

# Neoplasia 2023/24

## lecture 4: Environmental causes of cancer

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# ILOS

- 1. list the main environmental causative agents of cancer.
- 2. understand the difference between direct and indirect acting chemical carcinogens.
- 3. understand the pathogenesis of cancer development due to several etiologic agents.

# Carcinogenesis.. review

- Carcinogenesis, as we discussed in the previous lectures, results from one single clone that acquires certain mutations which allow this clone to proliferate rapidly.
- As the tumor mass grows, extra mutations occur that add certain phenotypes to this mass ( subclones are formed).

- SO: how do these mutations are acquired... what are the etiologic agents that can cause cancer???
- This is the main topic of this lecture.

# Etiology of cancer

- Cancer can be caused by inherited or acquired mutations.
- We will discuss some inherited mutations in the coming lectures: like RB, BRACA ...
- Environmental factors that cause mutations are mainly:
  - Chemicals
  - Radiation
  - infections

# Chemical carcinogenesis

- One of the first cancers linked to chemical carcinogens is scrotal squamous cell carcinoma
- Sir Percival Pott .. A London surgeon noted that scrotal cancer is common in chimney sweeps and he thought it is related to soot exposure.
- Danish chimney sweeps guild ruled that its members bathe daily
- This reduced scrotal cancer.. It is a very successful way to prevent cancer with life style changes ( a daily



So: chemicals can cause cancer

# Chemical carcinogens

- Chemicals cause cancer directly ( **direct** acting agents) or by being converted to a carcinogenic metabolite ( **indirect** acting agents)

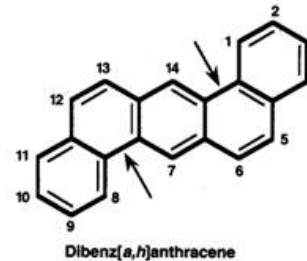
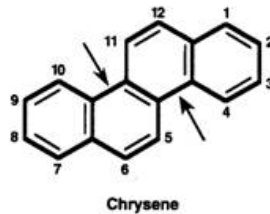
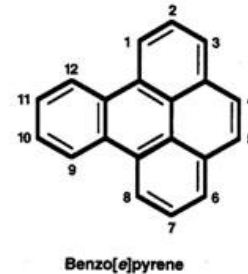
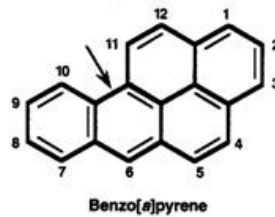
# Direct acting agents

- These are weak carcinogens that don't need metabolic conversion
- Examples: chemotherapy drugs (alkylating agents) can cause cancer, usually leukemia



# Indirect acting agents

- These **need metabolic conversion** to become carcinogenic
- Example: polycyclic hydrocarbons which are present in fossil fuel



# Indirect acting agents

- Benzo (a) pyrene is a polycyclic hydrocarbon present in cigarette smoke and can cause lung cancer
- polycyclic hydrocarbons are also present in smoked meat .Produced from animal fat during broiling meat.
- The main active product in polycyclic hydrocarbons is epoxides
- Epoxides react with DNA, RNA and cellular proteins

# Indirect agents

- **Aromatic amines and azo dyes. Example beta naphthalamine...** increases bladder cancer in workers in the aniline dye and rubber industries.
- **Aflatoxin B** .. Is a naturally occurring agent produced by aspergillus which is a fungus that grows on improperly stored grains and nuts. It increases incidence of hepatocellular carcinoma
- **Nitrites** used as food preservatives can produce nitrosamines which are probably carcinogenic.. Linked to gastric cancer

# Mechanisms of action of chemical agents

- Chemical carcinogens have **reactive electrophile group** that form chemical adducts with DNA, RNA and proteins
- Any gene can be a target for chemicals.. But mostly mutated are RAS and TP53.
- Aflatoxin causes TP53 mutation

- Some chemical carcinogens are augmented by subsequent promoters (hormones, drugs, phenols)
- The promoters are not carcinogenic by themselves .
- Promoter effect has to come after the initiator (tumorigenic substance)
- How do promoters work???? They induce cell proliferation which causes clonal expansion of the mutated cells.. These mutated cells now proliferate and accumulate additional mutations

# CARCINOGENESIS

INITIATION

PROMOTION

TRANSFORMATION

PROGRESSION

Carcinogen

Genetic Change

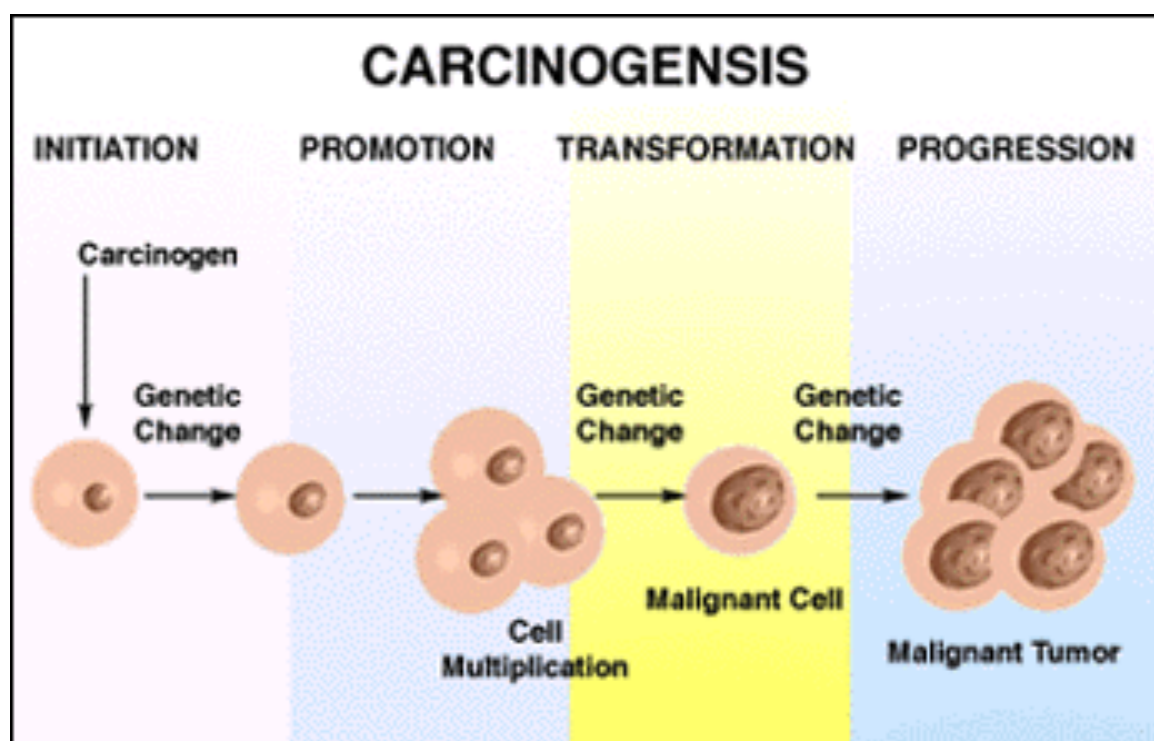
Genetic Change

Genetic Change

Cell  
Multiplication

Malignant Cell

Malignant Tumor



# Radiation carcinogenesis

- Miners of radioactive elements have 10 fold increase of lung cancer
- Survivors of atomic bombs in Hiroshima and Nagasaki .. Have increased incidence of leukemia... latent periods of 7 years. They also have increased risk of thyroid, breast ,colon and lung cancer
- Chernobyl nuclear power accident.. Also increased cancer
- Therapeutic radiotherapy of head and neck can cause papillary thyroid cancer years later

- Ionizing radiation causes chromosomal breakage, translocation and less commonly point mutations
- Ultraviolet radiation causes pyrimidine dimers.. Not repaired in xeroderma pigmentosum causing increased risk of skin cancers
- Non-melanoma skin cancers (squamous cell carcinoma and basal cell carcinoma) are associated with total accumulation of UV exposure
- Melanoma associated with intense intermittent exposure.. Like in sunbathing



# Viral and microbial carcinogens

- Oncogenic RNA viruses: HTLV 1, hepatitis C
- Oncogenic DNA viruses: human papillomavirus , EBV, hepatitis B
- Bacteria: H pylori

# HTLV 1= human T lymphocyte virus 1

- A retrovirus involved in T cell lymphoma/ leukemia
- The virus is endemic in Japan and the Caribbean
- It targets CD 4 T cells
- Transmitted sexually and through blood or breast feeding
- Leukemia develops in 3- 5% of those infected after 20-50 years
- Very latent period.. Suggests multistep process of accumulation of multiple oncogenic mutations

# HPV = human papilloma virus

- There are several types of HPV. Some produce benign warts (benign squamous cell papillomas), others cause cancer
- HPV 16 and 18 cause cancer . 16 and 18 are called high risk HPV
- Cancers associated with HPV:
  1. Squamous cell carcinoma of the cervix and anogenital region
  2. Oropharyngeal and nasopharyngeal carcinoma

# EBV = Epstein Barr virus

- It Causes:

1. Burkitt lymphoma
2. B cell lymphomas especially in people with low immunity and HIV infection
3. Hodgkin lymphoma
4. Nasopharyngeal carcinoma
5. T cell lymphomas
6. Gastric carcinoma
7. Natural killer lymphoma
8. Sarcomas especially in the immunocompromized

# Hepatitis B and C viruses

- 70-85% of hepatocellular carcinomas are associated with B or C

# Helicobacter pylori

- Can cause gastric carcinoma and lymphoma (MALTOMA)
- **H pylori cause cancer by inducing chronic inflammation**
- Sequence: inflammation, atrophy, metaplasia, dysplasia, Cancer
- This sequence needs decades to be completed and it occurs only in 3% of people with H pylori infection
- H pylori also have genes that are tumorigenic like cagA= cytotoxic associated A which simulates growth factors