

EPIDEMIOLOGY AND ETIOLOGY OF TUMORS

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Objectives

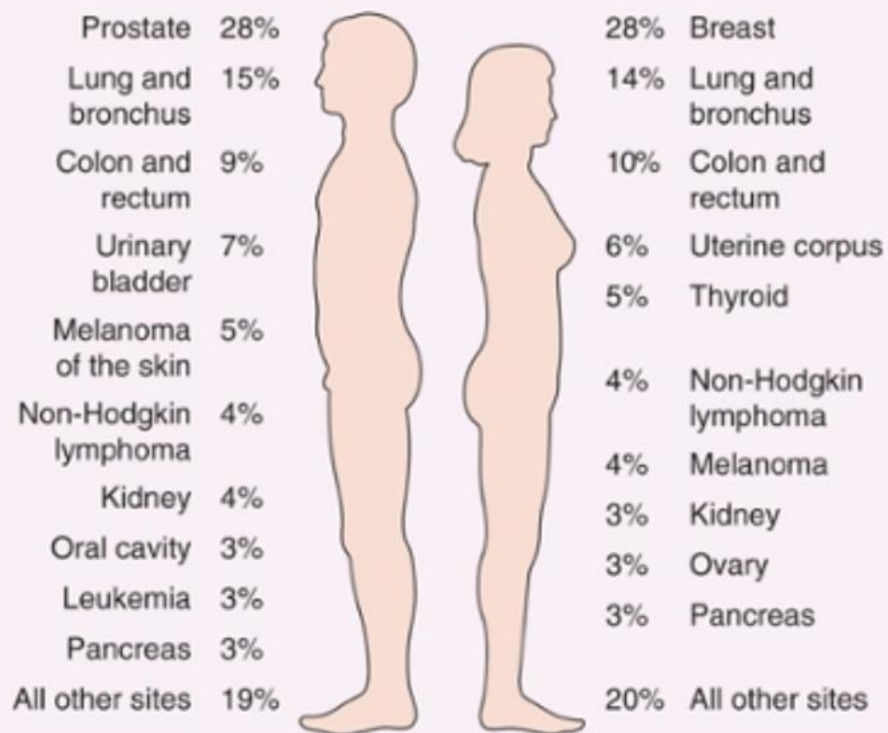
- To understand that the incidence of cancer varies with age, race, geographic and genetic factors.
- To explain the genetic predisposition to cancer.
- To identify the precancerous conditions.
- To list the various causes of tumors.

Epidemiology

- Studying the epidemiology of tumors will aid in the following:
 - Discover etiologic factors
 - Plan preventive measures
 - Know what types of tumors are common and what are rare
 - Develop screening methods for early diagnosis

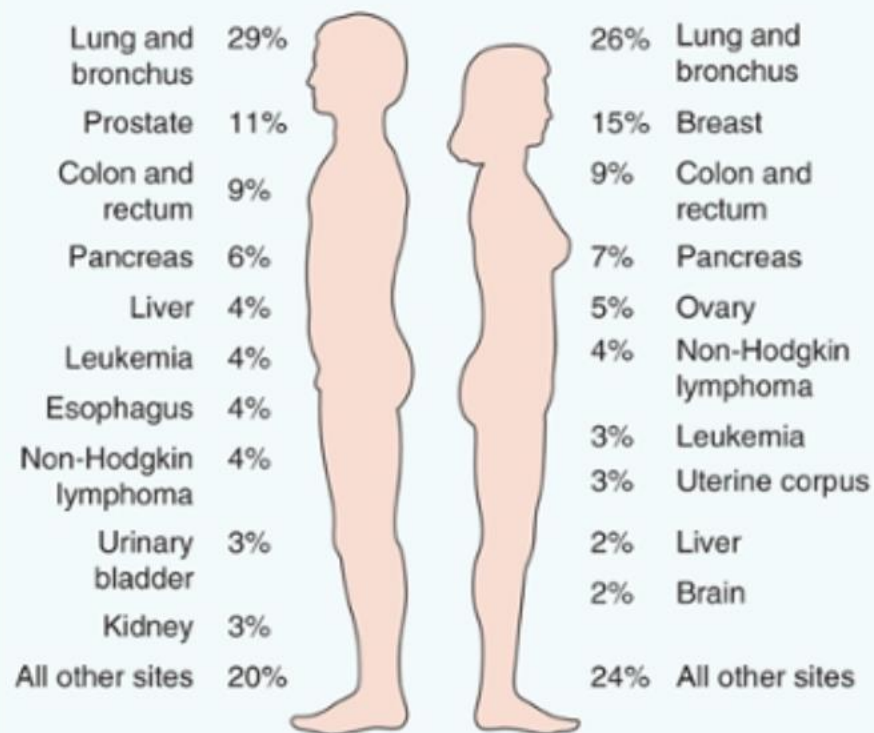
Cancer Incidence

A. 2010 ESTIMATED CANCER INCIDENCE BY SITE AND SEX*



* Excluding basal and squamous cell skin cancers and carcinoma in situ (except urinary bladder)

B. 2010 ESTIMATED CANCER DEATHS BY SITE AND SEX



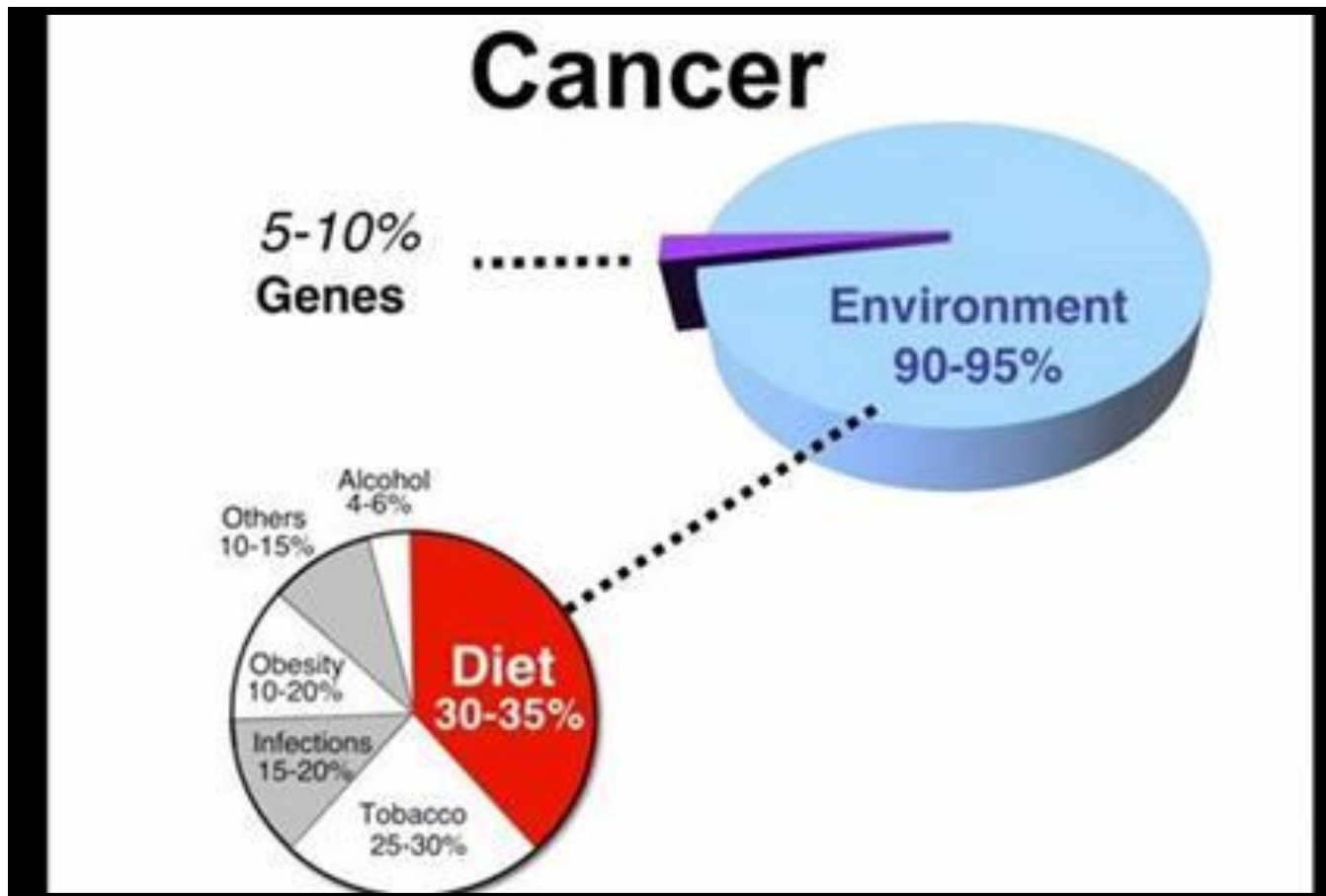
Cancer Incidence

- Factors affecting the incidence of cancer:
 - Geographic and environmental factors
 - Age
 - Hereditary factors
 - Acquired preneoplastic conditions

Geographic & Environmental Factors

- 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 is more common in African populations.

Geographic & Environmental Factors



Geographic & Environmental Factors

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

Geographic & Environmental Factors

Agent/Group of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use/Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	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 (e.g., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Leukemia	Principal component of light oil 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	Missile fuel and space vehicles Hardener for lightweight compounds metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors Found in solders Used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Ethylene oxide	Leukemia	Ripening agent for fruits and nuts Used in rocket propellant and chemical synthesis, in fumigants for foodstuffs and textiles, and in sterilants for hospital equipment
Nickel compounds	Nose, lung	Nickel plating Component of ferrous alloys, ceramics, and batteries Byproduct of stainless steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium Can be serious hazard in quarries and mines
Vinyl chloride	Angiosarcoma, liver	Refrigerant Monomer for vinyl polymers Adhesive for plastics Formerly used as inert aerosol propellant in pressurized containers

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.
- The most common malignant tumors in children are:
 - Leukemia
 - CNS tumors
 - Lymphomas
 - Soft tissue & bone sarcomas.

Hereditary Factors

- Hereditary factors include:
 - Autosomal dominant cancer syndromes
 - Autosomal recessive syndromes of defective DNA repair
 - Familial cancers of uncertain inheritance

Hereditary Factors

- Autosomal dominant cancer syndromes
 - Several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.
 - e.g. retinoblastoma in children:
 - 40% of retinoblastomas are familial in nature.
 - Carriers of this mutation have 10000 fold increase in the risk of developing retinoblastoma
 - e.g. multiple endocrine neoplasia (MEN syndrome)

Hereditary Factors

- Autosomal recessive syndromes of defective DNA repair
 - A group of rare autosomal recessive disorders is collectively characterized by chromosomal or DNA instability and high rates of certain cancers.
 - e.g. xeroderma pigmentosum

Hereditary Factors

- Familial cancers of uncertain inheritance
 - All the common types of cancers that occur sporadically have been reported to occur in familial forms where the pattern of inheritance is unclear.
 - e.g. breast, colon, ovary, brain
 - Familial cancers usually have unique features:
 - They start at early age
 - They are multiple or bilateral
 - They occur in two or more relatives

Hereditary Factors

Autosomal Dominant Cancer Syndromes	
Gene(s)	Inherited Predisposition
<i>RB</i>	Retinoblastoma
<i>TP53</i>	Li-Fraumeni syndrome (various tumors)
<i>p16INK4A</i>	Melanoma
<i>APC</i>	Familial adenomatous polyposis/colon cancer
<i>NF1, NF2</i>	Neurofibromatosis 1 and 2
<i>BRCA1, BRCA2</i>	Breast and ovarian tumors
<i>MEN1, RET</i>	Multiple endocrine neoplasia 1 and 2
<i>MSH2, MLH1, MSH6</i>	Hereditary nonpolyposis colon cancer
<i>PATCH</i>	Nevoid basal cell carcinoma syndrome
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	
Ataxia-telangiectasia	
Bloom syndrome	
Fanconi anemia	
Familial Cancers of Uncertain Inheritance	
Breast cancer (not linked to <i>BRCA1</i> or <i>BRCA2</i>)	
Ovarian cancer	
Pancreatic cancer	

Acquired Pre-neoplastic Conditions

- Acquired preneoplastic conditions are conditions that predispose to cancer.
 - Dysplastic bronchial mucosa in smokers → lung carcinoma
 - Liver cirrhosis → 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:
 - Chemicals
 - Radiant energy
 - Microbial agents

Etiology of Tumors



Hair coloring products



Insulation glass wool



Magnetic fields



Caffeine/Tea



Fluorescent lighting



Caprolactam



Coffee



Pickled vegetables (traditional in Asia)



Talc-based body powder



Aloe vera



Carpentry



Working as a barber/hair dresser



Nightshift Work



Art glass, glass containers and pressed ware (manufacture of)



High temperature frying



Glyphosate



Tobacco



Wood dust



Sunlight



Alcoholic beverages



Outdoor air pollution

CATEGORY 4
Probably Not Carcinogenic to Humans²

CATEGORY 3
Not Classifiable as to Carcinogenicity in Humans²

CATEGORY 2B
Possibly Carcinogenic to Humans²

CATEGORY 2A
Probably Carcinogenic to Humans²

CATEGORY 1
Carcinogenic to Humans²

Since 1979, IARC has reviewed hundreds of products, chemical compounds, lifestyles, viruses, workplaces and other agents for their carcinogenic potential. Here are some examples of IARC's hazard identifications¹.

Note: Of the hundreds of agents IARC has reviewed, this chemical, primarily used in the manufacturing of synthetic fibers, especially nylon, is the ONLY item IARC has ever placed in this category.³

Chemical Carcinogens

- Chemical carcinogens can be natural or synthetic.
- They can cause cellular damage via:
 - Direct
 - Indirect

Chemical Carcinogens

- 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 (e.g. alkylating agents).

Chemical Carcinogens

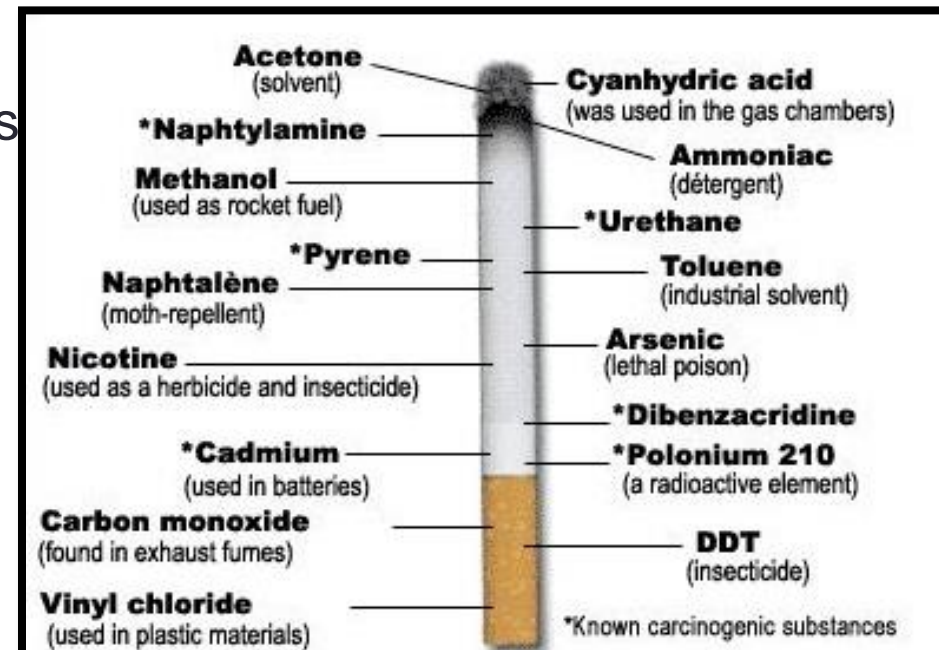
- Indirect-acting agents
 - They require metabolic conversion of the chemical compound (*procarcinogen*) to active & carcinogenic products (*ultimate carcinogen*).
 - e.g. benzo[*a*]pyrene, aromatic amines, azo dyes & Aflatoxin B₁

Chemical Carcinogens

- 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

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



Chemical Carcinogens

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



Chemical Carcinogens

- Nitrosamines & nitrosamides are used as preservatives & cause gastric carcinoma.
- Aflatoxin B₁, produced by *Aspergillus* which grows on improperly stored grains, it causes hepatocellular carcinoma.



Chemical Carcinogens

Direct-Acting Carcinogens

Alkylating Agents

β-Propiolactone
 Dimethyl sulfate
 Diepoxybutane
 Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)

Acylating Agents

1-Acetyl-imidazole
 Dimethylcarbonyl 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 B₁
 Griseofulvin
 Cycasin
 Safrole
 Betel nuts

Others

Nitrosamine and amides
 Vinyl chloride, nickel, chromium
 Insecticides, fungicides
 Polychlorinated biphenyls

Radiation

- Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen.
- Radiation has mutagenic effects: chromosomes breakage, translocations & point mutations.

Radiation

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

Viral & Microbial Oncogenes

- Viral & microbial oncogenes include:
 - RNA viruses
 - DNA viruses
 - Other micro-organisms e.g. H. Pylori bacteria

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.

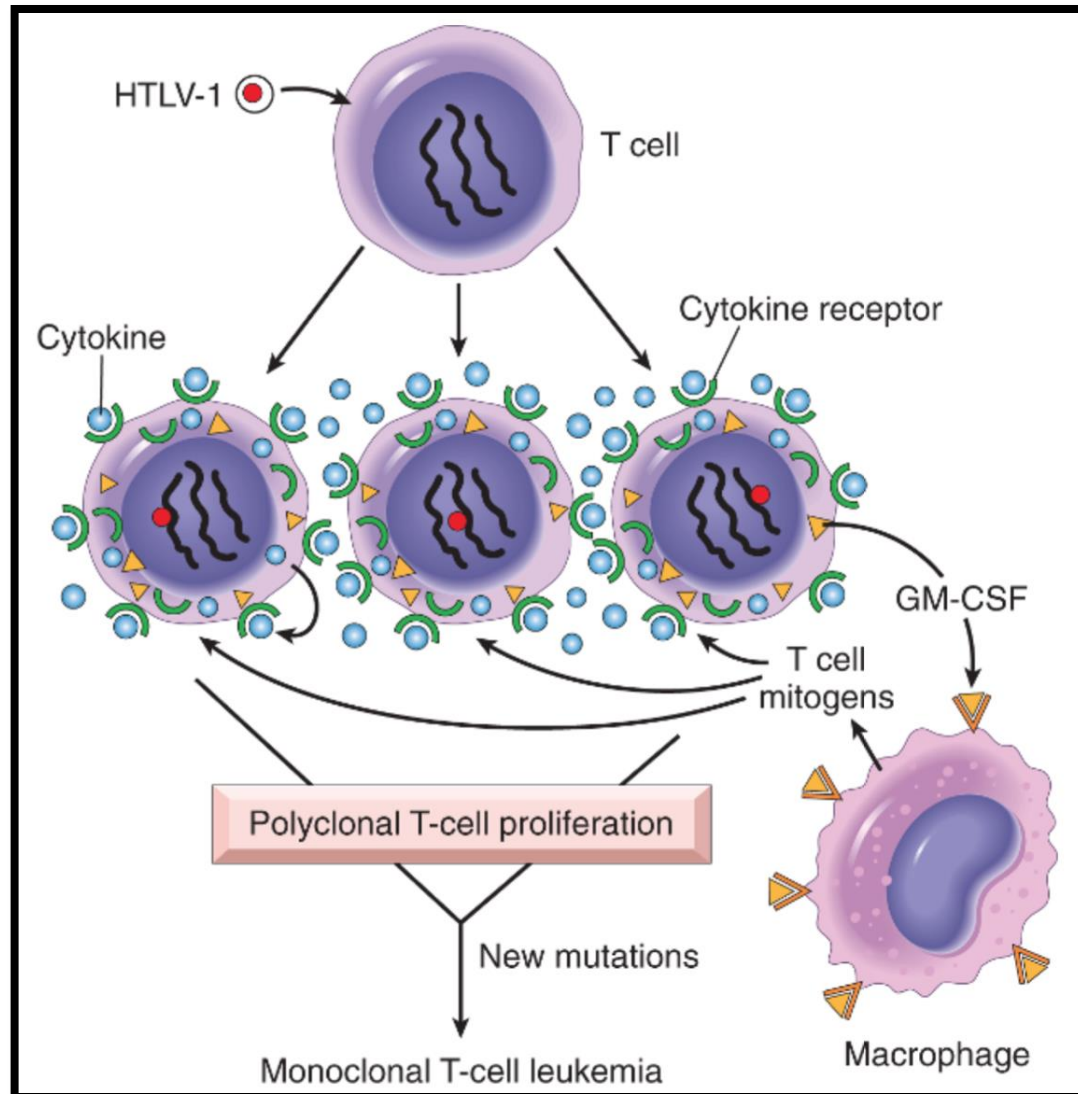
Viral & Microbial Oncogenes

- 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.

Viral & Microbial Oncogenes

- RNA oncogenic viruses:
 - 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



Viral & Microbial Oncogenes

- DNA oncogenic viruses:
 - DNA viruses form stable associations with hosts DNA, thus the transcribed viral DNA transforms the host cells.
 - e.g.
 - Human papilloma virus (HPV)
 - Epstein Barr virus (EBV)
 - Hepatitis B virus (HBV)
 - Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8])

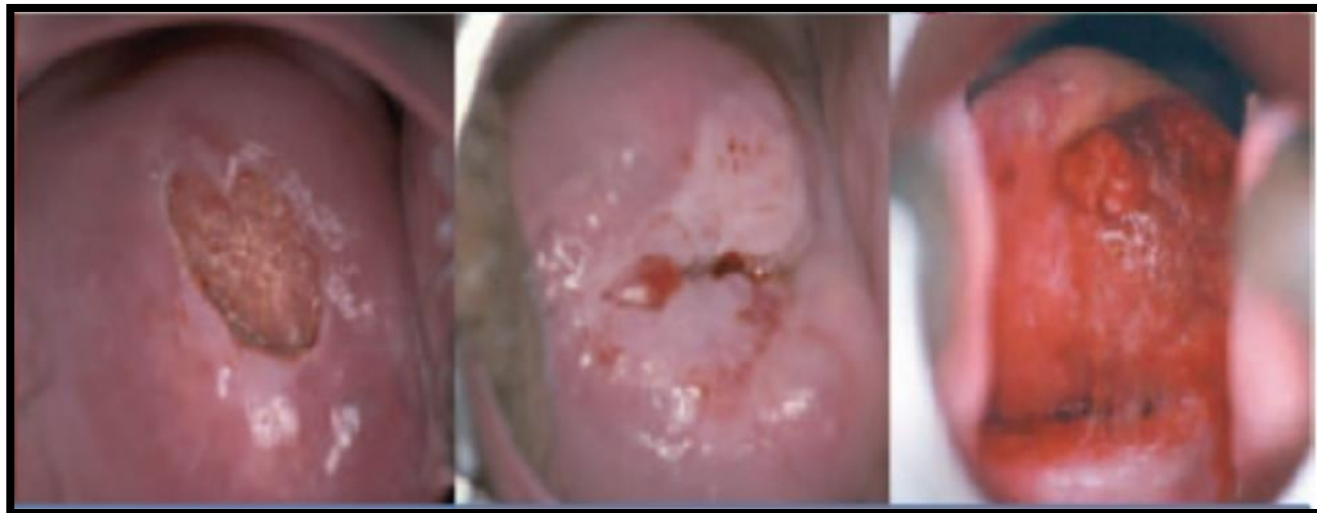
Viral & Microbial Oncogenes

- HPV infection:
 - HPV has more than 70 serotypes.
 - It is a sexually transmitted.
 - It causes benign warts, squamous cell carcinoma of the cervix, anogenital region, mouth & larynx.

Viral & Microbial Oncogenes

- HPV infection:
 - HPV types 6 and 11:
 - Genital warts
 - HPV types 16, 18, 31:
 - 85% of cervical carcinomas are caused by HPV 16 or 18
 - High risk HPV types integrates with the host's DNA

HPV Infection



Viral & Microbial Oncogenes

- HPV infection:
 - The oncogenic potential of HPV 16 and 18 can be related to products of two early viral genes, E6 and E7.
 - E6 protein binds to Rb tumor suppressor and releases the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle.
 - E7 protein binds to p53 & facilitates its degradation.

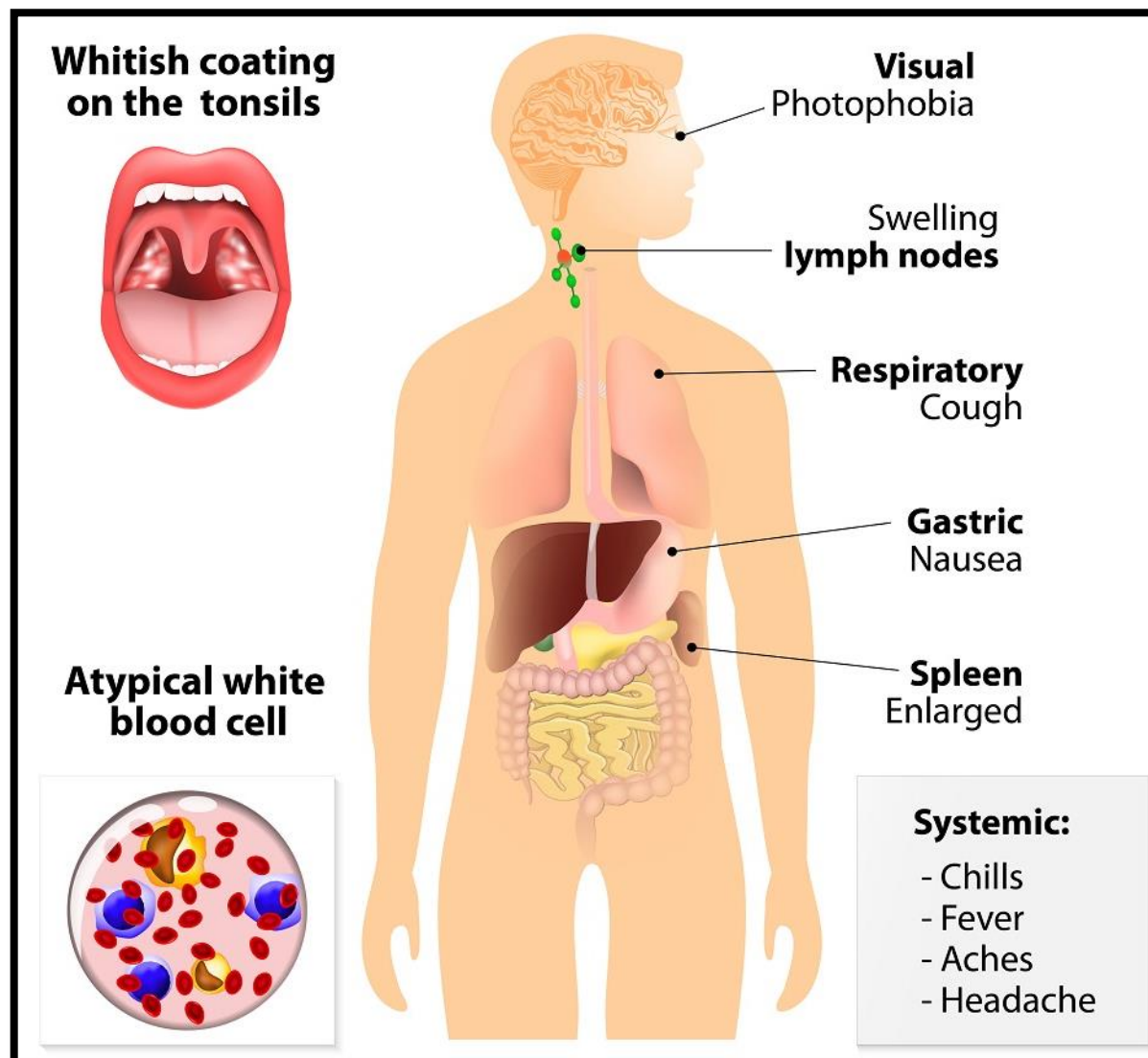
Viral & Microbial Oncogenes

- HPV infection:
 - 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

Viral & Microbial Oncogenes

- EBV infection:
 - It is a common virus worldwide.
 - It infects B lymphocytes & epithelial cells of the nasopharynx.
 - It causes infectious mononucleosis.
 - It causes several malignant tumors e.g.
 - Burkitt's Lymphoma
 - B-cell lymphoma in immunosuppressed
 - Nasopharyngeal carcinoma

EBV Infection – Infectious Mononucleoses



Viral & Microbial Oncogenes

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

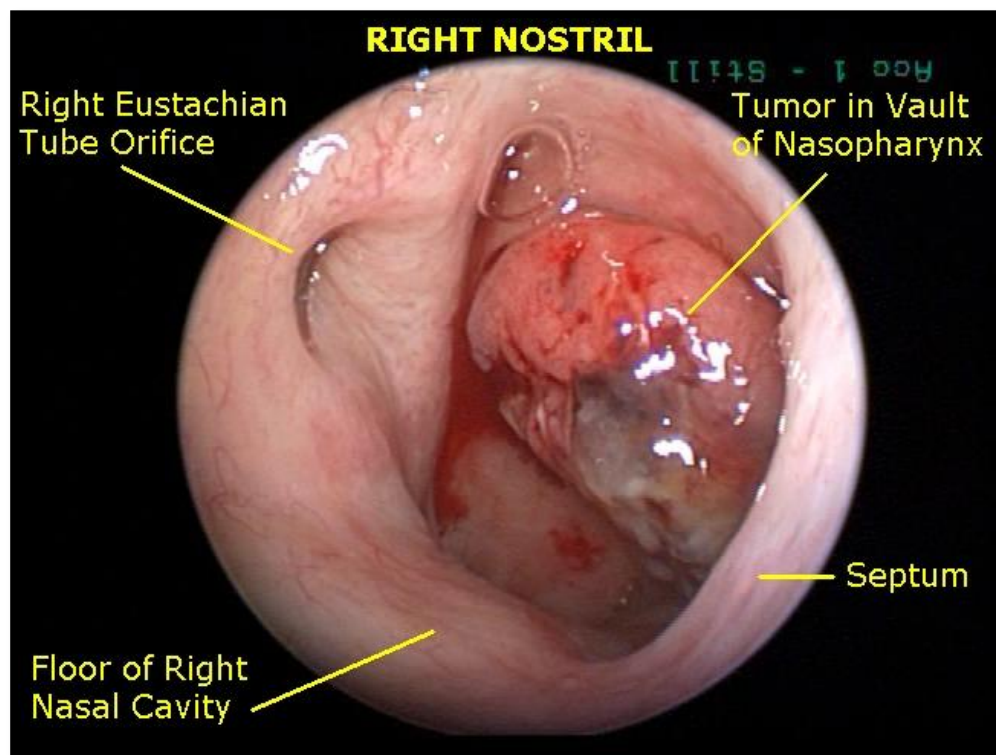
Viral & Microbial Oncogenes

- EBV infection:
 - EBV also causes Burkitt's lymphoma, a highly malignant B-cell tumor.
 - However, rare sporadic cases occur worldwide.
 - EBV-related Burkitt's lymphoma is the most common childhood tumor in Africa.
 - All cases have t(8:14) genetic mutation.

Viral & Microbial Oncogenes

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

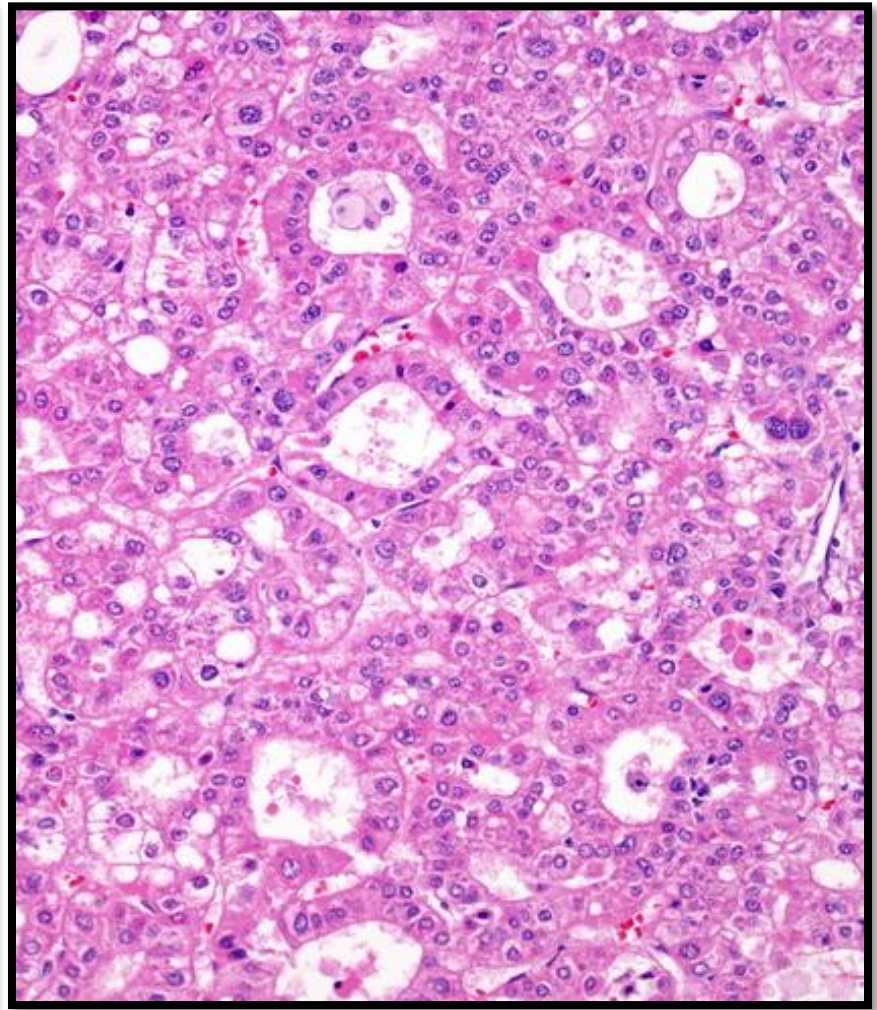
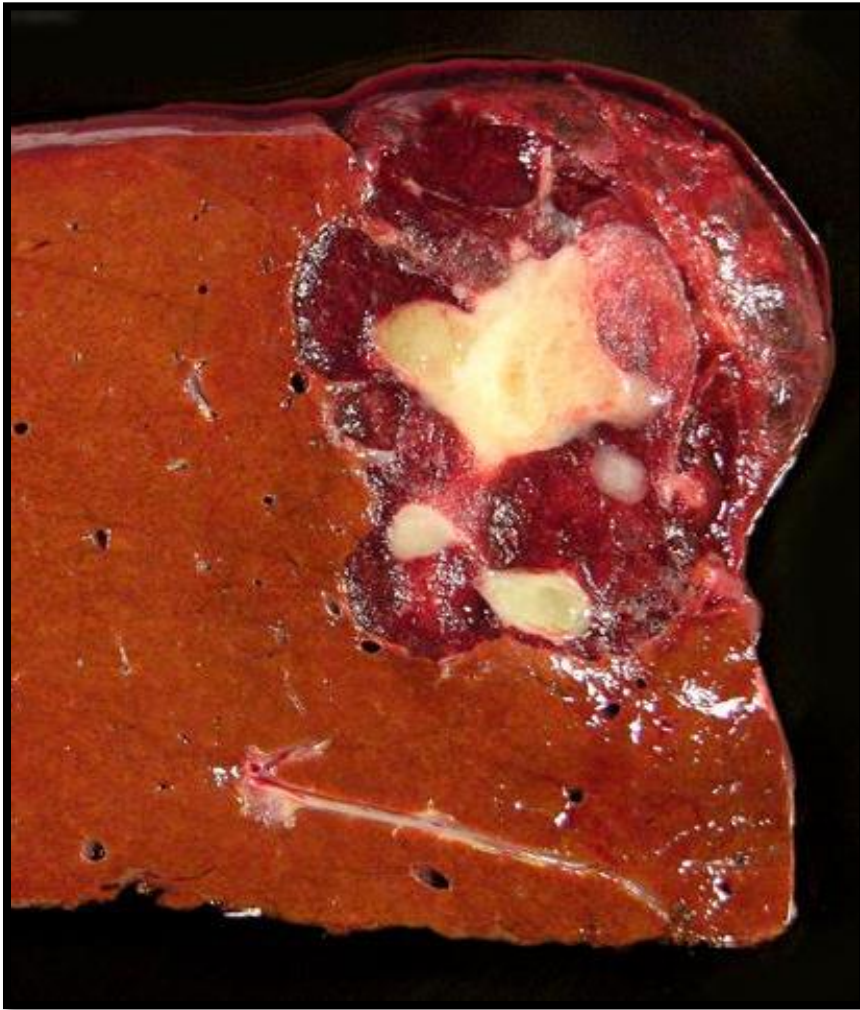
EBV Infection



Viral & Microbial Oncogenes

- HBV infection:
 - HBV infection has a strong association with liver cell carcinoma (HCC).
 - It is present world-wide, but most commonly in the far East & Africa.
 - HBV infection incurs up to 200-fold risk of HCC.

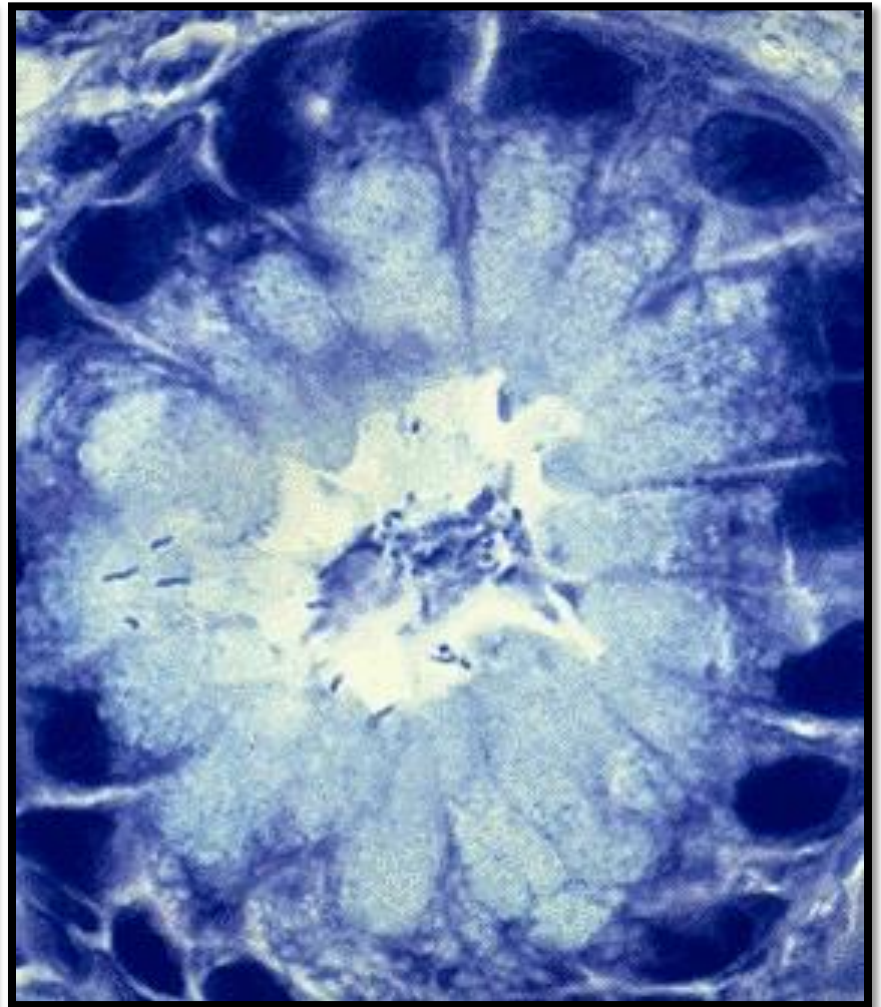
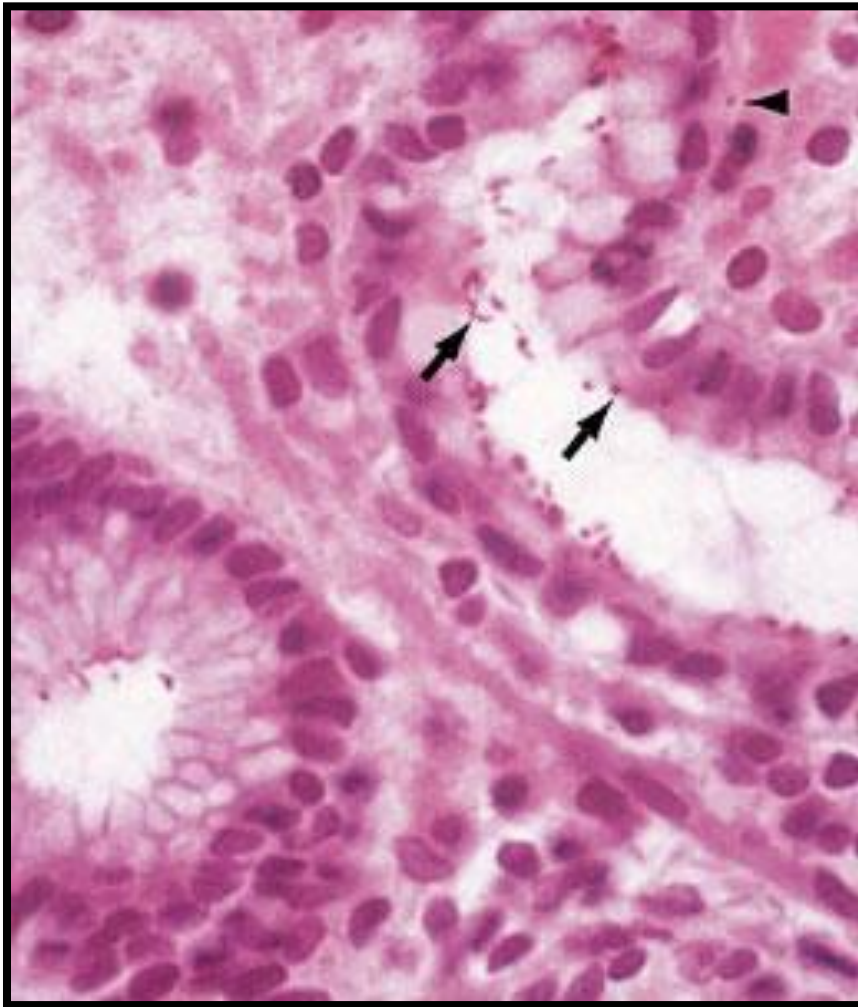
HBV Infection



Viral & Microbial Oncogenes

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

H. Pylori Infection



Reference

- Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed. Elsevier; 2013. Philadelphia, PA.

END OF LECTURE

Thank You