Lect·2

CHEMICAL CARCINOGENESIS

Overview

- Cancer is a disease characterized by genomic mutation, modified gene expression, cell proliferation, and aberrant cell growth.
- It ranks as one of the leading causes of death in the world.

Overview

- Multiple causes of cancer have been established including infectious agents, radiation, and chemicals.
- Estimates suggest that 70% to 90% of all human cancers have a linkage to environmental, dietary, and behavioral factors.

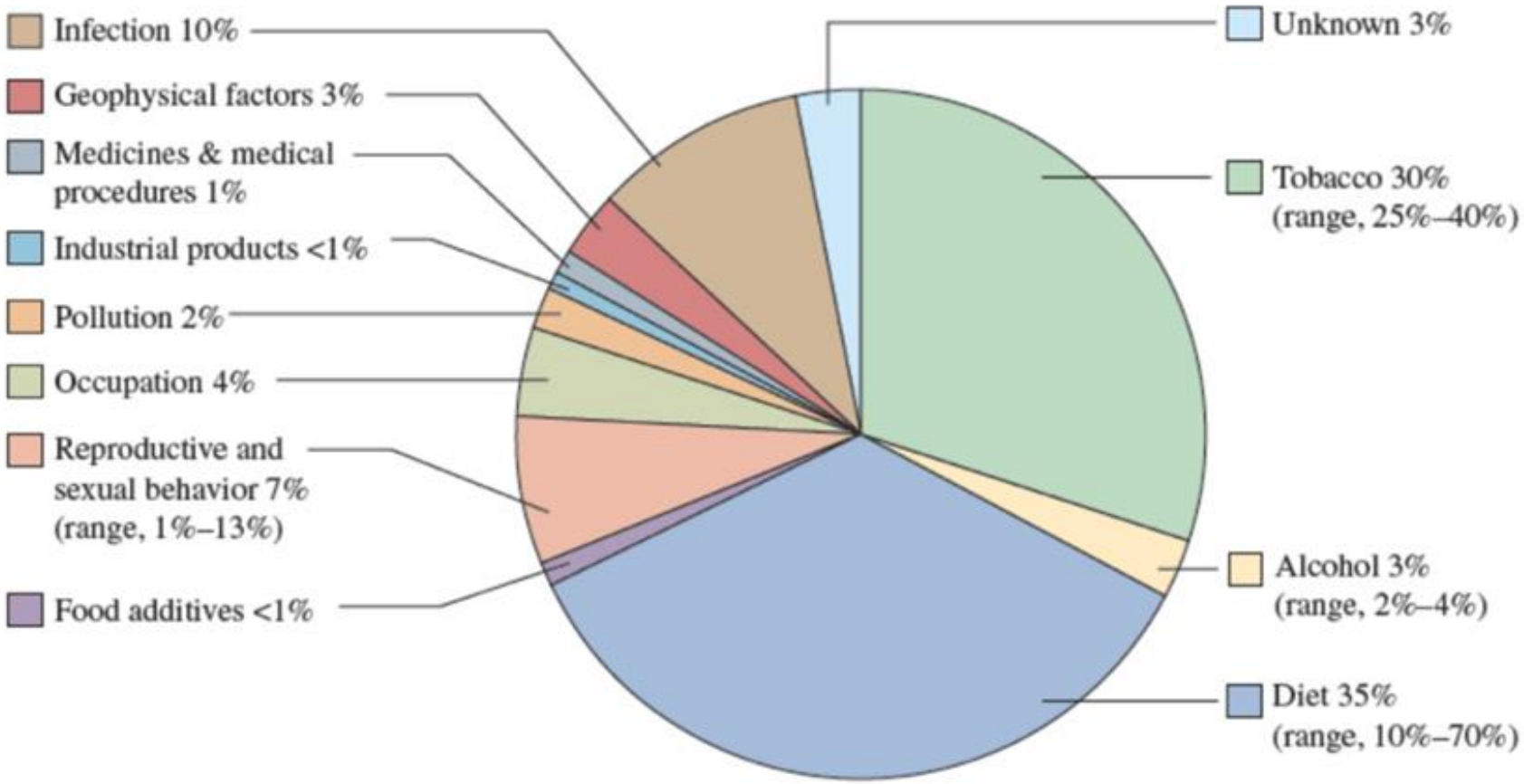


Figure 8-1. *Proportions of human cancer deaths attributed to various factors.* (Reproduced with permission from [no authors listed] Harvard reports on cancer prevention: causes of human cancer. Center for Cancer Prevention Harvard School of Public Health. *Cancer Causes and Control.* 1996;7 (Suppl 1): S3–S4, 1996.)

Overview

- The proposed eight "hallmarks of cancer" that involve:

(1) sustaining cell proliferation, (2) resisting cell death (apoptosis), (3) inducing angiogenesis, (4) enabling replicative immortality, (5) activating invasion and metastasis, (6) evading growth suppressors, (7) reprogramming of energy metabolism, and (8) evading immune destruction.

Definitions - Neoplasia

- Neoplasia is defined as new growth or autonomous growth of tissue.
- A neoplastic lesion is referred to as a neoplasm.
- A neoplasm can be either benign or malignant.
- Both types of lesions are induced by chemical carcinogens.
- Metastases are secondary growths derived from the cells of the primary malignant neoplasm.

Definitions - Benign neoplasms

- Benign neoplasms (e·g·, adenomas) are lesions characterized by expansive growth, frequently exhibiting slow rates of proliferation that do not invade surrounding tissue or other organs·
- Benign neoplasms can impair and damage the normal function of an organ through its growth by impeding blood flow·

Definitions - Benign neoplasms

- For benign neoplasms, the tissue of origin is frequently followed by the suffix "oma";
- For example, a benign fibrous neoplasm would be termed fibroma, and a benign glandular epithelium termed an adenoma.

Definitions - Malignant neoplasm

- A malignant neoplasm (e·g·, a carcinoma) demonstrates invasive growth characteristics, capable of spreading not only through the organ of origin but also via metastasis to other organs·
- Malignant neoplasms from epithelial origin are called carcinomas (from which the term cancer has evolved) while those derived from mesenchymal origin are referred to as sarcoma·

Definitions - Malignant neoplasm

- Thus, a malignant neoplasm of fibrous tissue would be a fibrosarcoma while that derived from bone would be an osteosarcoma.
- Similarly, a malignant neoplasm from the liver would be a hepatocellular carcinoma while that derived from skin squamous epithelium is referred to as a squamous cell carcinoma.

Definitions - Carcinogen

- A carcinogen is an chemical or physical or biological (viruses) agent, that causes or induces a cancer.
- Carcinogens have frequently been divided simplistically into two major categories based on their general mode of action: genotoxic and non-genotoxic.

Definitions - Genotoxic carcinogens

- Genotoxic carcinogens are those agents that interact with DNA to damage or change its structure, they are frequently mutagenic.

Definitions - Non-genotoxic carcinogens

- Non-genotoxic carcinogens are the agents that do not directly interact with nuclear DNA.
- Non-genotoxic carcinogens may change gene expression, modify normal cell function, bind to or modify cellular receptors, and increase the number of cells in the target tissue.

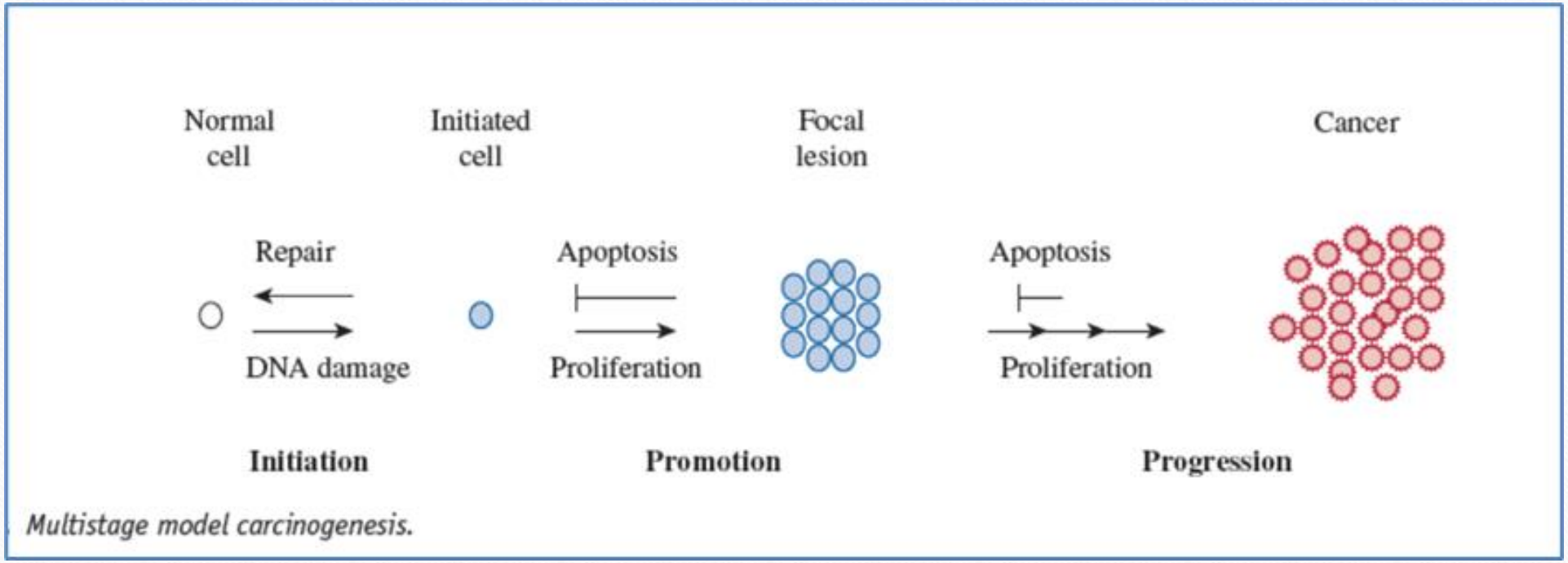
Multistage Carcinogenesis

- Once a neoplasm is formed, additional intracellular and extracellular changes occur in the process of the development of a malignant cancer
- Operationally, three defined stages, initiation, promotion, and progression have been identified.

Multistage Carcinogenesis

- These steps follow a temporal sequence of events demonstrable by histopathology and observed in a wide variety of target tissues.
- The defining characteristics of each of these stages are used to help characterize the multistage nature of chemically induce tumors

Multistage Carcinogenesis



Multistage model carcinogenesis.

Multistage Carcinogenesis -Initiation

- The first stage of the cancer process involves initiation, a process that is defined as a stable, heritable change.
- This stage is a relatively rapid, irreversible process that results in a carcinogen-induced mutational event.

Multistage Carcinogenesis -Initiation

- Chemical and physical agents, that function at this stage, are referred to as initiators or initiating agents.
- Among chemicals classified as initiating carcinogens are compounds such as polycyclic hydrocarbons and nitrosamines, biological agents, certain viruses, and physical agents such as x-rays and ultraviolet (UV) light.

Multistage Carcinogenesis -Initiation

- The initiating event becomes "fixed" when the DNA adducts or other damage to DNA is not correctly repaired or is incompletely repaired prior to DNA synthesis.
- This event can lead to inappropriate base pairing and formation of a mutation.

Multistage Carcinogenesis -Initiation

- Initiation by itself does not appear to be sufficient for neoplastic formation. Once initiated cells are formed, their fate has
- multiple potential outcomes:

1. the initiated cell can remain in a static nondividing state
2. the initiated cell may possess mutations incompatible with viability or normal function and be deleted through apoptotic mechanisms
3. the cell may undergo cell division resulting in the growth in the proliferation of the initiated cell.

Multistage Carcinogenesis - Promotion

- The second stage of the carcinogenesis process (the promotion stage) involves the selective clonal expansion of initiated cells to produce a preneoplastic lesion.
- Exogenous and endogenous agents, that function at this stage, are frequently referred to as tumor promoters, they are not mutagenic and generally are not able to induce tumors by themselves.

Multistage Carcinogenesis - Promotion

- The growth of preneoplastic lesions requires repeated applications or continuous exposure to tumor-promoting compounds.
- With repeated applications of the chemical only initiated cells continue to clonally expand and divide into a focal lesion.

Multistage Carcinogenesis - Promotion

- Carcinogens that function at the tumor promotion stage in general are organ specific.
- For example, phenobarbital functions at the tumor promotion stage selectively in the liver but will not promote tumorigenesis in the skin or most other tissues.

Multistage Carcinogenesis - Progression

- A progression, involves the conversion of the preneoplastic lesions to a neoplasm.
- In this stage, additional genotoxic events occur resulting in additional DNA damage including chromosomal damage such as aberrations and translocations.

Multistage Carcinogenesis - Progression

- The tumor microenvironment is an important component of this process and the presence of "normal" cells and stroma within the lesion is critical for the neoplastic cells to survive and propagate.

Multistage Carcinogenesis - Progression

- During the progression stage, the clonal nature of the neoplastic lesion is typically lost with a polyclonal appearance of cells within the lesion.
- The progression stage is an irreversible stage in that neoplasm formation, whether benign or malignant, occurs. With the formation of neoplasia, an autonomous growth and/or lack of growth control is achieved.

Mechanisms of Action of Chemical Carcinogens

- Two major processes are needed with regard to the induction of neoplasia by chemicals:

1. a mutational event and 2. a selective proliferation of the mutated cell to form a neoplasm.

- Chemicals that induce cancer have been classified into one of two broad categories genotoxic (DNA-reactive) agents and non-genotoxic (epigenetic) agents.

Mechanisms of Action of Chemical Carcinogens

- Genotoxic compounds interact with nuclear DNA of a target cell producing unrepaired DNA damage that is inherited in subsequent daughter cells.
- DNA-reactive carcinogens can be further subdivided according to whether they are active in their parent form (i.e., direct-acting: chemicals that can directly bind to DNA without being metabolized) and those that require metabolic activation (i.e., indirect-acting carcinogens: compounds that require metabolism in order to react with DNA).

Examples of Genotoxic Carcinogens

1. Direct-acting carcinogens

- Nitrogen or sulfur mustards, Propane sulfone, Methyl methane sulfonate, Ethyleneimine, and Dimethyl sulfate

2. Chemicals requiring activation (indirect-acting carcinogens)

- Polycyclic aromatic hydrocarbons and heterocyclic aromatics, Aromatic amines, N-Nitrosoamines, Azo dyes, and Hydrazines

Examples of Non-Genotoxic Carcinogens

1. Chloroform
2. Melamine
3. Phenobarbital
4. Toxaphene
5. 2,3,7,8-Tetrachlorodibenzop- dioxin (TCDD)
6. Polychlorinated biphenyls (PCBs)
7. Polybrominated biphenyls (PBBs)

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