontaneous, non-enzymatic process.

Nitrosamines: Carcinogenic nitrosamines are formed in the body through the interaction of secondary aliphatic amines with nitrites. Secondary amines and nitrites are

ubiquitous components of food products (formed during the cooking of meat and fish and also found in green plants). Under the influence of microsomal oxidases, these precursors are converted into methyl diazonium ions. Methyl diazonium ions methylate cellular DNA, potentially leading to the development of malignant neoplasms in the lungs, stomach, esophagus, liver, and kidneys.

Radiation Carcinogenesis: Radiation exposure can induce apurinic sites, single- or double-strand breaks, and the formation of cross-links within the DNA molecule. Ultraviolet (UV) radiation specifically facilitates the formation of pyrimidine dimers. Furthermore, radiation may exert indirect effects by accelerating the generation of free radicals that damage the genetic apparatus. On a regional scale, the high incidence of carcinoma and melanoma in Australia and New Zealand is linked to UV radiation. In Japan, the incidence of leukemia increased significantly among the population following the atomic bombings.

**Viral Carcinogenesis:** Viral-induced carcinogenesis in humans is relatively rare, occurring in approximately 10–12% of cases. It has been proven that DNA viruses can partially or fully integrate into the human host genome; the subsequent expression of viral genes produces proteins that disrupt the cell cycle.

- Human Papillomavirus (HPV) – associated with skin and cervical cancer.
- Epstein-Barr Virus (EBV) – associated with Burkitt’s lymphoma (nasopharyngeal cancer).
- Cytomegalovirus (CMV) – associated with Kaposi’s sarcoma.
- Hepatitis Viruses – lead to hepatocellular carcinoma (liver cancer) over a period of 20–25 years.

One of the key features of early carcinogenesis is the emergence of a high plasticity cell state (HPCS), characterized by loss of cellular identity and increased phenotypic flexibility. This state is often associated with the activation of epithelial-to-mesenchymal transition (EMT) programs, enhanced proliferative capacity, and resistance to therapy. Epigenetic mechanisms play a crucial role in regulating this plasticity, enabling cells to transition between different functional states during tumor evolution.

Currently, five primary mechanisms for the transformation of proto-oncogenes into oncogenes have been identified:

1. Insertion of new promoters into genomic DNA;
2. Emergence of new enhancer sequences;
3. Gene amplification;
4. Point mutations;
5. Chromosomal translocation.

Before cancer develops, 5–7 mutations typically occur in oncogenes and suppressor genes, accompanied by DNA hypomethylation and disruptions in DNA repair systems. In this process, a mutation initially occurs in a suppressor gene located on chromosome 5. A decrease in DNA methylation and the activation of the ras oncogene (located on chromosome 12) lead to the growth of adenomas. Defects in the repair system and the loss of suppressor genes result in genetic instability, leading to malignancy. The accumulation of mutations and dedifferentiation enable tumor cells to acquire invasive and metastatic properties. In metastatic cells, the composition of membrane proteins is altered. While integrins facilitate cell binding to collagen, fibronectin and laminins assist in attachment to other components of the intercellular matrix and basal membranes. In many tumors, fibronectin levels are reduced and altered integrins are synthesized, facilitating the migration of invasive cells through

connective tissues and capillary walls.

**Proto-oncogenes:**

1. Growth Factors (e.g., sex hormones, somatotropin) and their receptors: an excess of these can lead to disordered cell proliferation and tumor development.
2. Apoptosis Inhibitors: The Bcl-2 protein inhibits apoptosis; if cells with damaged DNA are not eliminated, they may transform into malignant cells.

**Oncogenes:**

1. Nuclear oncogenes: Genes such as jun, fos, myc, myb, erbA, and others, which upregulate the synthesis of oncoproteins.
2. Ras gene family: Proteins synthesized from this family increase cell division and protein synthesis. Hyperactivation of ras genes leads to excessive cellular proliferation and tumor progression.

**Tumor Suppressor Genes:**

- pRB (Retinoblastoma protein) gene: This protein restricts the transition of the cell from the G1 phase to the S phase by inactivating the E2F protein (the initiator of the S phase). Because it limits cell division, pRB is classified as a tumor suppressor.
- p53 protein gene: Upon DNA damage, this gene is activated to synthesize the p53 protein. If the damage is severe, p53 stimulates apoptosis to eliminate the damaged cell.
- p53 protein also increases the synthesis of Thrombospondin, which inhibits angiogenesis (the recruitment of blood vessels to the tumor), thereby preventing metastasis.

Genomic instability and the failure of DNA repair mechanisms are critical factors in tumor formation. Cancer stem cells play a leading role in tumor recurrence and the metastatic process. A profound understanding of oncogenic mechanisms provides a robust scientific foundation for the early detection, effective treatment, and advancement of preventive measures for cancer in the future.

## **CONCLUSION**

In conclusion, the process of carcinogenesis is directly linked to the chemical and physical damage of DNA; consequently, governing this process remains a primary objective for modern science. By mitigating exogenous factors that induce genomic damage—such as environmental pollutants and detrimental lifestyle habits—and by bolstering endogenous cellular defense mechanisms, the incidence of cancer can be significantly reduced. Future research should prioritize the advancement of genetic engineering and DNA repair technologies. A comprehensive understanding of

oncogenic mechanisms establishes a robust scientific foundation for the early detection, effective treatment, and optimization of preventive strategies for cancer in the years to come.

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