Pathology

Subject :

Lec no :   lec-23-

Done By :   Hala AL Beshtawe

NEOPLASIA

EPIDEMIOLOGY of CANCER

-The branch of medicine deals with the incidence and prevalence of disease in large populations and with detection of the source and cause of epidemics.

- Contributes substantially to the knowledge about the origin of cancer.

-The concept that **cigarette smoking is** causally associated with **lung cancer** arose from epidemiologic studies.

CANCER INCIDENCE:

❑ Worldwide Problem
❑ Increasing
❑ Due to genetic mutations in cells, which may be spontaneous or environmentally induced.

A 2016 ESTIMATED CANCER INCIDENCE BY SITE AND SEX*

Men 841,390   Women 843,820

Men		Women	
Melanoma of the skin	6%	3%	Melanoma of the skin
Oral cavity	4%	6%	Thyroid
Lung and bronchus	14%	13%	Lung and bronchus
Kidney	5%	29%	Breast
Liver	3%	3%	Kidney
Colon and rectum	8%	3%	Pancreas
		8%	Colon and rectum
Urinary bladder	7%	7%	Uterine corpus
Prostate	21%		
Leukemia	4%	3%	Leukemia
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
All other sites	23%	21%	All other sites

B 2016 ESTIMATED CANCER DEATHS BY SITE AND SEX

Men 314,290   Women 281,400

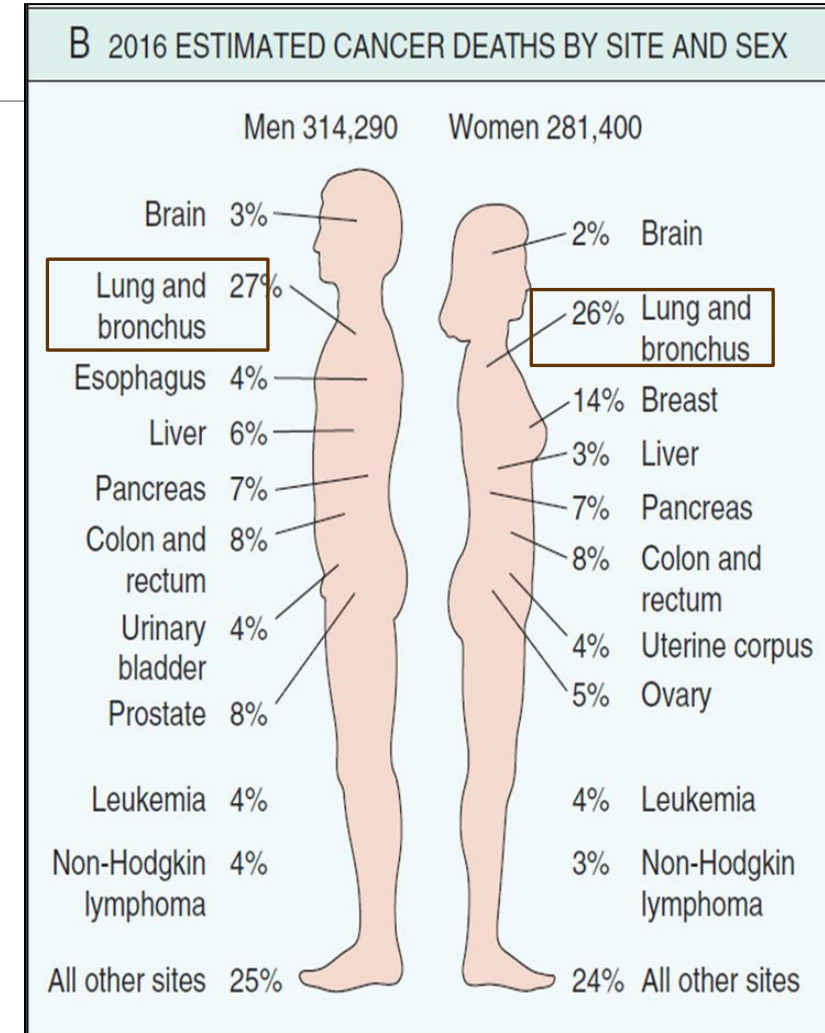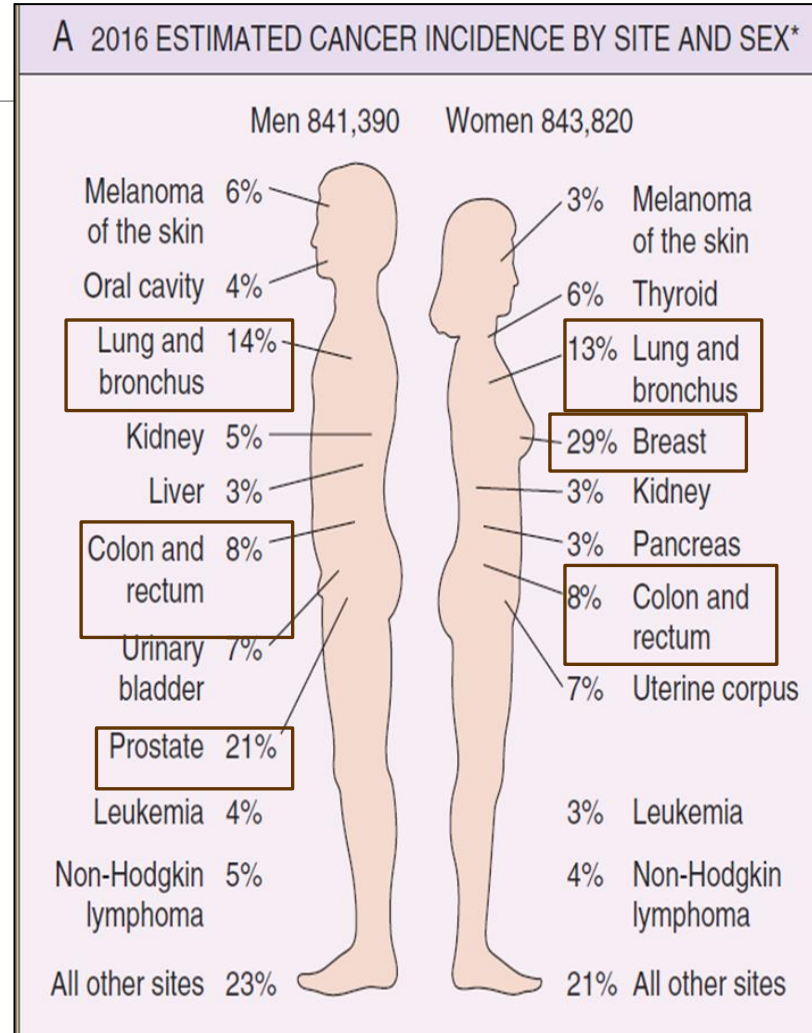| Men		Women	
Brain	3%	2%	Brain
Lung and bronchus	27%	26%	Lung and bronchus
Esophagus	4%	14%	Breast
Liver	6%	3%	Liver
Pancreas	7%	7%	Pancreas
Colon and rectum	8%	8%	Colon and rectum
Urinary bladder	4%	4%	Uterine corpus
Prostate	8%	5%	Ovary
Leukemia	4%	4%	Leukemia
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
All other sites	25%	24%	All other sites

Table (7) Ten most common cancers among Jordanians, Males, 2014

Rank	Site	Frequency	Percent
1	Colorectal	371	13.6
2	Lung	326	12.0
3	Urinary Bladder	244	9.0
4	Prostate	229	8.4
5	Non-Hodgkin lymphoma	153	5.6
6	Leukemia	129	4.7
7	Hodgkin disease	113	4.2
8	Stomach	99	3.6
9	Kidney	93	3.4
10	Larynx	85	3.1

JORDAN CANCER REGISTRY

Table (8) Ten most common cancers among Jordanian Females , 2014

Rank	Site	Frequency	Percent
1	Breast	1174	39.4
2	Colorectal	287	9.6
3	Thyroid	173	5.8
4	Uterous	161	5.4
5	Non-Hodgkin lymphoma	121	4.1
6	Ovary	88	3.0
7	Hodgkin disease	78	2.6
8	Lung	77	2.6
9	Leukemia	66	2.2
10	Brain, Nervous system	60	2.0

WHAT FACTORS may influence the incidence of cancer?

Incidence may be related to:

1. Geographic and Environmental factors.

2. Age.

3. Hereditary factors.

4. Acquired predisposing factors.

النوع الحيبي مسؤول عن اختلاف الاستجابه للطوى البيه الواحده قابليه

Genetic polymorphism is responsible for:

❖ Individual predisposition to disease

❖ Individual response to environmental agents

❖ Individual response to drugs

1. Geographic & environment (Multifactorial)

هذه الاملاحظات مرتبطة بالبيئة، العوامل الموجودة بها

-Environmental factors are the predominant determinant of the most common sporadic cancers

- **Prostatic CA ---- High in USA**

- **Colorectal CA ----High in USA**

- **Breast CA ---- High in USA**

> **Nearly all the evidence indicates that these geographic differences are environmental rather than genetic in origin.**

- **Gastric CA ---High in Japan**

- **Skin CA----High in New Zealand**

- **Hepatocellular CA --- High in Africa & China**

- **Nasopharyngeal CA --- Far East**

- **Burkitt Lymphoma --- Africa**

Environment:

-In the workplace, in food, and in personal practices.
-They can be as universal as sunlight or be largely restricted to urban settings (e.g., asbestos) or particular occupations

- Diet
- Obesity/Overweight الاشعاعة الاستوسى
- Occupation (asbestos, radon....)
- Sunlight
- Personal habits (smoking and alcohol consumption).
- Reproductive history (age at first sexual intercourse and the number of sex partners)
- **Infectious** agents (cause **~15% of cancers worldwide**)

2.Age:

- In general, cancer incidence increases with AGE

- The rising incidence with age may be explained by:

  1. The accumulation of somatic mutations associated with the emergence of malignant neoplasms
  2. The decline in immune competence that accompanies aging.

- However, certain cancers occur more in children:

1. Acute Leukemia

2. Some Lymphomas

3. Some CNS Tumors

4. Blastomas → retenoplastoma

→ Nephro plastoma

3. Heredity (5%-10% of cancers are familial)

موروث

very Imp

Table 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	يورث شكل سائد
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	يورث شكل متنحي
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

A. Inherited AD Cancer Syndromes:

Autosomal dominant

White tumor in the retina of the eyeball (gross view).
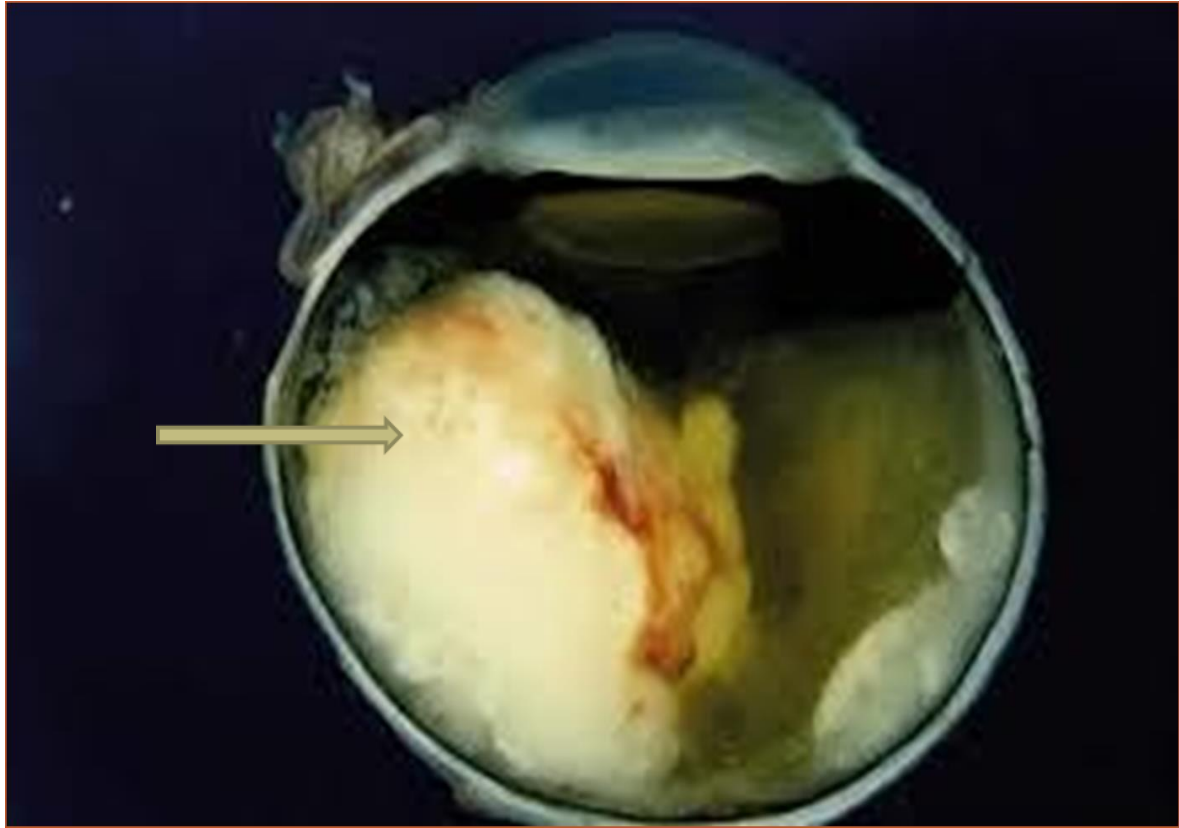
Retinoblastoma (malignant tumor) in the right eye of a child, is seen as a white patch.

*Inherited

Gross view of **familial polyposis coli (FAP),** the colon is studded with hundreds of mucosal polyps.

Endoscopic view of **familial polyposis coli (FAP)** showing numerous mucosal adenomatous polyps of the colon .
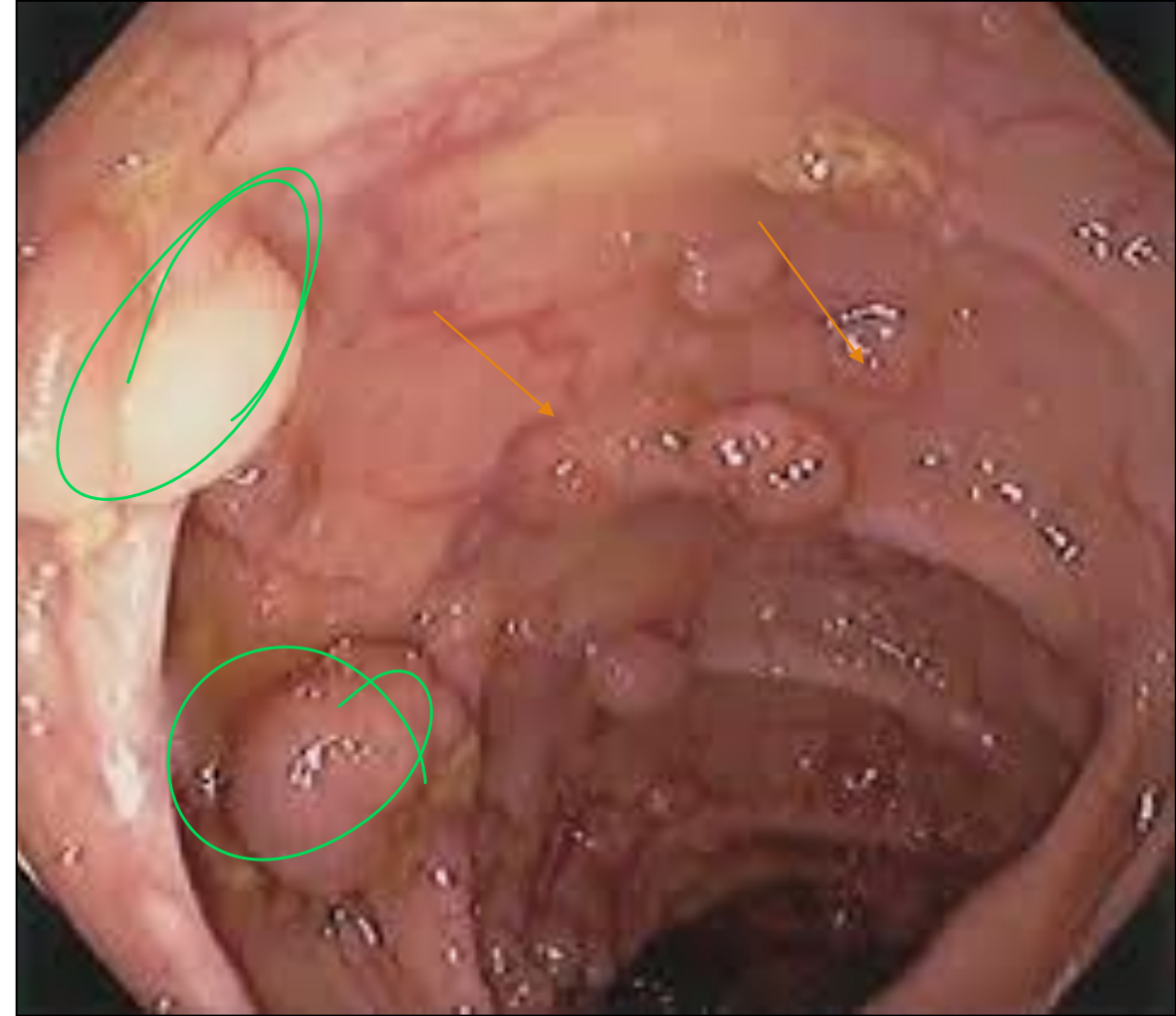
- **Neurofibromatosis** is an autosomal dominant hereditary neoplastic disease.
- Hundreds of neurofibromas with café aulait pigmentation of the skin

Neural
Fibrus
benign

© Jere Mammino, DO

Autosomal recessive

B. AR syndromes of Defective DNA Repair:

defect in DNA repair gene بتكون عندهم

1.Xeroderma Pigmentosum

شريحه التعرض لل

- Great predisposition to skin cancers, including (basal C. Ca, squamous C. Ca, & malignant melanoma) in sun-exposed areas like the face, hands & feet.
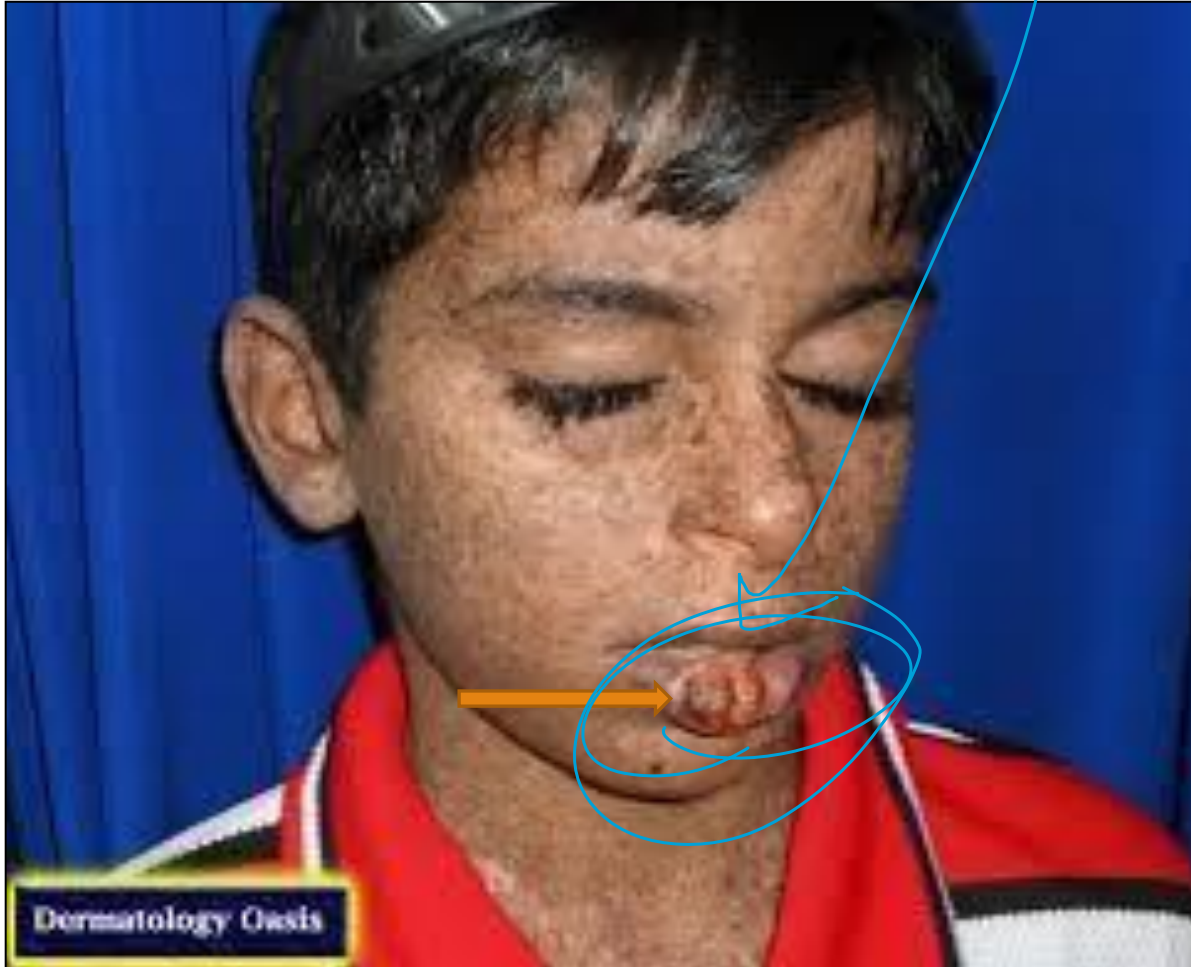
2. Ataxia Telangiectasia
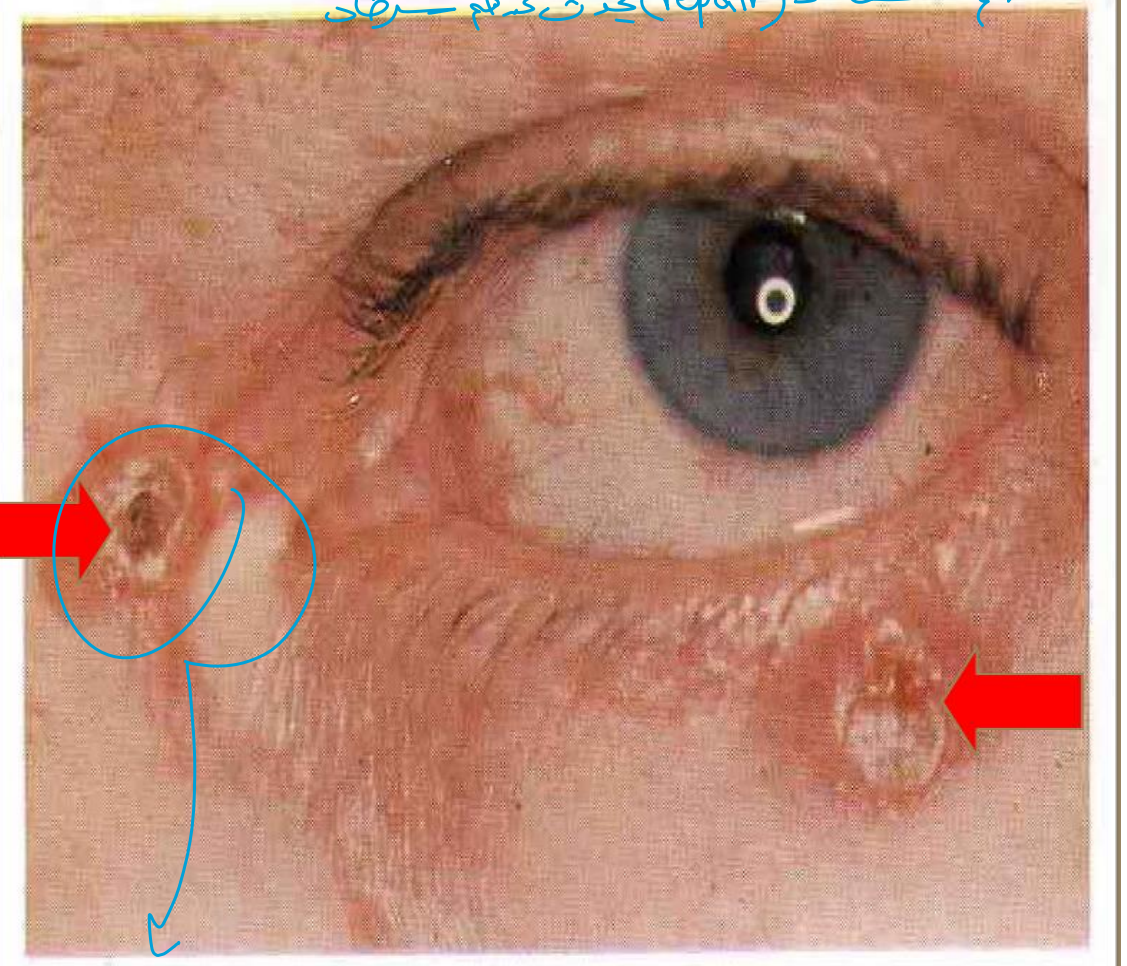
3. Bloom Syndrome

4. Fanconi Anemia.

فقط حفظ بس ما يعرض للامراض

Autosomal recessive syndrome

A child with XERODERMA PIGMENTOSUM
, a recessively inherited disease, there are hundreds of pigmented nevi in the skin with squamous cell carcinoma in the lower lip of a young boy.

Dermatology Oasis

→ defect in the DNA → UV-light عندما يتعرض الشخص لأشعة الشمس و لا يحصل مشكلة (repair) يحدث عنده — ظهور

14.23 Basal cell carcinoma ('rodent ulcer')

C. Familial cancers with no specific phenotype

- Evident familial clustering of cancer, but the role of inherited predisposition is not clear.

- There is a familial predisposition to:

- CA of COLON

- CA of BREAST (Not linked to BRCA1 or BRACA2)

- CA of OVARY

- **Younger age groups**
- **Multiple or bilateral** → left right } Breast Cancerus هذا تکون المرأة تعانی من
- **Two or more family members are affected.**
- **The transmission pattern of familial cancers is not clear.**
- **In general, relatives have a relative risk between 2 & 3**

4. Acquired predisposing conditions

(handwritten annotations: Inflammation; drop in the immunity; يحدث معهم تجدث; ظروف مكتسبة ان)

- These are associated with increased risk for CA and most are related to rapid or abnormal cell proliferation due to either:
  - **Chronic inflammation**
  - **Immunodeficiency states**
  - **Precursor lesions**

benign tumor تعتبر احسن من tumor

هل كل ورم حميد سيتحول إلى حسم؟ (لا كلا)

❑ Are benign tumors precancerous?

- In general, the answer is **no**, but there are exceptions
- It is better to say that each benign tumor is associated with a particular risk, ranging from high to virtually nonexistent.

- **For example, large colon villous adenoma can undergo malignant transformation.**

However, the leiomyomata of the uterus do not transform into malignancy.

Smooth muscle cancer in uterus

Acquired Preneoplastic Disorders:

ماقبل الورم

↑ Cancer risk & mutations عشوائي مؤدي ⟶ ↓ LI/S proliferation & regeneration ↓; كل ᴛᴏ

(1) Persistent regenerative cell replication:

- e.g.: - Hepatocellular ca in **liver cirrhosis** ⟶ high regeneration in hepatocytes ⟶ ↑ hepatocellular carcinoma

   - SCCa in the margins of a chronic skin fistula like in osteomyelitis; or in a long-unhealed skin wound. ⟶ the cause is ① Infections ② long period of regeneration
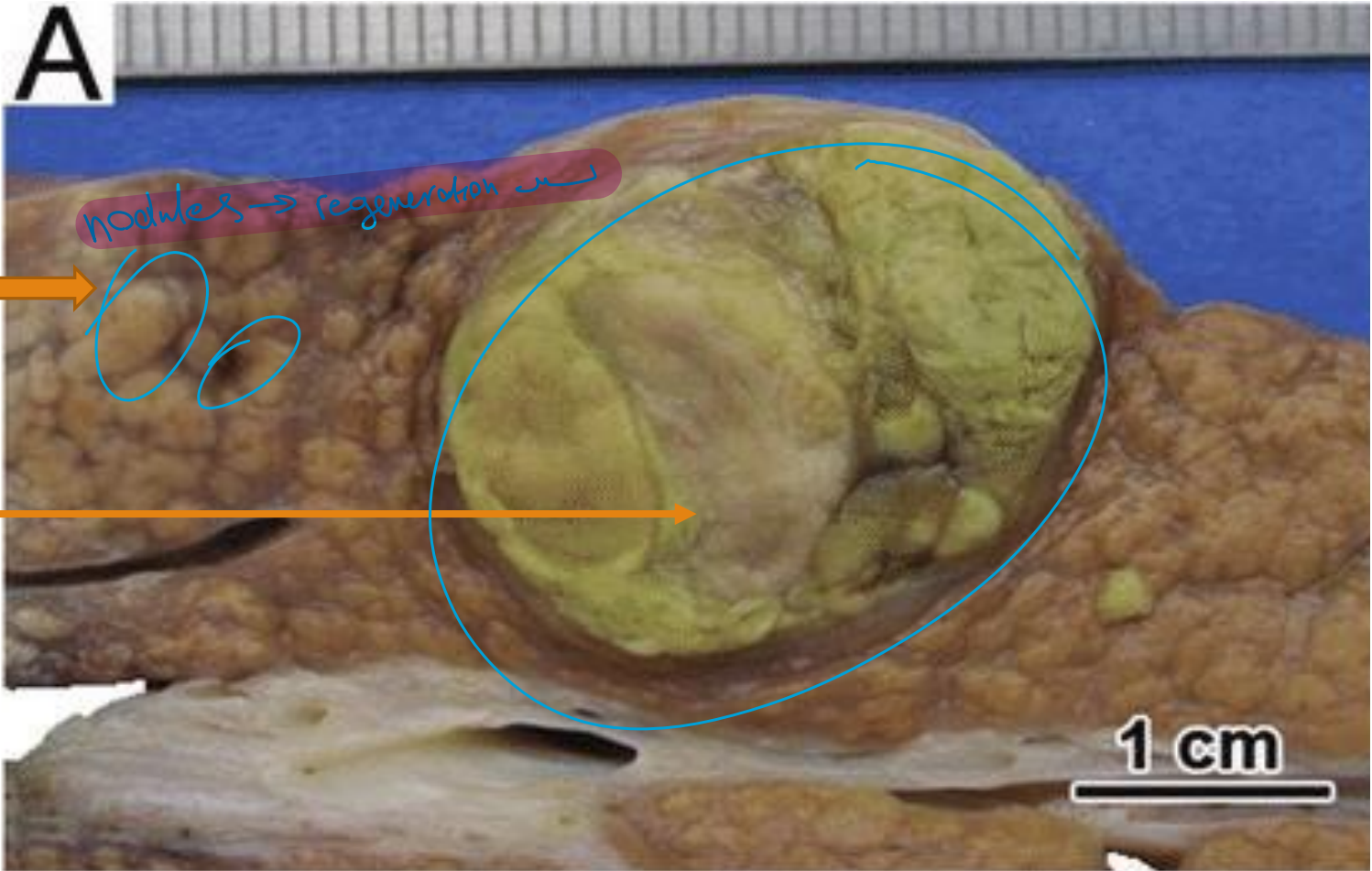
(2) Hyperplastic & dysplastic proliferation

   -e.g.: - Endometrial ca in atypical endometrial hyperplasia

      - Bronchogenic lung ca in the dysplastic bronchial mucosa of smokers

dysplasia ≠ Cancer

Cancer الى تتقدم ممكن هي لكن

Macronodular cirrhosis

Liver: Large number of hyperplastic nodules, separated from each other by fibrous trabeculae

Hepatocellular carcinoma

(3) Gastric ca in chronic atrophic gastritis

→ chronc Inflamation

(4) An incidence (5%) of colorectal cancer in long-standing chronic ulcerative colitis.

→ chronc Inflamatory diseases in colon

→ mucosal surface (s في)

lmf + ulceration

(5) Leukoplakia of the oral cavity, vulva, or penis increases the risk of SCCa.

(6) Villous adenoma of the colon has a high risk of transformation to colorectal ca.

(7) Some benign tumors, **e.g.** colonic tubular adenomas, as they enlarge to more than 2 cm, can undergo a malignant transformation in 50% of cases.

(8) Marjolin's ulcer (squamous cell carcinoma of the skin) arising in an old burn.

Colon: Papillary (Tubular) adenoma & carcinoma.

A circumferential ulcerating cancer is present (right center, red arrow) in direct continuity with large sessile adenomas to its left (blue star), also, there are two small pedunculated polypoidal adenomas (green arrows)

Leukoplakia in oral mucosa, white patch of mucosal thickening caused by irritation induced by ill-fitted denture. **A precancerous lesion.**

Squamous cell carcinoma arises in leukoplakia at the lower lip.
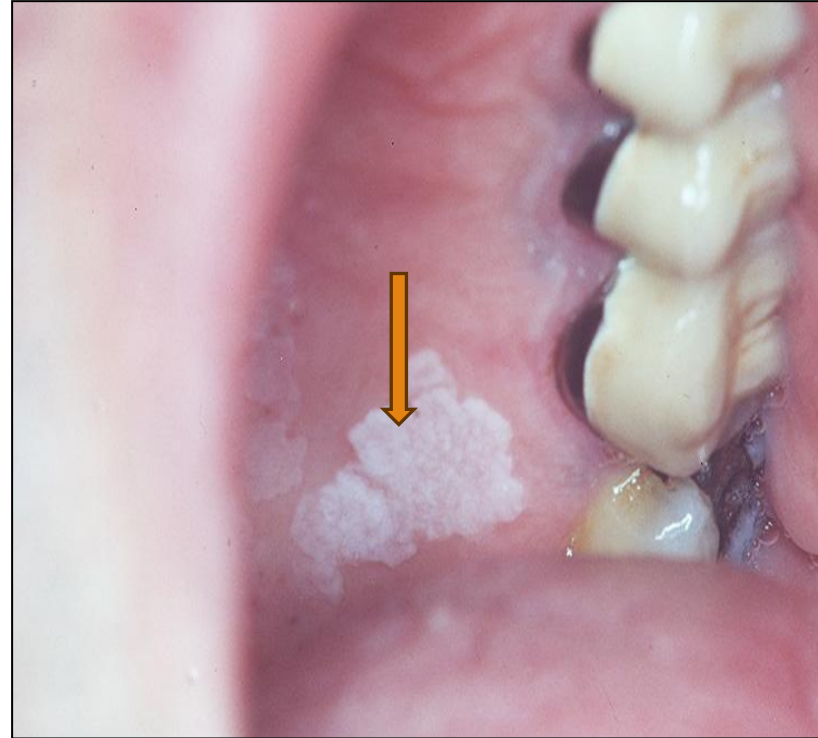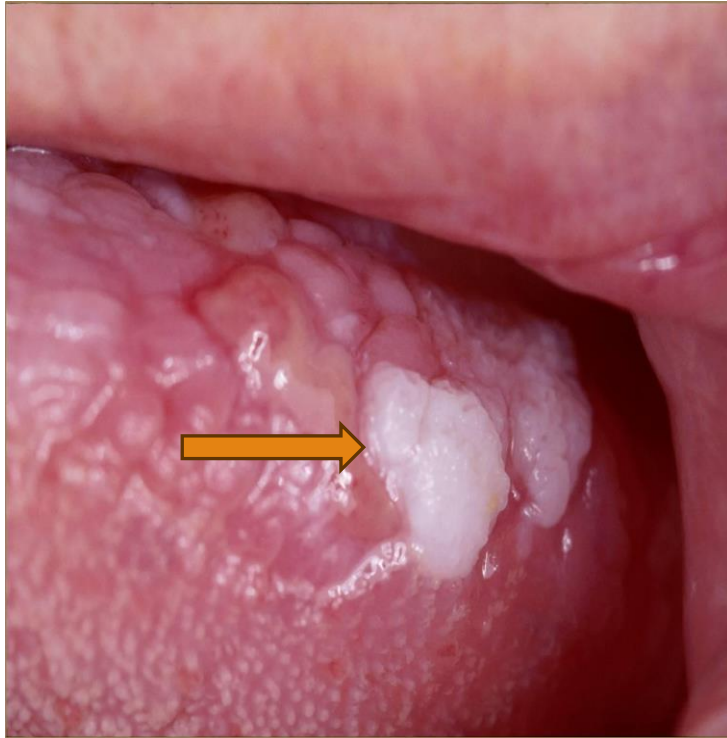
Carcinogenic agents

عوامل تؤدي إلى حدوث Cancer

1- Chemical carcinogens

2- Radiant carcinogens

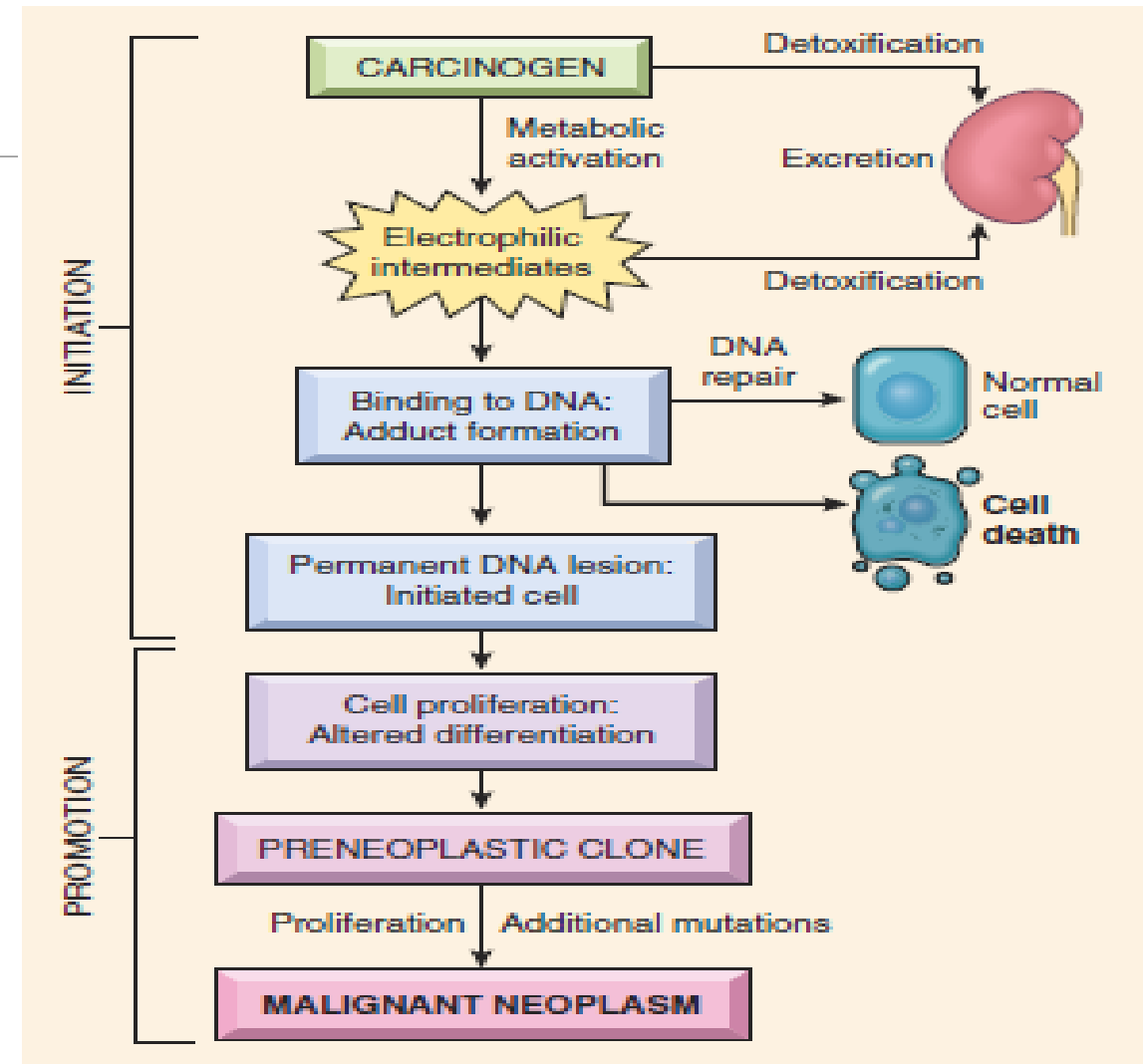3- Microbial carcinogens, mainly viral

1. Chemical carcinogens:

- Chemical carcinogens are electrophilic and enter nucleus, damage DNA→ mutation → **Initiated Cell.**

❖**Initiator (Mutagen)**– A chemical inducing irreversible DNA damage.

❖**Promoter**- A chemical augmenting effect of the initiator by promoting cell growth and division.

→ Proliferation

☐ **Mechanisms of Action of Chemical Carcinogens:**

- Chemical carcinogens contain highly reactive electrophile groups (i.e., have electron-deficient atoms) that react with the electron-rich atoms) that combine to DNA, RNA or protein-producing mutations.

- Genes commonly affected are RAS & TP53

    ---May be very specific ' Signature Mutation,' e.g. Aflatoxin-induced TP53 mutation.

- Some strong chemicals act as initiators and promoters.

❑ **Promoters**

- Act by stimulating cell **proliferation**.
- Promotors are NOT carcinogenic by themselves

- They have to **FOLLOW** the application of the initiator.

Examples:
- **HORMONES**

- **PHORBOL ESTERS**

- **PHENOLS**

- **DRUGS**

❖ Chemical Carcinogens are divided into:

1. Direct-Acting Agents:

   - Directly produce damage without prior metabolic conversion to become carcinogenic.

   - They are, in general, **weak** carcinogens.

Stronger

2. Indirect-Acting Agents (most of them):

   - (Procarcinogen): Need metabolic conversion in the liver by cytochrome P-450 dependent mono-oxygenases → **ultimate carcinogen**

Major types of chemical carcinogens:

لا يحتاجو إلى Conversion في liver

1- Alkylating Agents: Direct, used in chemotherapy of cancer - may induce Leukemia.

2- Polycyclic Hydrocarbons: Indirect & very strong - include benzopyrene in cigarette smoke
→ CA Lung

3- Aromatic Amines & Azo dyes: Indirect -Rubber & Food Industry e.g. β-naphthylamine →
Bladder CA

4- Natural plant and microbial products: includes Aflatoxin B1 produced by the fungus
Aspergillus flavus (a mold that grows on improperly stored grains and nuts). → Hepatocellular CA.

5- Nitrosamines: Endogenous or food preservatives cause Gastric & Colon CA