جامعة الملك سعود
King Saud University

pathology
MED 439

MED439
KING SAUD UNIVERSITY

Epidemiology & Etiology of tumors

Objectives:

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

Color Index:
Slides
Important
Male's slides only
Female's slides only
Notes
Extra information

Epidemiology of tumors will aid in:

- Know what types of tumors are common and what are rare
- Develop screening methods for early diagnosis E.g.
  - -pap smear for cervical cancer
  - -Mammogram for breast cancer
- Plan preventive measures
- Knowing Risk Factors
- Discover etiologic factors

Cancer incidence

Factors affecting the incidence of cancer:
(each point will be explained in details)

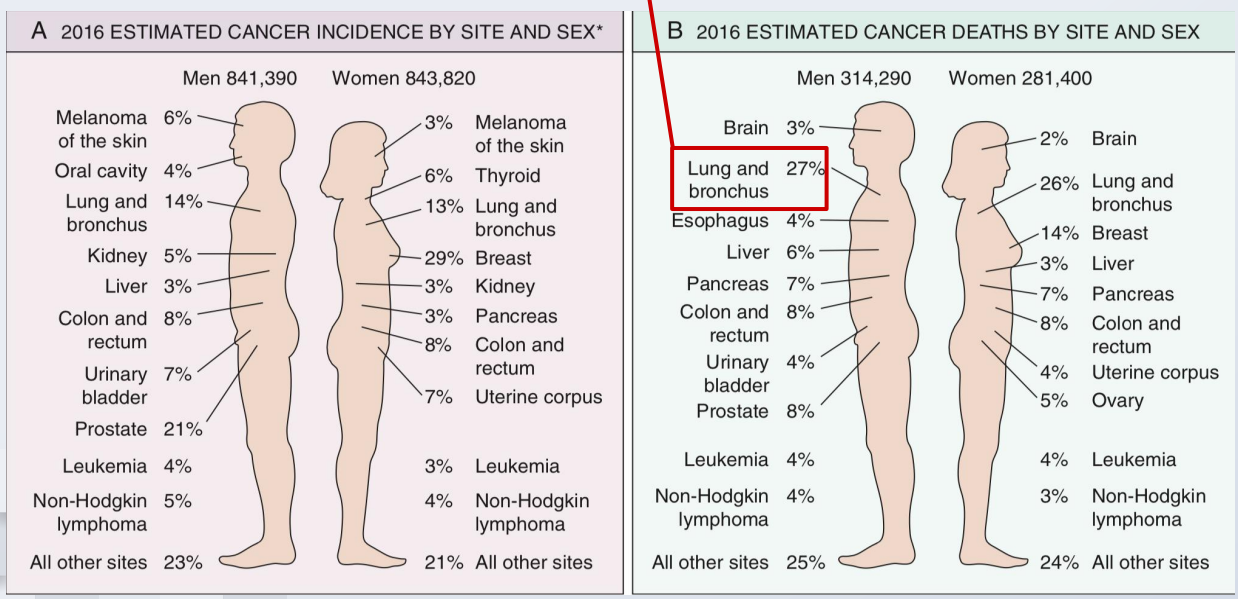
1- Geographic and environmental factors

2- Hereditary factors

3- Age

4- Acquired preneoplastic conditions

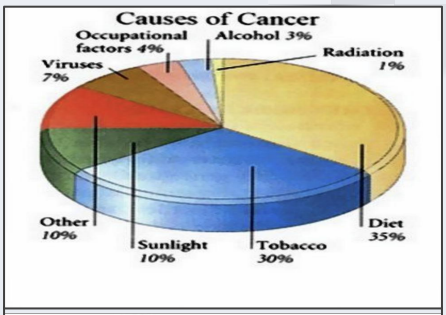
The most fatal disease (lead to death), due to weak symptoms.

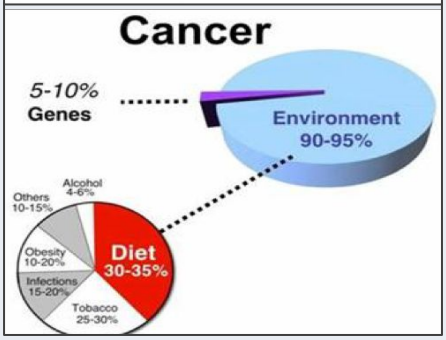


Female: Picture not important

Factors affecting the incidence of cancer:

1- Geographic and environmental factors





*Used as insulator for buildings, no longer used because of toxicity

Geographic

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

Environmental

- Exposure to asbestos* → mesothelioma
- Smoking → lung carcinoma
- Multiple sexual partners → cervical carcinoma
- Fat-rich diet → colon carcinoma

Table 6.2 Occupational Cancers From female Slides, "please see table 6-3 for occupational cancer"

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

Factors affecting the incidence of cancer:

2- Hereditary Factors

*Inherited Cancer Syndromes: **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. 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*** 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.

*__Retinoblastoma:__ a malignant cancer of the eye (nomenclature exception)
It requires **one inherited Mutant gene,** and another developing mutant gene **(2 Hits)**

From female slides, 'please see table 6-4 for more examples"

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

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. (has 2 peaks)

- 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.

Factors affecting the incidence of cancer:

4- Acquired Preneoplastic Conditions

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

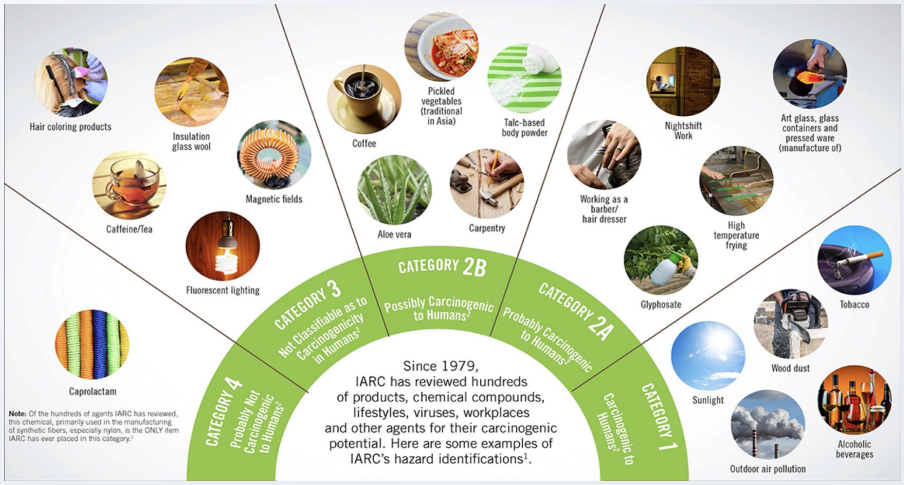
-Villous adenoma of the colon or rectum → colorectal adenocarcinoma

Etiology of Tumors

Classes of carcinogenic* agents:

*causes cancer

1. Radiant energy
2. Chemicals
3. Microbial agents



Female Dr: picture not important

1- Radiation

Radiation has mutagenic effects:

- chromosomes breakage
- translocations
- point mutations.

Its sources :

- UV rays of sunlight
- X-rays
- nuclear fission
- radionuclides

is an established carcinogen.

UV rays of sunlight

1. It causes skin cancers: melanoma, squamous cell carcinoma & basal cell carcinoma.
2. It is capable of DNA damage & mutations of p53 tumor suppressor gene.
3. When extensive exposure to UV rays occurs, the repair system is overwhelmed à skin cancer.

2- Chemical Carcinogens

Chemical carcinogens can be :

Natural or synthetic.

They can cause cellular damage via :

Direct-acting agents	Indirect-acting agents
• They don't require metabolic conversion to become carcinogenic. • general weak carcinogens but are important because some of them are cancer chemotherapy drugs, which treat cancer but may cause it (e.g. alkylating agents).	• They require metabolic conversion of the chemical compound (*procarcinogen*) to active & carcinogenic products (ultimate carcinogen). Safe by themselves, but when converted become carcinogens • e.g. benzo(a)pyrene, aromatic amines, azo dyes & Aflatoxin B1.

Mechanisms of action:

- Most chemical carcinogens are mutagenic i.e. cause genetic mutations -the commonly mutated oncogenes & tumor suppressors are RAS and TP53.
- All direct chemical carcinogens & ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms.
- They react with the electron rich atoms in the RNA, DNA & other cellular proteins.

Chemical Carcinogens examples:

Alkylating agents	Polycyclic hydrocarbons
- chemotherapy.	- Cigarette smoking - Animal fats during broiling meats - Smoked meats & fish

Aromatic amines & azo dyes

- B-naphthylamine cause bladder cancer in rubber industries & aniline dye.
- Some azo dyes, used to color food, cause bladder cancer.
- Nitrosamines & nitrosamides are used are preservatives & cause gastric carcinoma. Found in pickled food.
- Alfatoxin B1, produced by Aspergillus (fungus) which grow on improperly stored grains, it causes hepatocellular carcinoma. Found in some badly stored nuts.

2- Chemical Carcinogens cont.

Table 6.5 Major Chemical Carcinogens From Female slides

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

3- Viral & microbial oncogenes

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

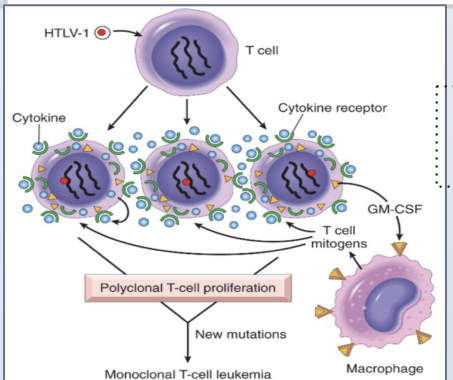
Viral & microbial oncogenes include:

- RNA viruses
- DNA viruses
- Other microorganisms e.g. H. pylori bacteria

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

A. Viral Oncogenes

Genome	Viruses	
RNA not common	**HTLV-1** Human T cell *lymphotropic* virus-1.	• Retrovirus, infects & transforms **T cells** • Has Long latent period (20-30 years) • Causes T-cell leukemia/Lymphoma • Transmitted like HIV (STD through body fluid), but only 1% of infected develop T-Cell leukemia/ lymphoma. • No cure or vaccine • **Treatment**: chemotherapy with common relapses • Endemic* in Japan & the caribbean



*regularly found among particular people or in a certain area

*warts are squamous cell papilloma

DNA
More common

HPV Human papilloma virus	• More than 70 serotypes • Sexually transmitted (STD) • Double stranded DNA • Infects squamous epithelium • Causes benign warts, squamous cell carcinoma of the cervix, anogenital region, mouth & larynx & Vulva (anywhere with squamous epithelium) • HPV alone isn't sufficient to cause carcinoma, it contributes with many factors to cause cervical carcinoma, e.g. : cigarette smoking, coexisting infections, hormonal changes	**Types 6 & 11 :** - Low risk - cause genital or oral warts* - **benign** **Types 16, 18, 31:** - High risk HPV types integrates with host's DNA - 85% of cervical carcinoma are caused by HPV 16 or 18 - causes cancer - **malignant**
EBV Epstein Barr virus	• Common virus worldwide . • Infects B-cells & epithelial cells of nasopharynx. • Causes infectious mononucleosis (Flu like symptoms, benign) • Causes B lymphocyte cellular proliferation • Causes loss of growth regulation • Predisposes the cells to genetic mutations, especially t(8:14). (Translocation)	
HBV Hepatitis B virus	• Ds DNA, most contagious virus • Easily transmitted (body fluids, sexually) • Causes liver cirrhosis • Has a strong association with liver cell carcinoma (HCC) • present worldwide, but commonly in the far East & Africa. • HBV infection Incurs up to 200-fold risk of HCC	

HHV-8 (Human herpesvirus-8) Also called **KSHV** (Kaposi sarcoma herpes virus) Causes Kaposi sarcoma in AIDS patients

E = Exon
****NOTE:** We switched E6&E7 Roles based on Robbins, it was mostly a typo in the original slides

HPV types: (16 & 18):

1. The oncogenic potential of **HPV 16 & 18** can be related to products of two early viral genes, **E6 & E7,** HPV 16 & 18 causes over-expression of these viral genes.
2. **E7**** protein binds to **Rb** *tumor suppressor*, replaces normal transcription factors **(E2F)** and decreases Rb synthesis. It promotes progression through cell cycle
3. **E6**** protein binds to **p53** (gate keeper) & facilitates its degradation (causing uncontrollable cell cycle)

Fem Dr. Explanation: normally, Rb is linked with E2F, when E6 protein comes it displaces E2F from Rb, which promotes cell cycle

Malignant Tumors caused by **EBV**

Nasopharyngeal carcinoma:
- Malignant neoplasm arising from the nasopharygeal epithelium.
- Endemic in South china & parts of Africa
- 100% of cases have EBV genome

Burkitt's lymphoma:
- Highly malignant B-cell tumor.
-Rare sporadic* cases occur worldwide
- Most common childhood tumor in Africa
- All cases have t(8:14) mutation

*occurring at irregular intervals or only in a few places.

B-cell Lymphoma in immunosuppressed

B. Microbial oncogenes

Helicobacter pylori bacteria (H. Pylori)	• Infects & lives in the stomach (antrum of stomach) • It can cause : **peptic ulcers , Gastric lymphoma (** mucosal associated Lymphoid tumor MALT **), Gastric carcinoma and adenocarcinoma**

MCQs

1- Which one is an RNA oncogene virus ?			
a- HPV	B- EBV	C- HTLV-1	D- HBV
2- Which one causes infectious mononucleosis ?			
A- HPV	B- EBV	C- H.Pylori bacteria	D- HBV
3- Where is liver cell carcinoma more common ?			
A- Africa	B- North America	C- Japan	D- Europe
4- What is the most common malignant tumor in children ?			
A- CNS tumors	B- Lymphomas	C- Leukemia	D- soft tissue
5-Which one is the most important example of direct acting agents?			
A- Alkylating	B- Azo dye	C- Aromatic amine	D- Alfatoxin B1
6-Which one is caused by alfatoxin B1?			
A- Liver carcinoma	B- H.C.C	C- Bladder cancer	D- Both A&B

MCQ: 1-C 2-B 3-A 4-C 5-A 6-D

SAQs

1- List the factors that contribute with HPV to the development of cervical carcinoma .

2- Give two examples of Autosomal *dominant* cancer syndromes.

3- Give 3 examples of indirect-acting agents.

SAQ:
1. slide 19
2. Slide 5
3. Slide 8

- غادة العثمان

- البندري العنزي
- بنان القاضي
- رغد خالد سويعد
- رغد العسيري
- روان باقادر
- ريناد الحميدي
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