Epidemiology & Etiology of tumors

Editing File

- ★ Objectives:
- ★ Understand that the incidence of cancer varies with age, race, geographic and genetic factors.
- ★ explain the genetic predisposition to cancer.
- ★ identify the precancerous conditions.
- ★ list the various causes of tumors.

Color Code:

Female's Notes
Male's Notes
Important
Extra

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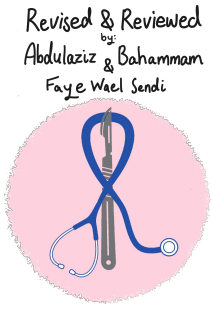
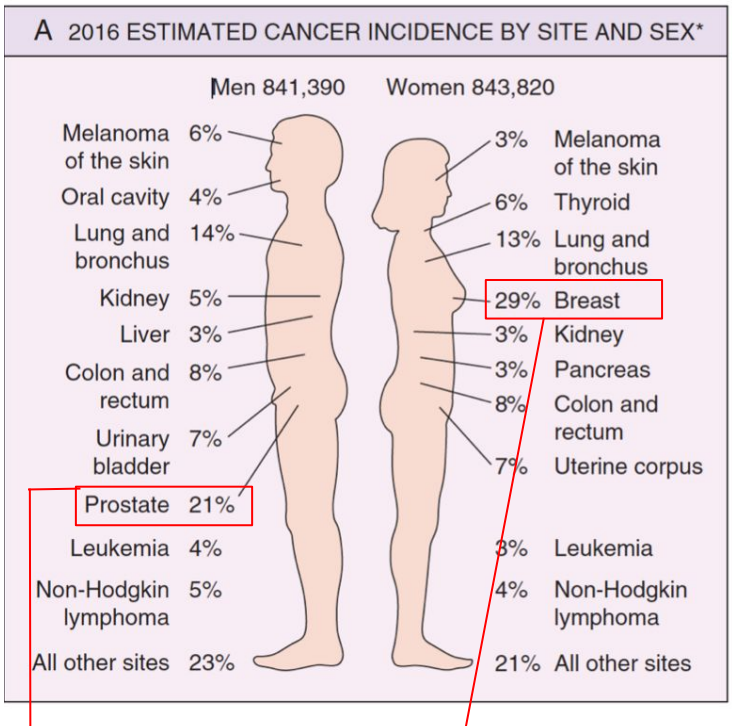
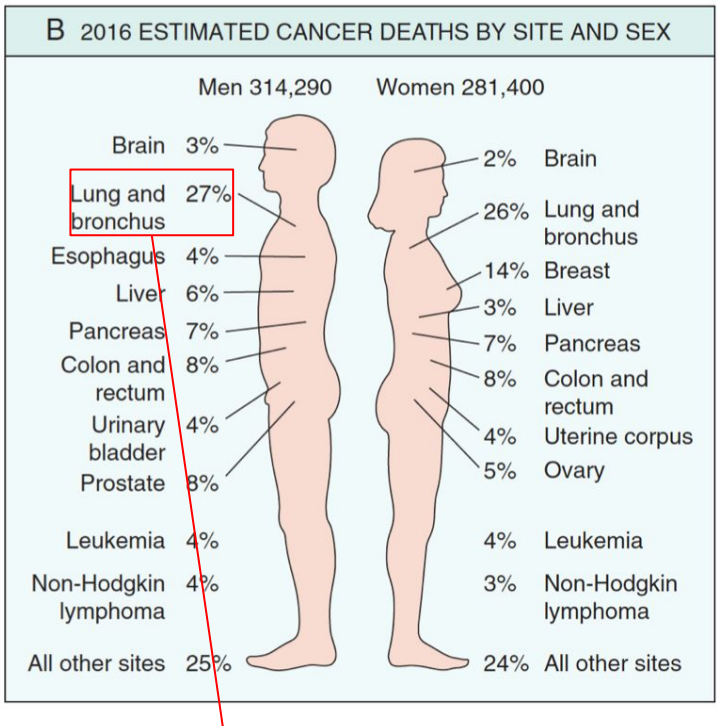


Epidemiology of tumors will aid in:

1st	Know what types of tumors are **common** and what are **rare**
2nd	Develop **screening** methods for **early diagnosis(** E.g. pap smear for cervical cancer - Mammogram for breast cancer)
3rd	Plan **preventive measures**
4th	Discover **etiologic factors**

Cancer incidence





Notes:
*The most common types of cancer in female is breast cancer

*The most common types of cancer in male is prostate cancer

The most fatal disease (lead to death), due to weak symptoms*439

Factors affecting the incidence of cancer:

Geographic

Environmental

Hereditary Factors

Age

Acquired Preneoplastic Conditions

1 Geographic

- ★ The rate of gastric carcinoma in Japan is **7** times its in North America & Europe.
- ★ The rate of breast carcinoma in North America is 5 times its rate in Japan
- ★ Liver cell carcinoma (a.k.a. Hepatocellular carcinoma) is more common in African populations.

Table 6.2 Occupational Cancers

Agents or Groups of Agents	Human Cancers for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung carcinoma, skin carcinoma	By-product of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents; formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung carcinoma	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

2 Environmental

★ Exposure to asbestos

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mesothelioma

★ Smoking

↓

lung carcinoma

★ Multiple sexual partners

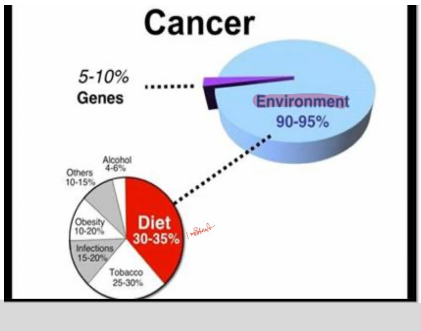
↓

cervical carcinoma

★ Fat-rich diet

↓

colon carcinoma



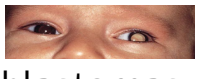
Factors affecting the incidence of cancer:

3 Age

★ Generally, the frequency of cancer **increases** with age
★ Most cancer **mortality** occurs between **55** and **75** years of age and it also **increases** during **childhood**.(elderly and kids)

★ The most **common** malignant tumors in **children** are:
- Leukemia, No.1 most common
- CNS tumors, most common Solid organ tumor
- Lymphomas
- Soft tissue & bone sarcomas.

4 Hereditary Factors

Autosomal **dominant** cancer syndromes	Autosomal **recessive** syndromes of defective DNA repair	Familial cancers of **uncertain** inheritance
Several well-defined cancers in which inheritance of a **single mutant gene** greatly increases the risk of developing a tumor.	A group of rare autosomal recessive disorders is collectively characterized by **chromosomal** or **DNA instability** and high rates of certain cancers. 439(Gene responsible for repair may be mutated)	All the common types of cancers occur in familial forms where the **pattern of inheritance is unclear**.
Example: 1-**Retinoblastoma***(malignant cancer of eye) in children:  · 40% of retinoblastomas are familial in nature. · Carriers of this mutation have 10000 fold increase in the risk of developing retinoblastoma 2-**multiple endocrine neoplasia.** (MEN syndrome	Example: **xeroderma pigmentosum**	unique Features: · They start at early age · They are multiple or bilateral (affecting both sides of an organ e.g. both lungs) · They occur in two or more relatives
		Example: **breast, colon, ovary, brain**.

Factors affecting the incidence of cancer:

Hereditary Factors

Table 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links

Acquired Preneoplastic Conditions

5

*Preneoplastic=تزيد العرضة

★ They **predispose** to cancer

-Dysplastic bronchial mucosa in smokers → lung carcinoma
-Liver cirrhosis(تليف الكبد) → liver cell carcinoma
-Margins of chronic skin fistulae. → squamous cell carcinoma
-Endometrial hyperplasia. → endometrial carcinoma
-Leukoplakia of the oral cavity, vulva or penis. → squamous cell carcinoma
-Villous adenoma of the colon or rectum. → colorectal adenocarcinoma.

Chemical Carcinogens

Certain chemicals have been found to cause cancer in humans.
These chemical carcinogens can be natural or synthetic

They can cause cellular damage by two ways :

Direct-acting agents

They **require no metabolic conversion** to become carcinogenic

They are in general **weak carcinogens** but are important because some of them are cancer chemotherapy drugs for example : alkylating agents.

alkylating agents used in regimens that may cure certain types of cancer (e.g., Hodgkin lymphoma), only to evoke a subsequent, second form of cancer.

Procarcinogen → Metabolise → Carcinogenic
لوحده ما يسبب سرطان Procarcinogen

Indirect-acting agents

They **require metabolic conversion** of the chemical compound (procarcinogen) to active & carcinogenic products (ultimate carcinogen).

Examples :
benzo(a)pyrene, aromatic amines, azo dyes & Aflatoxin B1

·benzo(a)pyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking.

·These products are implicated in the causation of lung cancer in cigarette smokers.

·Polymorphisms of endogenous enzymes such as cytochrome P-450 may influence carcinogenesis.

Mechanisms of action

1. Most chemical carcinogens are **mutagenic** (cause genetic mutations) .
2. The commonly mutated oncogenes & tumor suppressors are RAS and TP53.
   Oncogenes : جينات تكون الطفرات فيها سببا لظهور خلية سرطانية
   Tumor suppressors : جينات تنظم انقسام الخلية وتمنع تحولها الى خلية سرطانية
3. All direct chemical carcinogens & ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms.
4. They react with the electron rich atoms in the RNA, DNA & other cellular proteins.

Examples for Chemical Carcinogens

1) Alkylating agents :

2) Polycyclic hydrocarbons :

- Cigarette smoking
- Animal fats during broiling meats
- Smoked meats & fish

3) Aromatic amines & azo dyes :

B-naphthylamine cause bladder cancer in rubber industries & aniline dye.
Some azo dyes, used to color food, cause bladder cancer.

Food dyes

4) Nitrosamines & nitrosamides :

Are preservatives & cause gastric carcinoma.
Alfatoxin B1, produced by Aspergillus which grow on improperly stored grains, causes hepatocellular carcinoma

Aspergillus which grow on corn

Table 6.5 Major Chemical Carcinogens

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone Dimethyl sulfate Diepoxybutane Anti-cancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz(*a*)anthracene Benzo(*a*)pyrene Dibenz(*a,h*)anthracene 3-Methylcholanthrene 7, 12-Dimethylbenz(*a*)anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine) Benzidine 2-Acetylaminofluorene Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1 Griseofulvin Cycasin Safrole Betel nuts
Others
Nitrosamine and amides Vinyl chloride, nickel, chromium Insecticides, fungicides Polychlorinated biphenyls

Other Chemical Carcinogens

Radiation

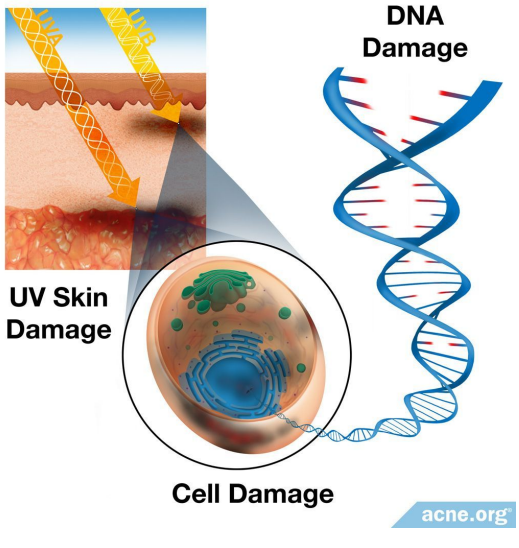
1. Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen.

2. Radiation has mutagenic effects: chromosomes breakage, translocations & point mutations.

3. UV rays of sunlight cause skin cancers: melanoma, squamous cell carcinoma & basal cell carcinoma.

4. It is capable of DNA damage & mutations of p53 tumor suppressor gene.

5. When extensive exposure to UV rays occurs, the repair system is overwhelmed → skin cancer.



Melanoma

Still looking to this Meme ?
Go and finish this Lecture !

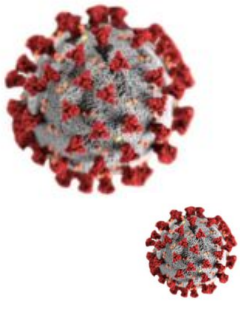
Viral & Microbial Oncogenes

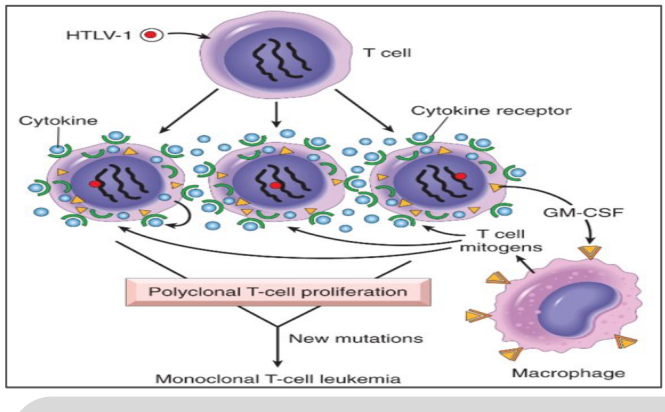
Viral and microbial oncogenes include:	RNA viruses	DNA viruses	Other microorganisms e.g. H. Pylori bacteria

Host cells have endogenous gene to maintain a normal cell cycle.
Oncogene viruses induce cellular proliferation, mimic or block cellular signals necessary for the cell cycle regulation.

A) RNA oncogenic viruses:

- Human T cell lymphotropic virus-1 (HTLV-1), a retrovirus, infects & transforms T-lymphocytes.
- It causes T-Cell leukemia/Lymphoma after a prolonged latent period (20-30 years).
- It is endemic in Japan & the Caribbean
- It is transmitted like HIV but only 1% of infected patients develop T Cell leukemia/Lymphoma.
- No cure or vaccine to HTLV-1.
- Treatment: chemotherapy with common relapses





HTLV-1 Infection

B) DNA oncogenic viruses:

DNA viruses form stable associations with hosts DNA, thus the transcribed viral DNA transforms the host cells.

Examples	Human papillomavirus (HPV)	Epstein Barr virus (EBV)	Hepatitis B virus (HBV)	Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8])

c) HIV Infection:

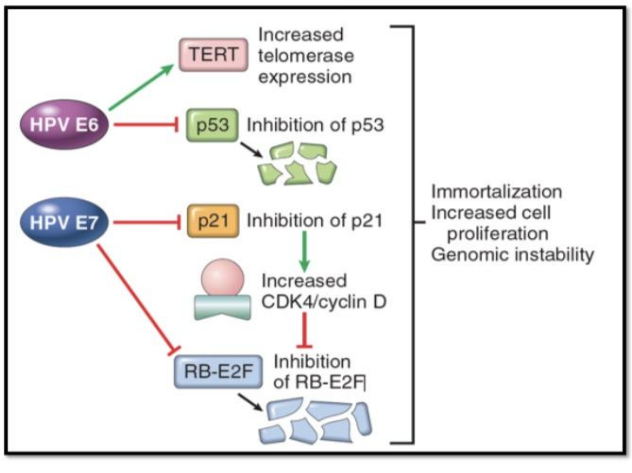
- Has More than 70 serotypes.
- It is a sexually transmitted.
- It causes benign warts, squamous cell carcinoma of the cervix, anogenital region, mouth & larynx.
- HPV types 6 and 11: Genital warts (low risk)
- HPV types 16, 18, 31: (high risk) (they cause carcinoma)
  - 85% of cervical carcinomas are caused by HPV 16 or 18
  - High risk HPV types integrates with the host's DNA
- HPV infection alone is not sufficient to cause carcinoma and other factors also contribute to the development of cervical carcinoma e.g.
  - cigarette smoking
  - coexisting infections
  - hormonal changes

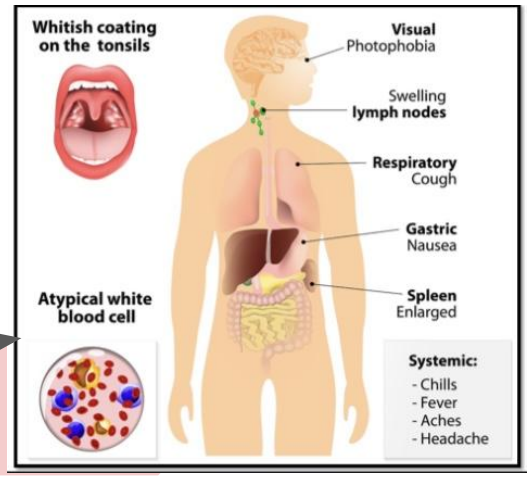
HIV INFECTION: (types 18-16)

1st The oncogenic potential of HPV 16 and 18 can be related to products of two early viral genes, E6 and E7

2nd E7 protein binds to Rb tumor suppressor and releases the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle.

3rd E6 protein binds to p53 & facilitates its degradation.





D) EBV infection:

1. It is a common virus worldwide

2. -It infects B lymphocytes & epithelial cells of the nasopharynx
-It causes B lymphocyte cellular proliferation.

3. It causes several malignant tumors e.g.
- Burkitt's Lymphoma(most common)
- B-cell lymphoma in immunosuppressed
-Nasopharyngeal carcinoma

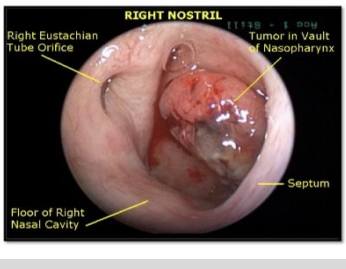
4. It causes infectious mononucleosis

5. -Nasopharyngeal carcinoma is a malignant neoplasm arising from the nasopharygeal epithelium.
- It is endemic in South China and parts of Africa
- 100% of cases contain EBV genome in these endemic areas

6. EBV causes Burkitt's Lymphoma, a highly malignant B-cell tumor, most common childhood tumor in Africa,All cases have t(8:14) genetic mutation

t(8;14)= genetic translocation

7. -EBV causes B lymphocyte cellular proliferation.
-It causes loss of growth regulation
It predisposes the cells to genetic mutations, especially t(8:14).

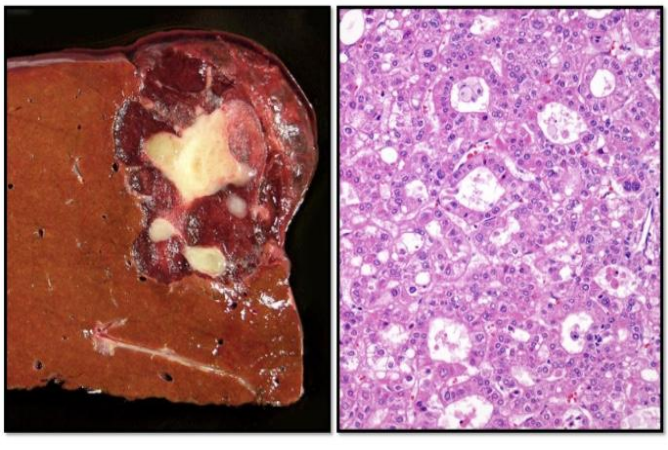


E) HBV infection:

HBV infection has a strong association with liver cell carcinoma (HCC).

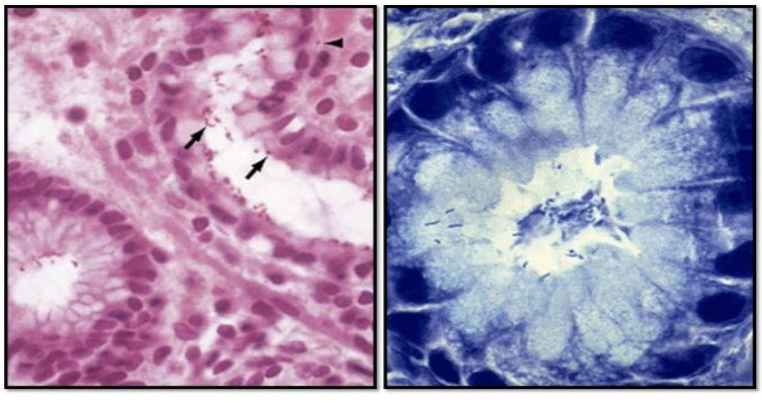
HBV infection incurs up to 200-fold risk of HCC.

It is present world-wide, but most commonly in the far East & Africa



F) Helicobacter Pylori bacteria:

- It is bacteria that infects the stomach
- It causes:
  - Peptic ulcers
  - Gastric lymphoma (Mucosal Associated Lymphoid Tumor (MALT)
  - Gastric carcinoma



1	Which one causes infectious mononucleosis?			
	A	HBV	B	HIV
	C	HTLV-1	D	EBV
2	85% of cervical carcinomas are caused by:			
	A	HIV type 6 or 11	B	HIV type 16 or 18
	C	HBV	D	HIV type 31
3	Which of the following chemical carcinogens require no metabolic conversion to become carcinogenic ?			
	A	Direct-acting agents	B	Indirect-acting agents
	C	Semi-acting agents	D	None of them

Answers: 1-D, 2-B, 3-A

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