General oncology 4

Inherited and acquired predispositions to cancers and precanceroses

GENETIC PREDISPOSITION TO CANCER

Less than 10% of cancer patients have inherited mutations that predispose to cancer, and the frequency is even lower (around 0.1%) for certain types of tumors.

Genetic predisposition to cancer can be divided into three categories

Autosomal Dominant Inherited Cancer Syndromes

Defective DNA-Repair Syndromes

Familial Cancers

Autosomal Dominant Inherited Cancer Syndromes

Genes	Inherited predispositions
RB	Retinoblastoma
p53	Li-Fraumeni syndrome (various tumors)
p16/INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PTCH	Nevoid basal cell carcinoma syndrome
PTEN	Cowden syndrome (epithelial cancers)
LKB1	Peutz-Jegher syndrome (epithelial cancers)
VHL	Renal cell carcinomas

Retinoblastoma
RB gene

Features

Gross - White, solid tumor

Microscopic - Small round cell tumour:

- Scant cytoplasm.

Flexner-Wintersteiner rosette - **key feature**.

- Rosette with empty centre (donut hole).
- Circular rosette with neuropil at the centre.

Mitoses - common.

Familial adenomatous polyposis
APC gene

most common adenomatous polyposis syndrome.
hundreds to thousands of adenomatous polyps
develops **early in life** (teens or 20s)
100% risk of developing colorectal ca
75% of FAP are autosomal dominant disorder.
Most polyps are **smaller than 1 cm** in size
Gastric polyps occur in **30% to 100% of cases,** then **duodenum (60 to 90%), jejunum (40%)** and **ileum (20%)**
The gross pathology and microscopic features are **identical to the sporadic adenomas**.
Numerous **small polyps** which appear **basophilic** due to **low-grade dysplasia**
cancer formation is **delayed** to around **50-55 years** of age in **attenuated FAP**
prophylactic colonectomy is the standard of care

Neurofibromatosis 1
NF1 gene

Neurofibromin that is expressed in brain and peripheral nerves.
NF1 is characterized by **multiple cafe-au-lait spots** and **neurofibromas (usually plexiform or diffuse type)**. Other manifestations include: **CNS lesions** (optic nerve glioma, astrocytoma, heterotopias), **pigmented hamartoma of iris (Lisch nodule), skeletal abnormalities, vascular abnormalities** (renovascular hypertension), **gynecomastia, non-neural tumors** (pheochromocytoma, myelogenous leukemia), and **GIST**

Lisch nodule

cafe-au-lait

neurofibromas

Neurofibromatosis 2
NF2 gene

autosomal dominant disorder
inactivating germline mutations in the **tumor suppressor gene NF2**
The diagnostic hallmark of NF2 is **bilateral vestibular schwannomas**
There is **no risk of malignant transformation** in schwannomas of NF2, however they cause **significant morbidity** and **reduced life-span** due to their location in brain and spinal cord. Patients develop **deafness, vision loss, imbalance** and **gait abnormalities, muscle weakness, paralysis, pain**, and **seizures**

Multiple endocrine neoplasia (MEN) 1 and 2
MEN1, RET genes

MEN1 – Wermer syndrome
(parathyroids, pancreas and pituitary benign tumors)

MEN 2A - Sipple syndrome (medullary thyroid ca, pheochromocitoma)

MEN 2B – multiple neuromas

neuroma

Medullary thyroid ca

Cowden syndrome (epithelial cancers) or multiple hamartoma syndrome

PTEN gene

an autosomal dominant inherited condition characterized by benign overgrowths called hamartomas

Skin - trichilemmomas, oral papillomas, shiny palmar keratoses. At birth pigmented genital lesions, lipomas, epidermal nevi, and cafe-au-lait spots. Squamous cell carcinomas.
Thyroid - benign follicular adenomas or multinodular goiter
Genitourinary - endometrial cancers, testicular lipomatosis
Gastrointestinal - polyps
Breast - breast cancer.
Central Nervous Systém – macrocephaly, varying degrees of autism spectrum disorder and intellectual disability

Trichilemmomas

Goiter

Intraductal papilloma

Von Hippel Lindau
VHL gene

characterized by visceral cysts and benign tumors with potential for subsequent malignant transformation

Tumor/Cyst type	Prevalence
Pancreatic cysts	50-91%
Cerebellar hemangioblastoma	44-72%
Renal cysts	59-63%
Retinal hemangioblastoma	45-59%
Renal cell carcinoma	24-45%
Spinal cord hemangioblastoma	13-59%
Papillary cystadenoma of the epididymis	10-60% of males
Pheochromocytoma	0-60%
Neuroendocrine tumor of the pancreas	5-17%
Serous cystadenoma of the pancreas	12%
Medullary hemangioblastoma	5%

INHERITED AUTOSOMAL RECESSIVE SYNDROMES OF DEFECTIVE DNA REPAIR

Xeroderma pigmentosum

Ataxia-telangiectasia

Bloom syndrome

Fanconi anemia

Xeroderma pigmentosum

Symptoms may include a severe sunburn after only a few minutes in the sun, freckling in sun exposed areas, dry skin and changes in skin pigmentation.
Nervous system - hearing loss, poor coordination, loss of intellectual function and seizures.
Complications include a high risk of skin cancer, cataracts

The average life expectancy of an individual with any type of XP and no neurological symptoms is approximately **37 years**, and **29 years** if neurological symptoms are present

Fanconi anemia

Features
bone marrow failure, skeletal abnormalities, and an increased risk for cancer

FAMILIAL CANCERS

Familial clustering of cases, but role of inherited predisposition not clear for each individual

Breast cancer

Ovarian cancer

Pancreatic cancer

Interactions between Genetic and Nongenetic Factors

It is generally difficult to sort out the hereditary and acquired basis of a tumor, because these factors often interact closely

The genotype can significantly influence the likelihood of developing environmentally induced cancers.

Inherited variations (polymorphisms) of enzymes that metabolize procarcinogens to their active carcinogenic forms can influence the susceptibility to cancer

NONHEREDITARY PREDISPOSING CONDITIONS

Chronic Inflammation and Cancer

In 1863 Virchow proposed that cancer develops at sites of chronic inflammation

Precancerous Conditions

Certain non-neoplastic disorders—the chronic atrophic gastritis of pernicious anemia, solar keratosis of the skin, chronic ulcerative colitis, and leukoplakia of the oral cavity, vulva, and penis—have such a well-defi ned association with cancer that they have been termed **precancerous conditions**

Certain forms of benign neoplasia also constitute precancerous conditions.

The villous adenoma of the colon, as it increases in size, becomes malignant in up to 50% of cases

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Bronchitis		Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder infl	Bladder carcinoma	Chronic indwelling urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell ca	
Chronic pancreatitis	Pancreatic carcinoma	Alcoholism
Hereditary pancreatitis	Pancreatic carcinoma	Mutation in trypsinogen gene
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	

Asbestosis

long-term inflammation and scarring of the lungs due to asbestos fibers.
Symptoms may include shortness of breath, cough, wheezing, and chest tightness.
Complications may include lung cancer, mesothelioma, and pulmonary heart disease

CANCERS ASSOCIATED WITH INFECTIOUS AGENTS		
Opisthorchis, cholangitis	Cholangiosarcoma, colon ca	Liver flukes (Opisthorchis viverrini)Bile acids
Chronic cholecystitis	Gallbladder cancer	Bacteria, gallbladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	Helicobacter pylori
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin lymphoma and Hodgkin lymphoma	Epstein-Barr virus
AIDS	Non-Hodgkin lymphoma, squamous cell carcinoma, Kaposi sarcoma	Human immunodefi ciency virus, human herpesvirus type 8
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonorrhea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma	Schistosomiasis

AIDS

Human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV), a retrovirus

Associated cancers:
Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma

Carcinogenic Agents and Their Cellular Interactions

Chemical
Physical
Biological

MICROBIAL CARCINOGENESIS

Oncogenic RNA Viruses
Human T-Cell Leukemia Virus Type 1.
Oncogenic DNA Viruses
Human Papillomavirus.
Epstein-Barr Virus.
Hepatitis B and C Viruses
Bacteria
Helicobacter pylori

Helicobacter pylori

is a gram-negative, microaerophilic, spiral (helical) bacterium usually found in the stomach
H. pylori infection - ulcers of the stomach or first part of the small intestine