Cancer Biology

Lecture No. 2

Presented by

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Lecture No 2.

Causes of Cancer

Lecture's Structure:

- Causes of cancer are not well known
- The hit theory
- Development of Cancer
- Chemical carcinogens
- Endogenous Carcinogenesis
- Irradiation Carcinogenesis
- Viral Carcinogenesis

Causes of Cancer

Causes of cancer are not well known?

- Otherwise cancer would has been prevented.
- lifetime accumulation of ‘‘hits’’ on a person’s DNA.

Carcinogen

Cancer may result from genetic susceptibility to environmental agents such as chemicals; radiation; or viral, bacterial, or parasitic infections; or from endogenously generated agents such as oxygen radicals.

Causes of Cancer

The Hit Theory

Cancer is an aging disease, This has led to the idea that it takes multiple cellular hits to explain the age-related incidence of malignancy.

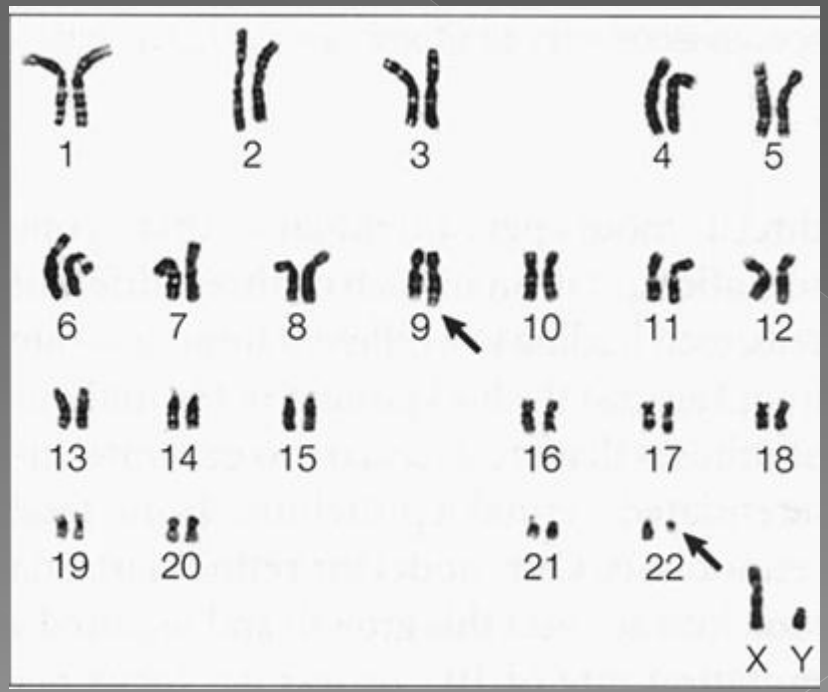
"The number of hits needed to produce the initiation of a malignant event may vary from one to six or more. However, progression to a full-blown invasive metastatic cancer almost always requires multiple Hits".

Causes of Cancer

The Hit Theory

Example 1: Cancers need only one hit

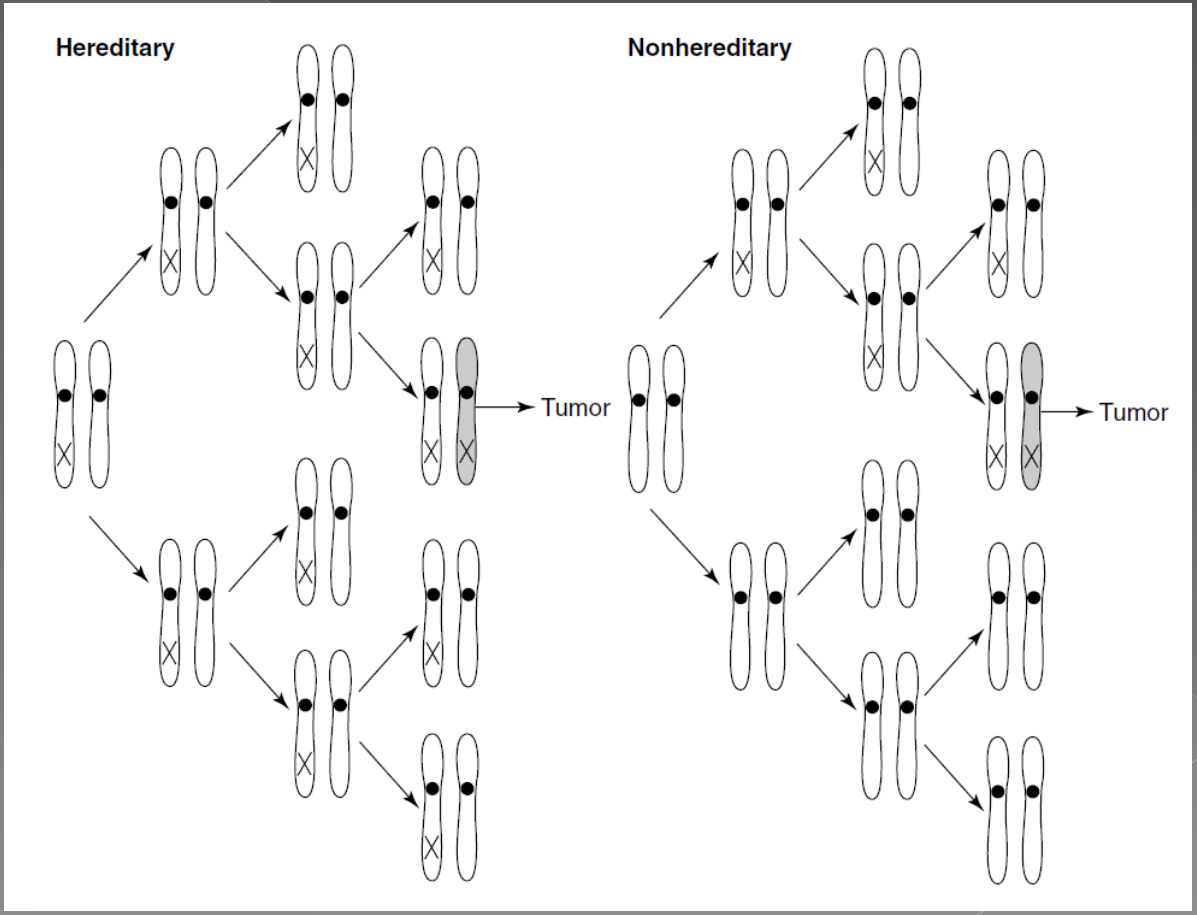
Chronic myleogenous leukemia (CML). (Philadelphia chromosome and the translocation between chromosomes 9 and 22. So a single treatment is effective.



Causes of Cancer

The Hit Theory

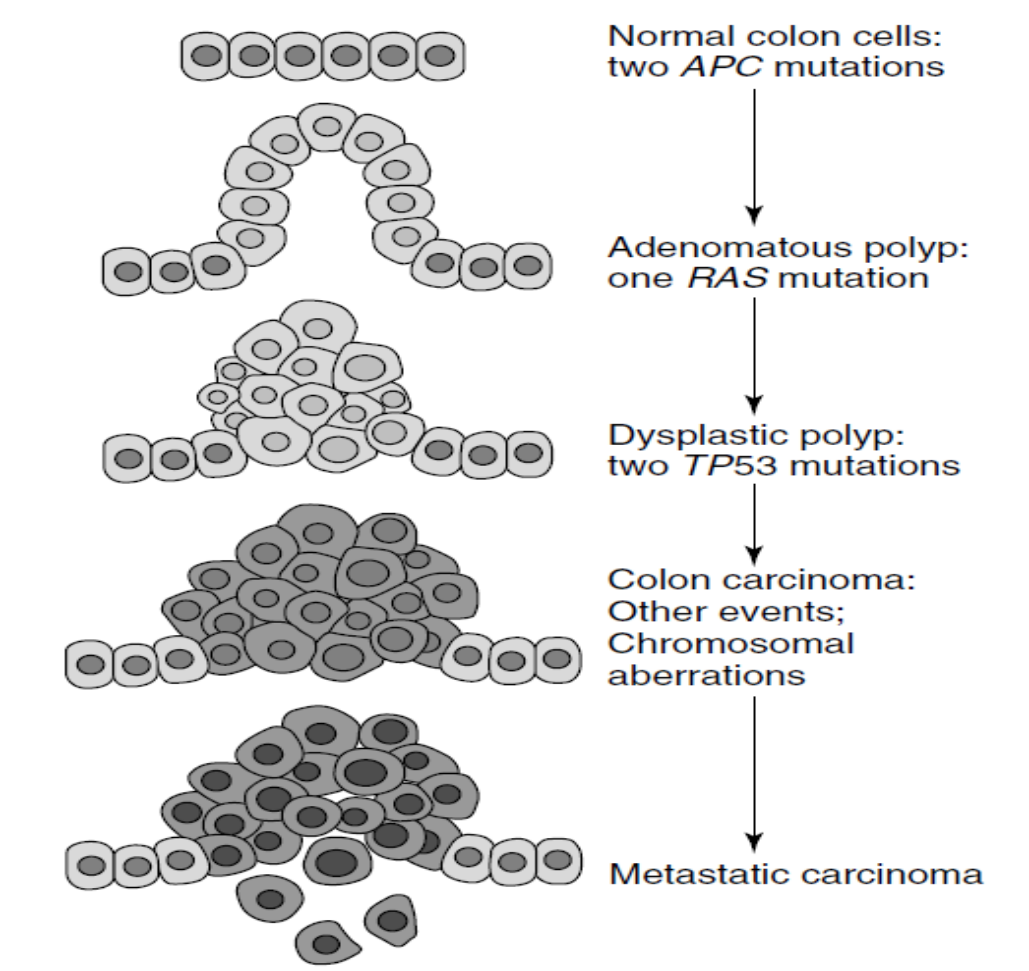
Example 2: Retinoblastoma: Two hits are required



Causes of Cancer

The Hit Theory

Example 3: Five hit scenario for colorectal cancer



Causes of Cancer

Development of Cancer

Development of cancer is a multistage Process.

Initiation vs **Promotion** and **Progression**

Causes of Cancer

Development of Cancer

Tumour Initiation:

- Requires a small amount of time
- Irreversible
- Heritable

Tumour Promotion:

- A slow gradual process and requires a more prolonged exposure to the promoting agent.

- Occupies the greater part of the latent period of carcinogenesis.

- Partially reversible.

- A cell proliferation phase that propagates the initiated damage and leads to the emergence of an altered clone of cells.

Causes of Cancer

Development of Cancer

Tumour progression:

- Irreversible (Because of the pronounced changes in the genome that have occurred leading into this phase).

- The progression phase as the gradual evolution of genotypically and phenotypically altered cells that occurs due to genetic instability of the progressing cells. This process leads to the development of cell heterogeneity

Causes of Cancer

Development of Cancer

Mechanisms of Tumor Initiation

This could come about by either direct genotoxic or mutational events, in which a carcinogenic agent reacts directly with DNA, or by indirect or ‘‘epigenetic’’ events that modulate gene expression without directly reacting with the base sequence of DNA.

The mutational Theory

1. Agents that damage DNA are frequently carcinogenic.
2. Most carcinogenic agents are mutagens.
3. Incidence of cancer in patients with DNA repair deficiencies is increased.

Causes of Cancer

Development of Cancer

Mechanisms of Tumor Promotion

- The initiated cells undergo a clonal expansion under the influence of promoting agents that act as mitogens for the transformed cell type.
(Promoting actions appear to be mediated by cell membrane events)

- Genetic alterations that occur during tumor progression do not occur in a given sequence and are different for different cancers.

- They may be different in different patients who have the same histological tumor type (Individualized medicine).

Causes of Cancer

Development of Cancer

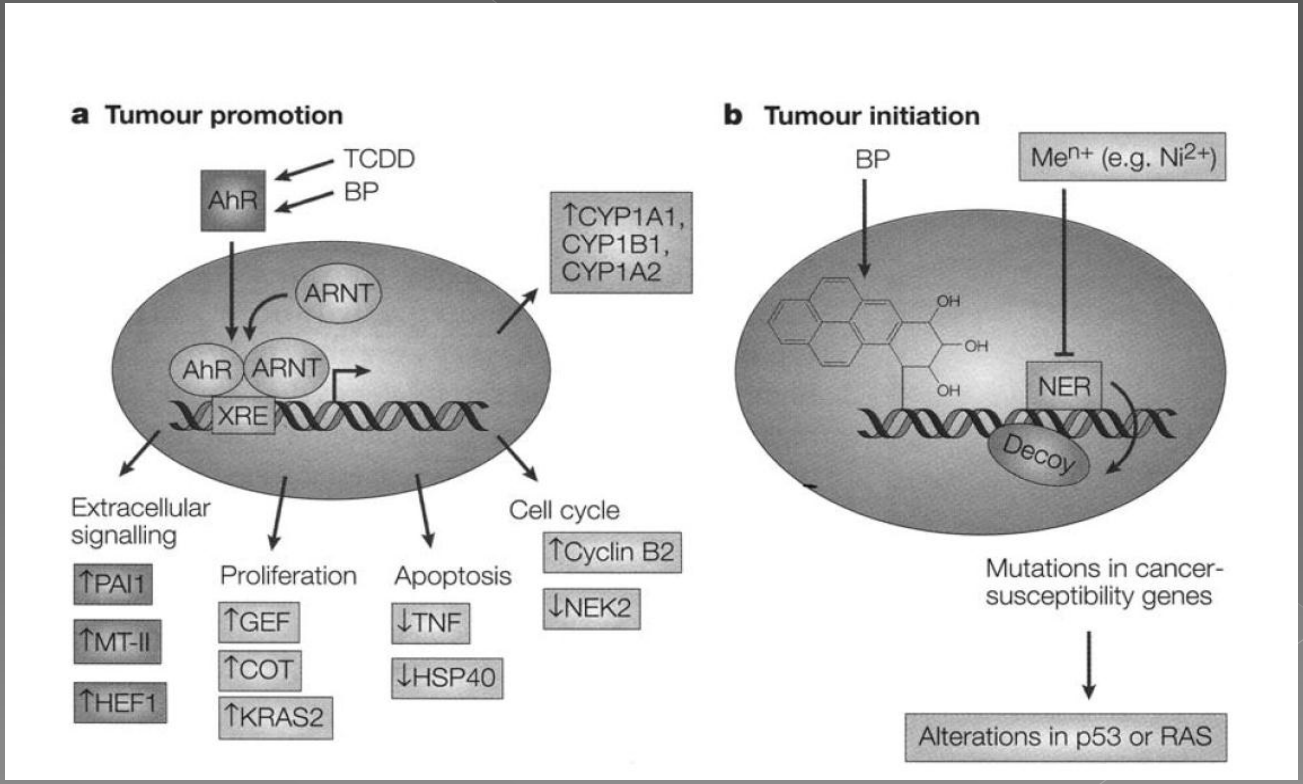
Mechanisms of Propagation

- More genetic alterations
- Genetic instability is the hallmark of the progression phase of carcinogenesis and leads to the chromosomal translocations and aneuploidy

Causes of Cancer

Development of Cancer

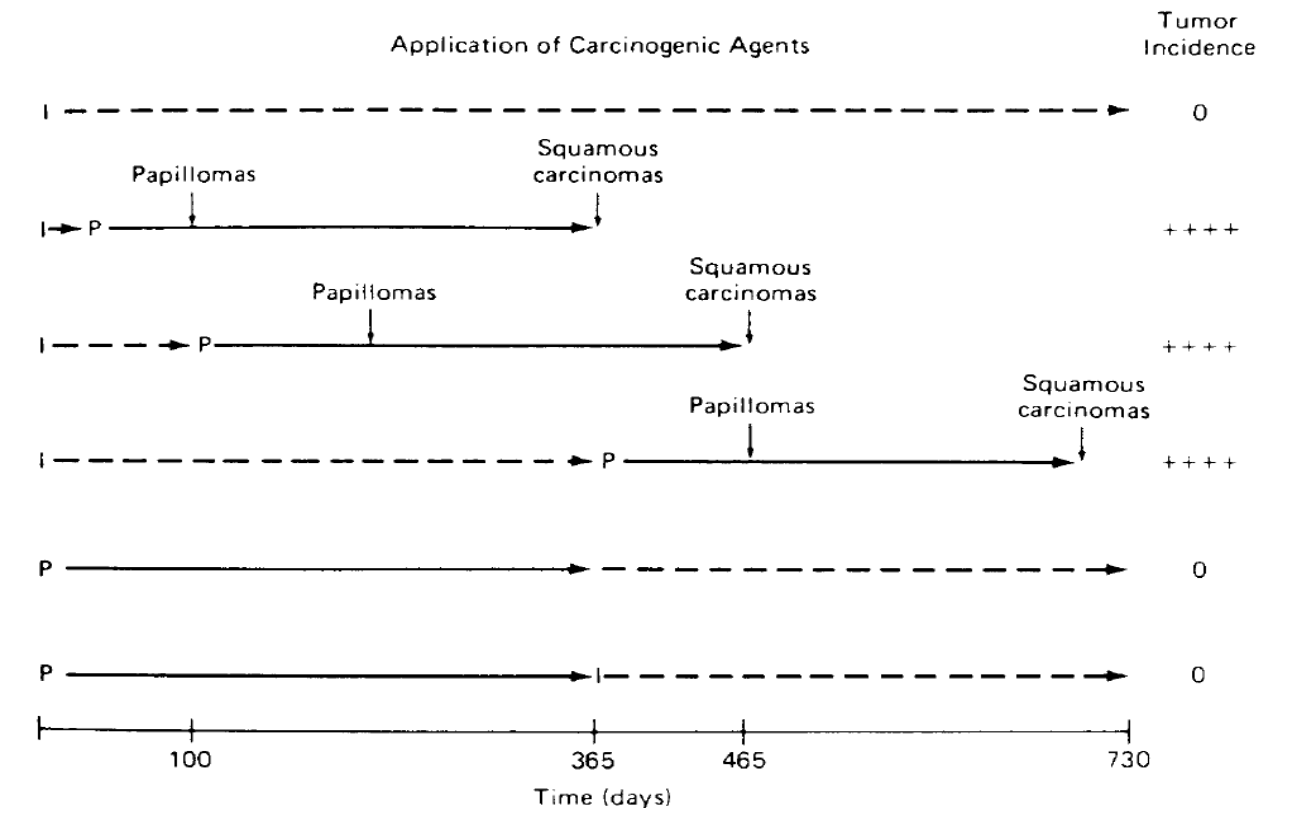
Some of the gene expression alterations
that occur during tumor initiation and promotion



Causes of Cancer

Development of Cancer

Carcinogens have different initiation, promotion and progression potentials.



Causes of Cancer

Chemical Carcinogens

- Covalent bonds with proteins and nucleic acids

- Metabolic Activation of Chemical Carcinogens

- Rings of a polycyclic hydrocarbon are inserted between the stacked bases of doublehelical DNA and distort the helix, leading to a frame-shift mutation during DNA replication.

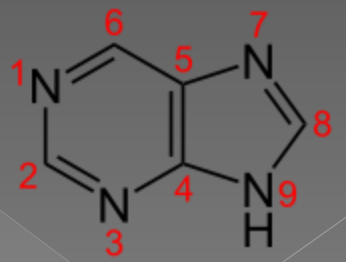
Causes of Cancer

Chemical Carcinogens

Alkylated bases in DNA can mispair with the wrong base during DNA replication.

Example: O6 methylguanine pairs with thymine instead of cytosine during DNA replication.

Carcinogens cause modifications of N-3 or N-7 positions on purines. This induces an instability in the glucosidic bond between the purine base and deoxyribose, resulting in loss of the base and creation of an a purinic site in DNA. This ‘‘open’’ apurinic site can then be filled by any base.



Purine

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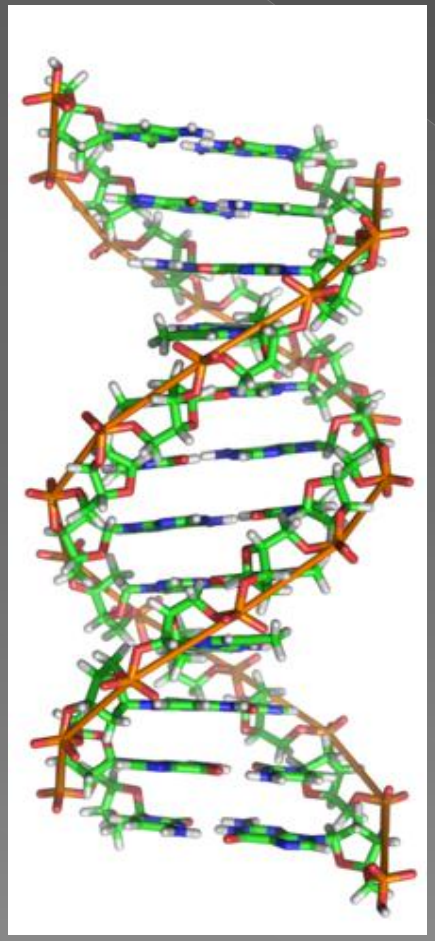
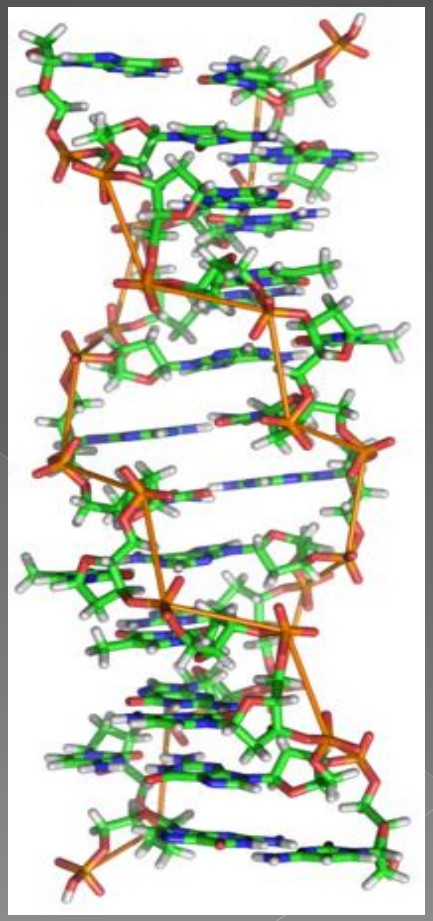
Chemical Carcinogens

Conformational changes in DNA structure



B-Form



Z-Form

Causes of Cancer

Chemical Carcinogens

Interaction of Chemical Carcinogens with Oncogenes and Tumor Suppressor Genes

Carcinogens can activate cellular oncogenes (proto-oncogenes) by a variety of mechanisms:

- Base substitution (point) mutations,
- Chromosomal translocations,
- Gene amplification

Example:

the p53 gene.

high incidence of p53 point mutations in hepatocellular carcinomas in patients from parts of China and south Africa, where exposure to aflatoxin B1 is endemic.

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Chemical Carcinogens

Interaction of Chemical Carcinogens with Oncogenes and Tumor Suppressor Genes

Nickel have been linked to:

DNA hypermethylation

Histone deacetylation

Both of which can alter chromatin structure and cause epigenetic silencing of tumor suppressor Genes

Causes of Cancer

Chemical Carcinogens

Complete carcinogens

(polycyclic aromatic hydrocarbons, nitrosamines, certain aromatic amines, and aflatoxin B1)

- They can cause DNA damage and produce tissue necrosis, which is itself enough to stimulate several rounds of cell proliferation in response to the tissue damage. In this situation, the promotion–progression phases are often collapsed in time, resulting in the production of aneuploid malignant cells.

Causes of Cancer

Endogenous Carcinogenesis

1- An inherent error rate in the fidelity of DNA replication and /or repair could give rise to mutations, some of which by chance could be in key genes involved in regulation of cell proliferation and differentiation.

2- Depurination, this results from breakage of the N-glycosidic bond connecting a purine base to the deoxyribosephosphate backbone of DNA and creates a gap in the base sequence. When DNA polymerase encounters such a gap during DNA replication, it may insert the wrong base.

3- Deamination, by which the amino groups are removed from cytosines.

4- Damage to DNA by oxygen radicals.

Causes of Cancer

Endogenous Carcinogenesis

Oxygen Free radicals

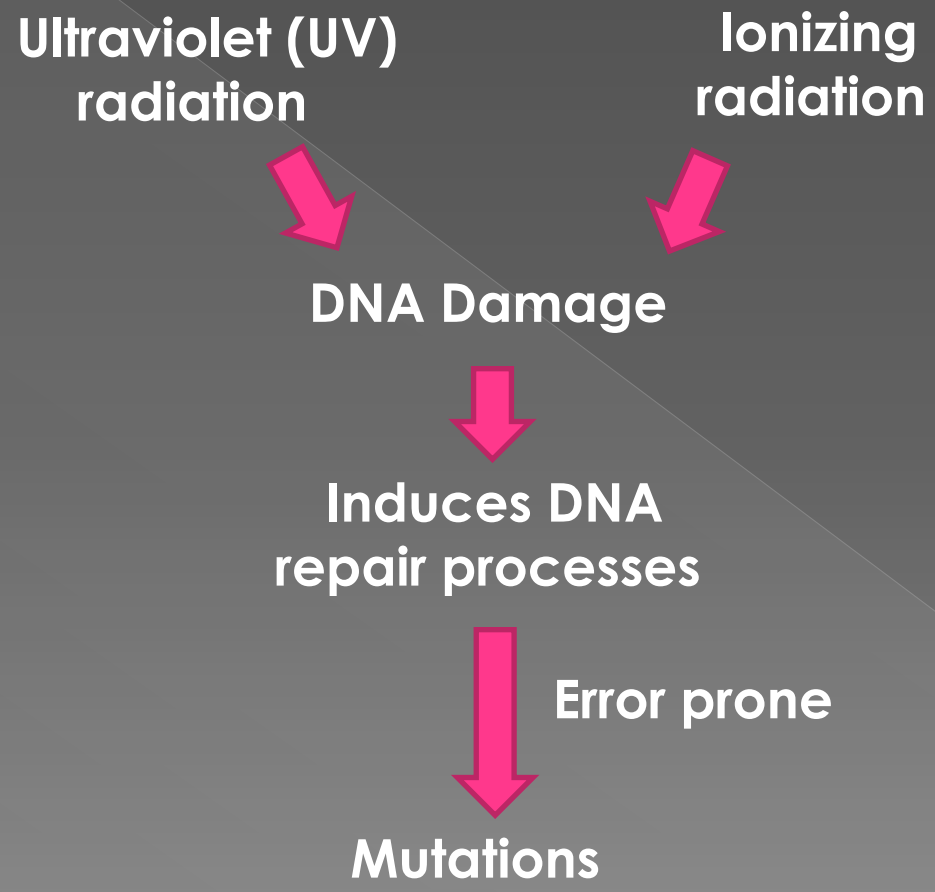
Oxidation products formed during normal metabolic processes in cells include superoxide(O_2), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH).

Damaging DNA and producing mutagenesis.

This may occur in the cell nucleus by an interaction of H_2O_2 with chromatin-bound metals

Causes of Cancer

IRRADIATION CARCINOGENESIS



Causes of Cancer

Viral Carcinogenesis

Onco-viruses can be transmitted through the germline of animal species, and thus these viral genes can be passed from one generation to the next, often in a silent form.

Example: Polyoma viruses

Table 2–4. Examples of Oncogenic Viruses

Virus	Species of Isolation
I. Oncogenic RNA viruses	
A. Acute-acting type*	
Rous sarcoma	Chickens
Fujinami sarcoma	Chickens
Retculoendotheliosis	Chickens and turkeys
Avian erythroblastosis	Chickens
Avian myeloblastosis	Chickens
Avian myelocytomatosis	Chickens
Moloney sarcoma	Mice
Abelson leukemia	Mice
FBJ osteosarcoma	Mice
Harvey/Kirsten sarcoma†	Rat
Rat sarcoma	Rat
Feline sarcoma	Cat
Woolly monkey sarcoma	Woolly monkey
B. Chronic type‡	
Avian leucosis	Chickens
Mouse leukemia**	Mice
Feline leukemia	Cat
Bovine leukemia	Cow
Gibbon ape leukemia††	Gibbon ape
Mouse mammary tumor	Mice
Human T lymphotropic viruses	Human
II. Oncogenic DNA viruses	
A. Papovaviruses	Rabbit, man, dog, cow, and others
Papilloma	Mouse
Polyoma	Monkey
SV40	Human
JC	Human
BK	
B. Adenoviruses	Human,‡‡ monkey, birds, cow
C. Herpes viruses	
Epstein-Barr	Human
Lucke carcinoma	Frog
Marek's disease	Chicken

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Viruses play important roles in the Causation of Human Cancer

Epidemiological data showing a correlation between living in an area of endemic viral infection and a type of cancer

Serological evidence of antibody titers to viral antigens in patients with a given cancer type.

Evidence for insertion of viral DNA into a cancer-bearing host's cell genome.

Evidence for a consistent chromosomal translocation, particularly those involving an oncogene, in virally infected patients.

Data showing that viral infection of cells in culture or transfection of viral genes into cells causes cell transformation and the ability of such cells to produce tumors in nude mice.

Development of cancers of the suspected target organ in transgenic mice produced by embryonic gene transfer of viral genes.

Causes of Cancer

Viruses play important roles in the Causation of Human Cancer

Table 2–5. Human Cancer Viruses and Associated Cancers, Strength of Association, and Necessary Preconditions

Virus	Cancer	Strength of Epidemiologic Association	Required Precondition
HBV	Hepatocellular carcinoma	Strong	None
HTLV-I	T-cell lymphoma	Strong	None
EBV	Burkitt's lymphoma	Strong	Chronic malaria
EBV	High-grade lymphoma	Strong	HIV
HPV	Cervical cancer	Consistent	?None
EBV	Nasopharyngial carcinoma	Inconsistent	—
HSV-2	Cervical cancer	Inconsistent	—

QUESTIONS