NEOPLASIA II

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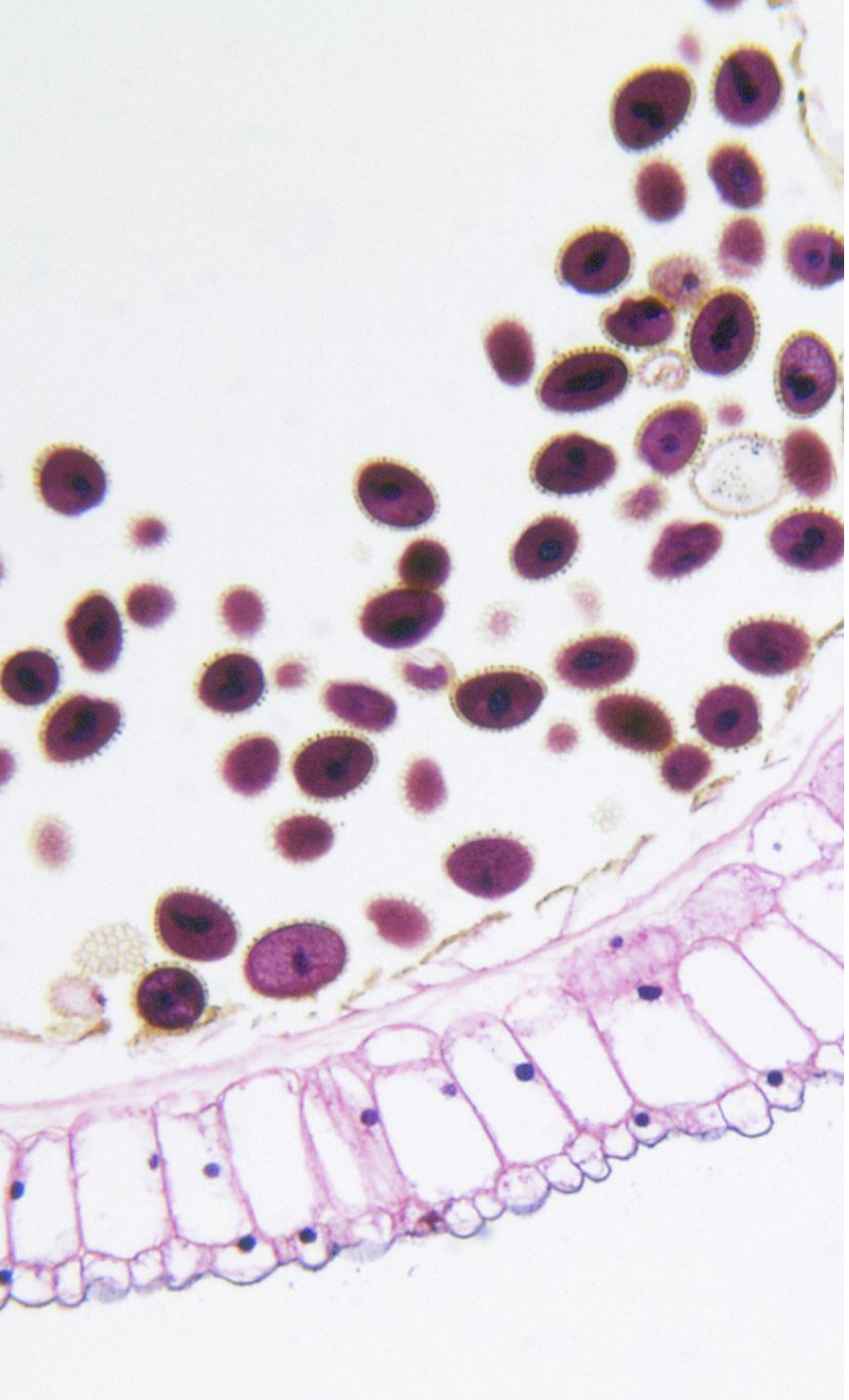
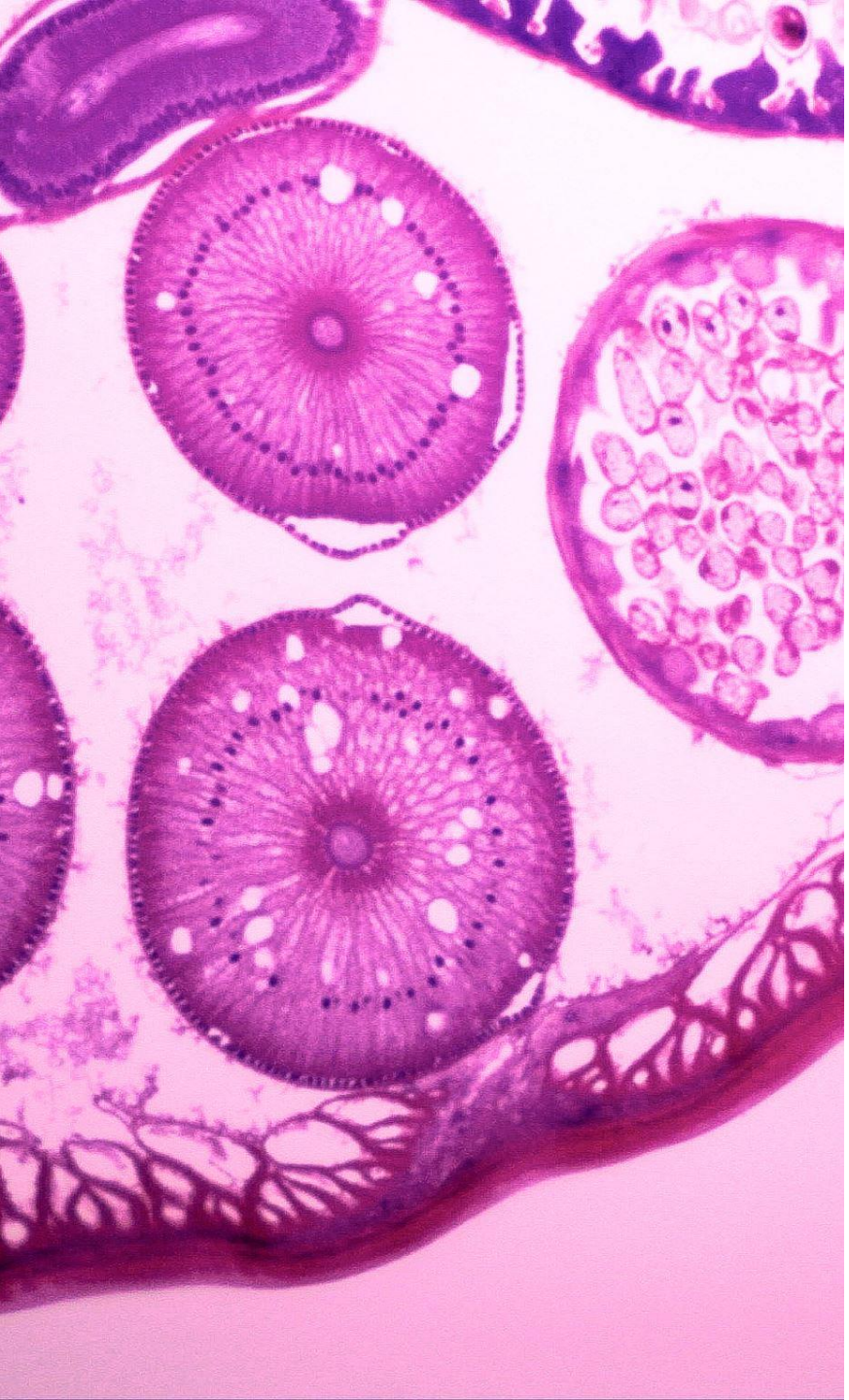


LOCAL INVASION

- The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue

- Nearly all benign tumors grow as cohesive expansile masses that remain localized to their site of origin and lack the capacity to infiltrate, invade, or metastasize to distant sites.



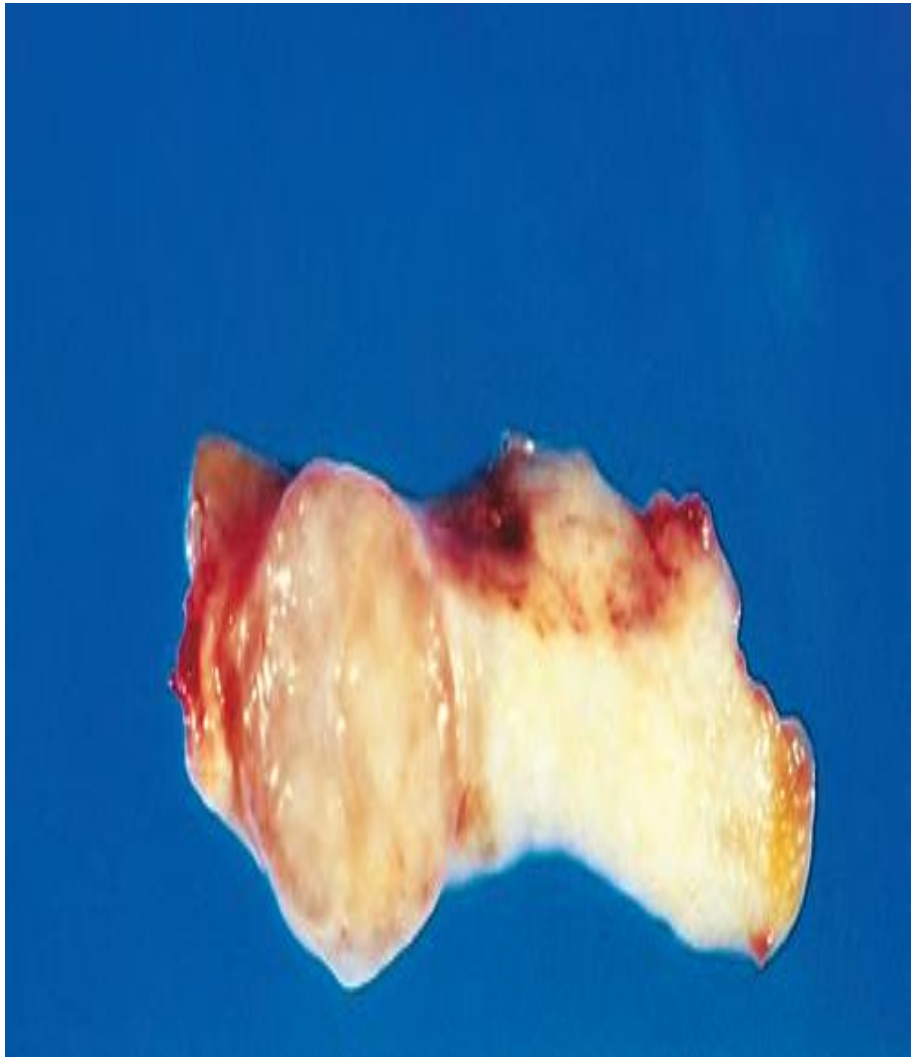
LOCAL INVASION

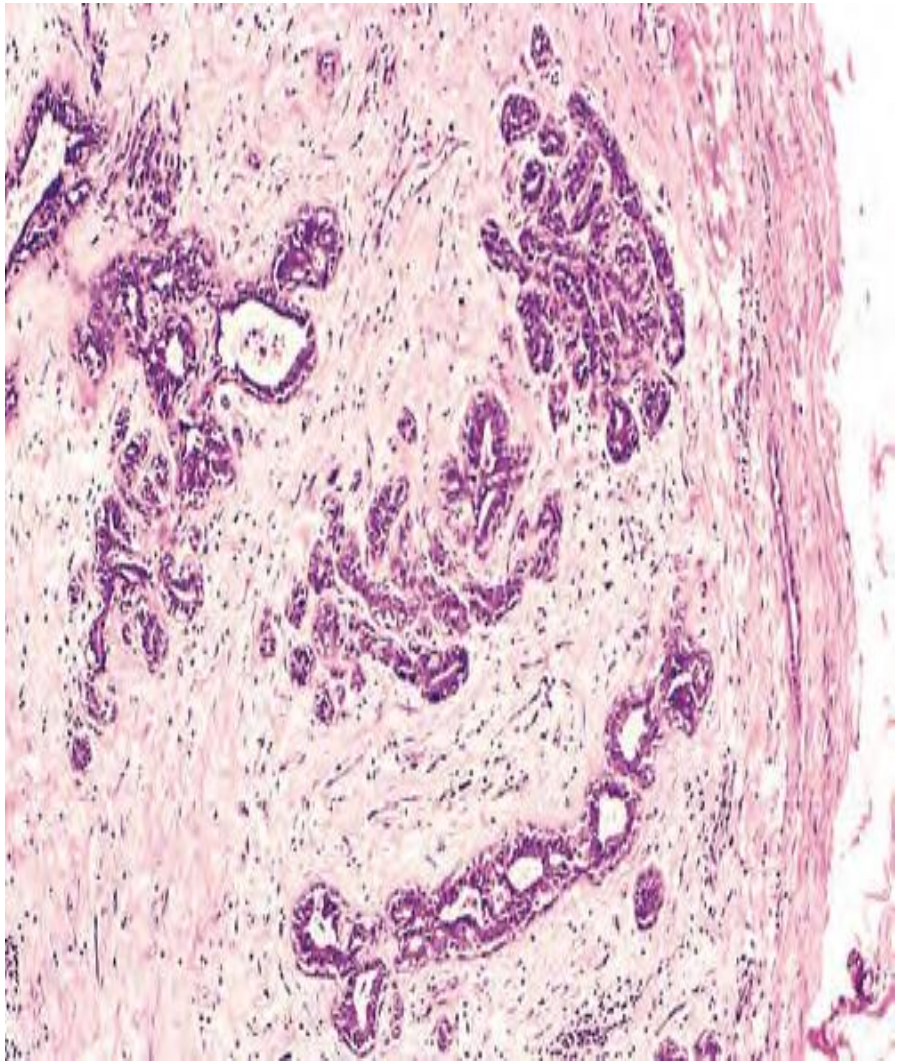
- Because benign tumors grow and expand slowly, they usually develop a rim of compressed fibrous tissue called a capsule that separates them from the host tissue.

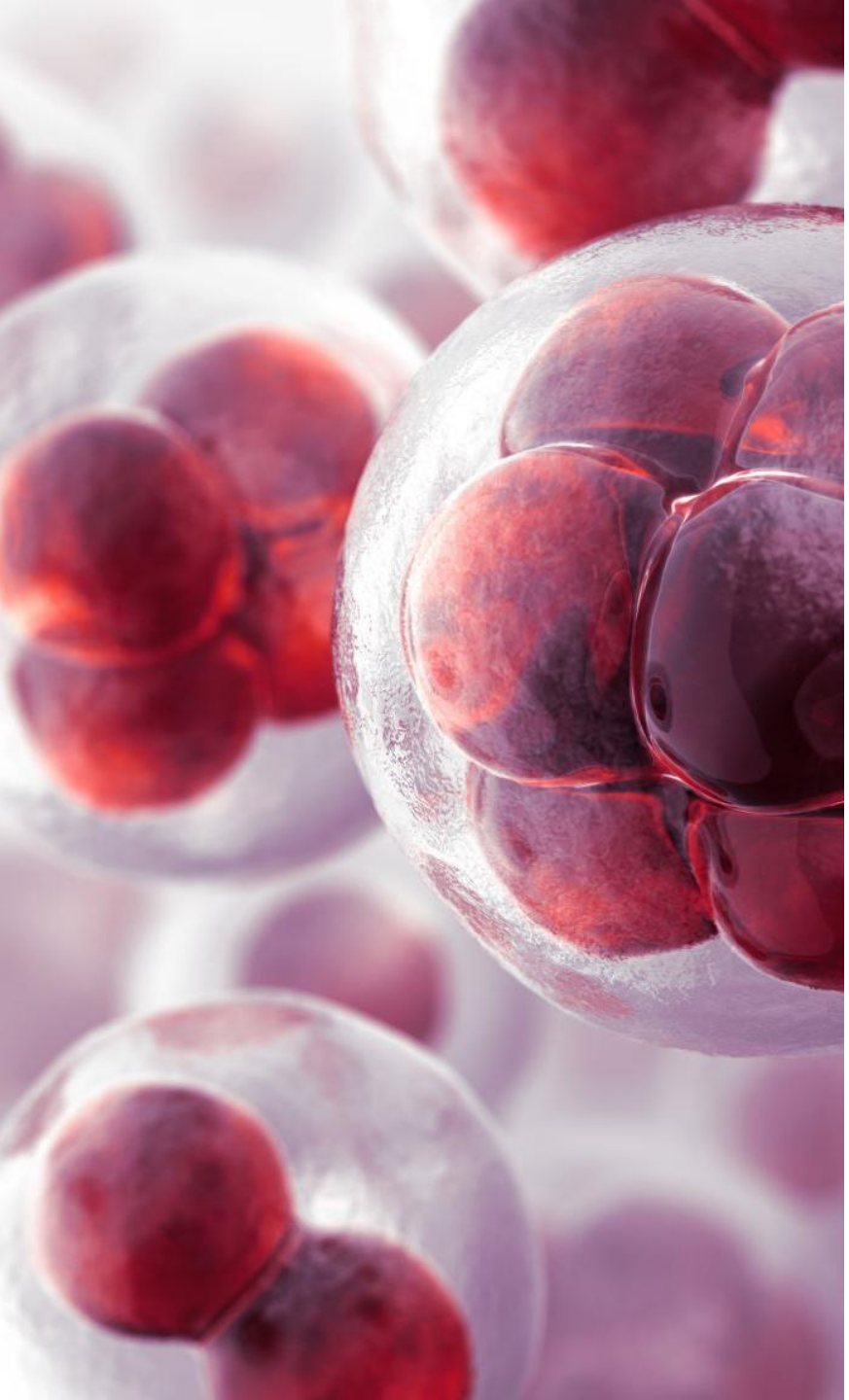
- Encapsulation does not prevent tumor growth, but it creates a tissue plane that makes the tumor discrete, readily palpable, moveable (non-fixed), and easily excisable by surgical enucleation.

- **Few exceptions to this rule:**

Hemangiomas (neoplasms composed of tangled blood vessels) are often unencapsulated and permeate the site in which they arise (e.g., the dermis of the skin and the liver); when such lesions are extensive, they may be unresectable.

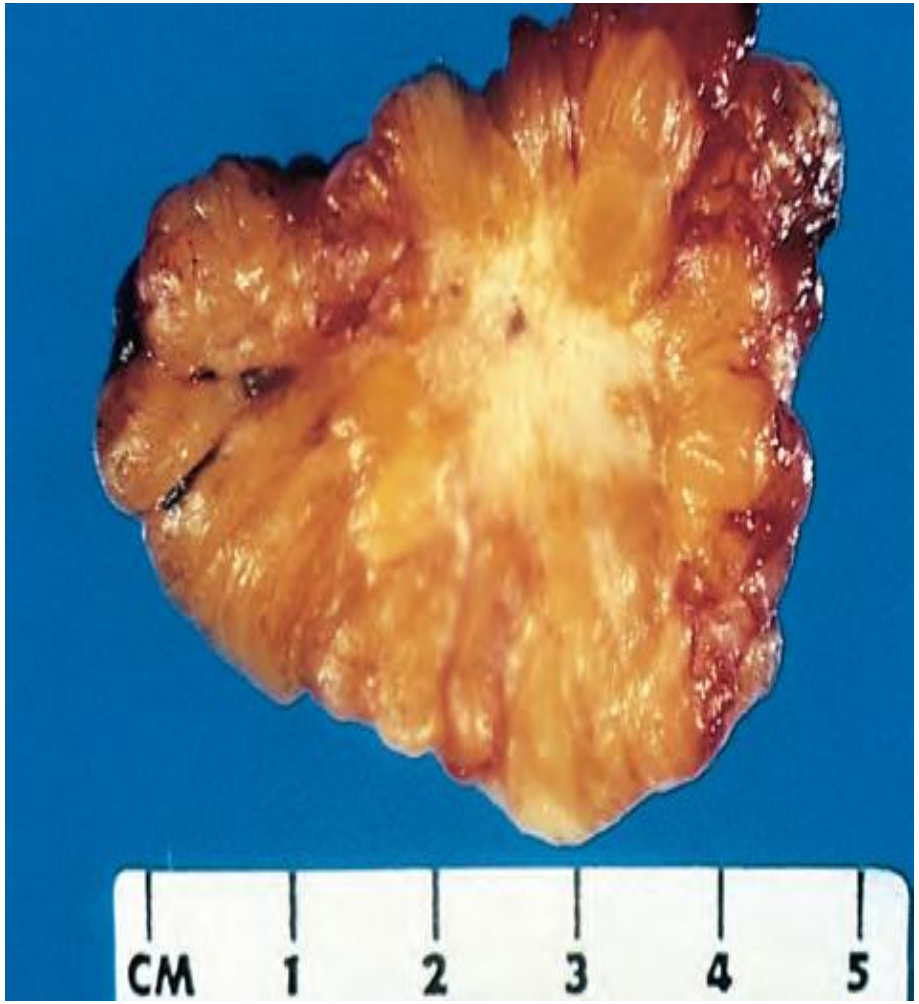






LOCAL INVASION

- Malignant tumors are poorly demarcated from the surrounding normal tissue.
- Slowly expanding malignant tumors, however, may develop an apparently enclosing fibrous capsule and may push along a broad front into adjacent normal structures.
- Next to the development of metastases, invasiveness is the most reliable feature that differentiates cancers from benign tumors.
- Most malignant tumors do not recognize normal anatomic boundaries and can be expected to penetrate the wall of the colon or uterus, for example, or fungate through the surface of the skin. Such invasiveness makes their surgical resection difficult or impossible.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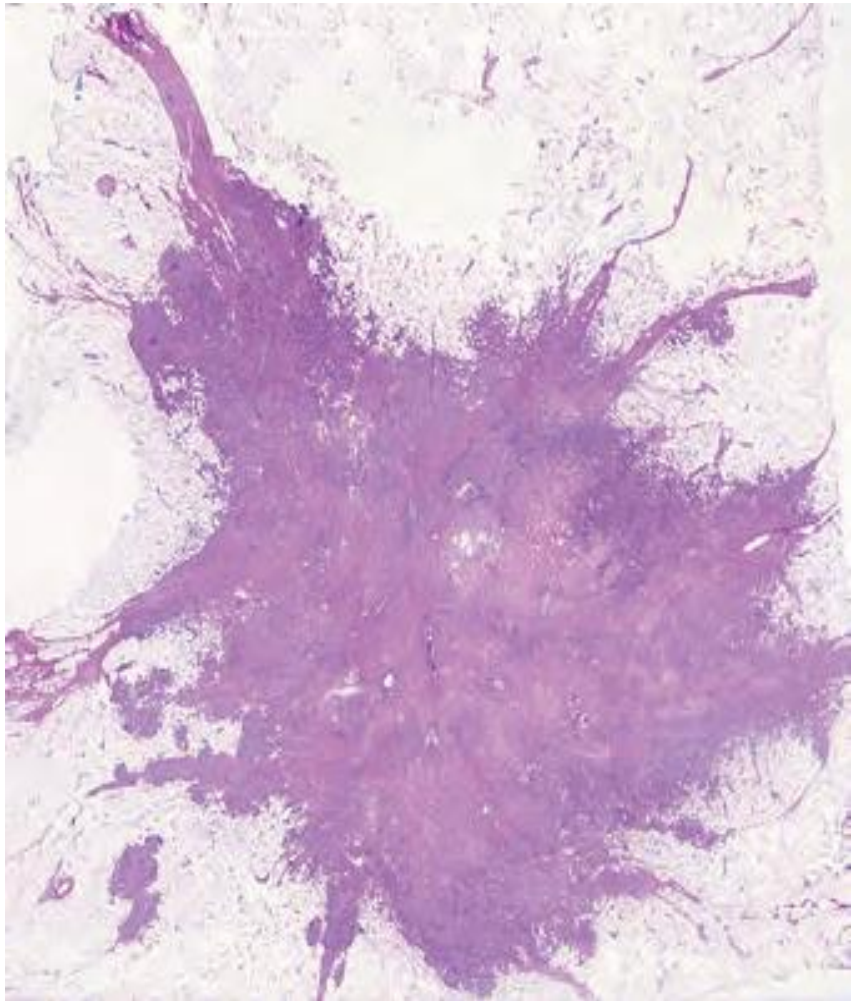
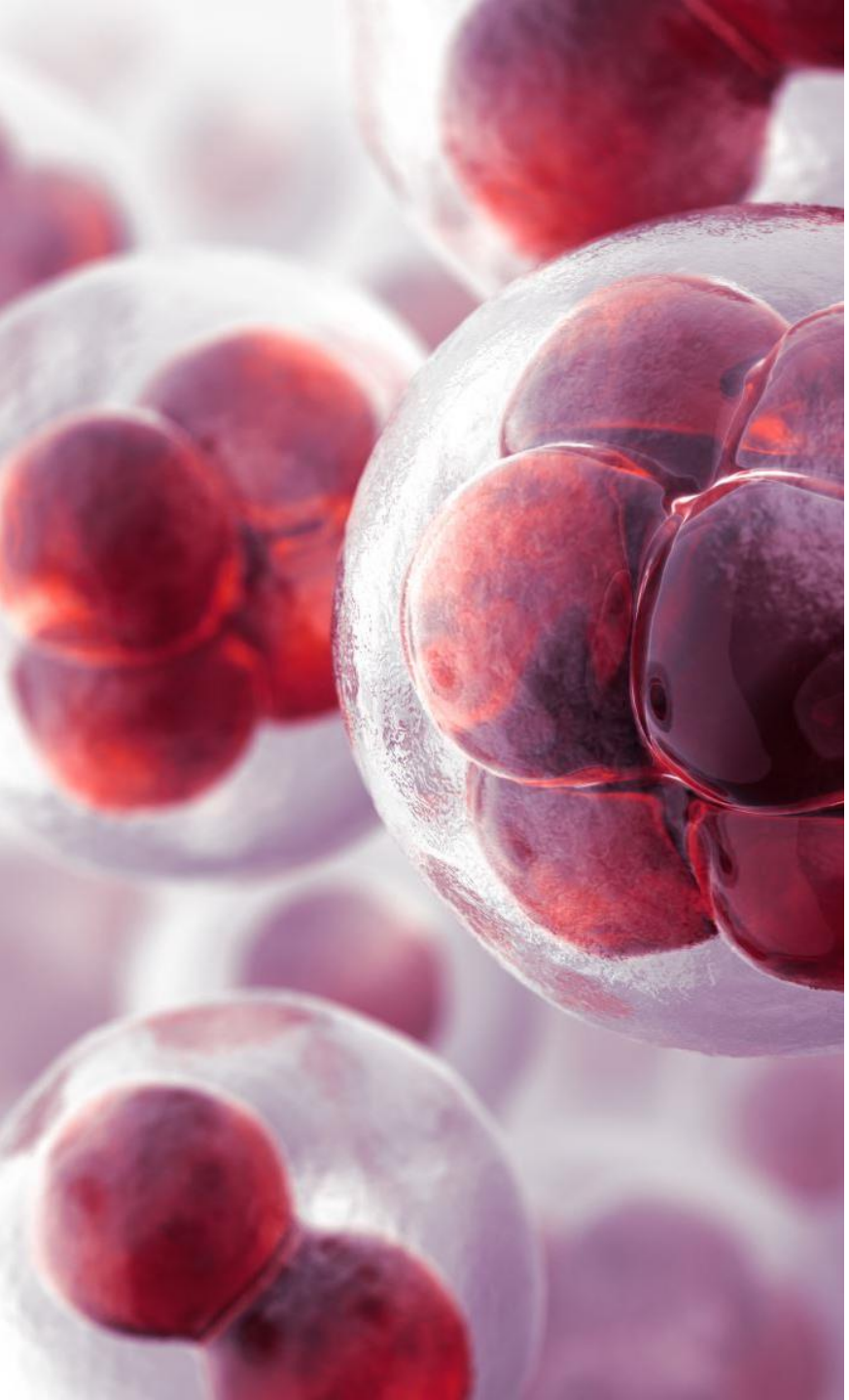
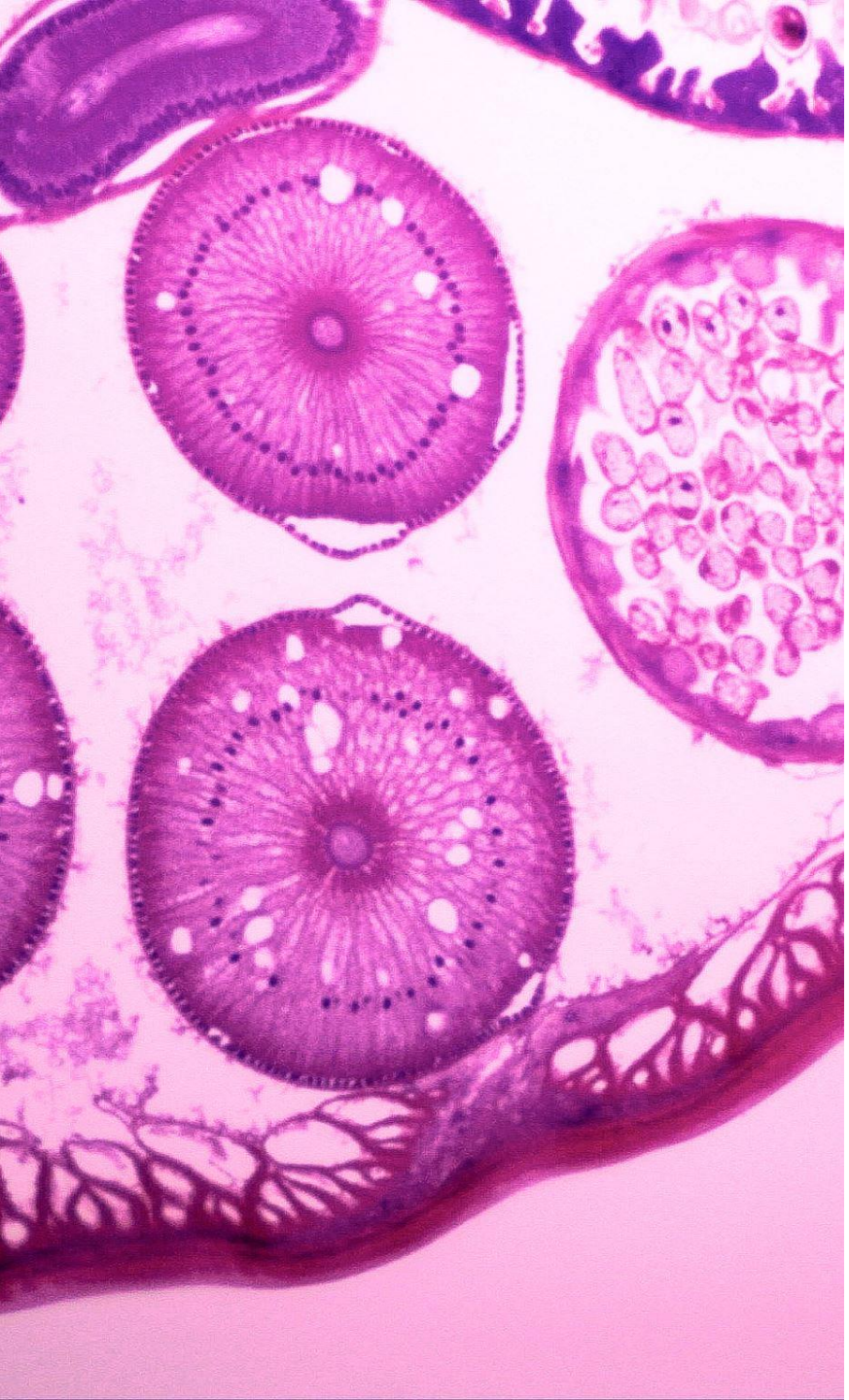




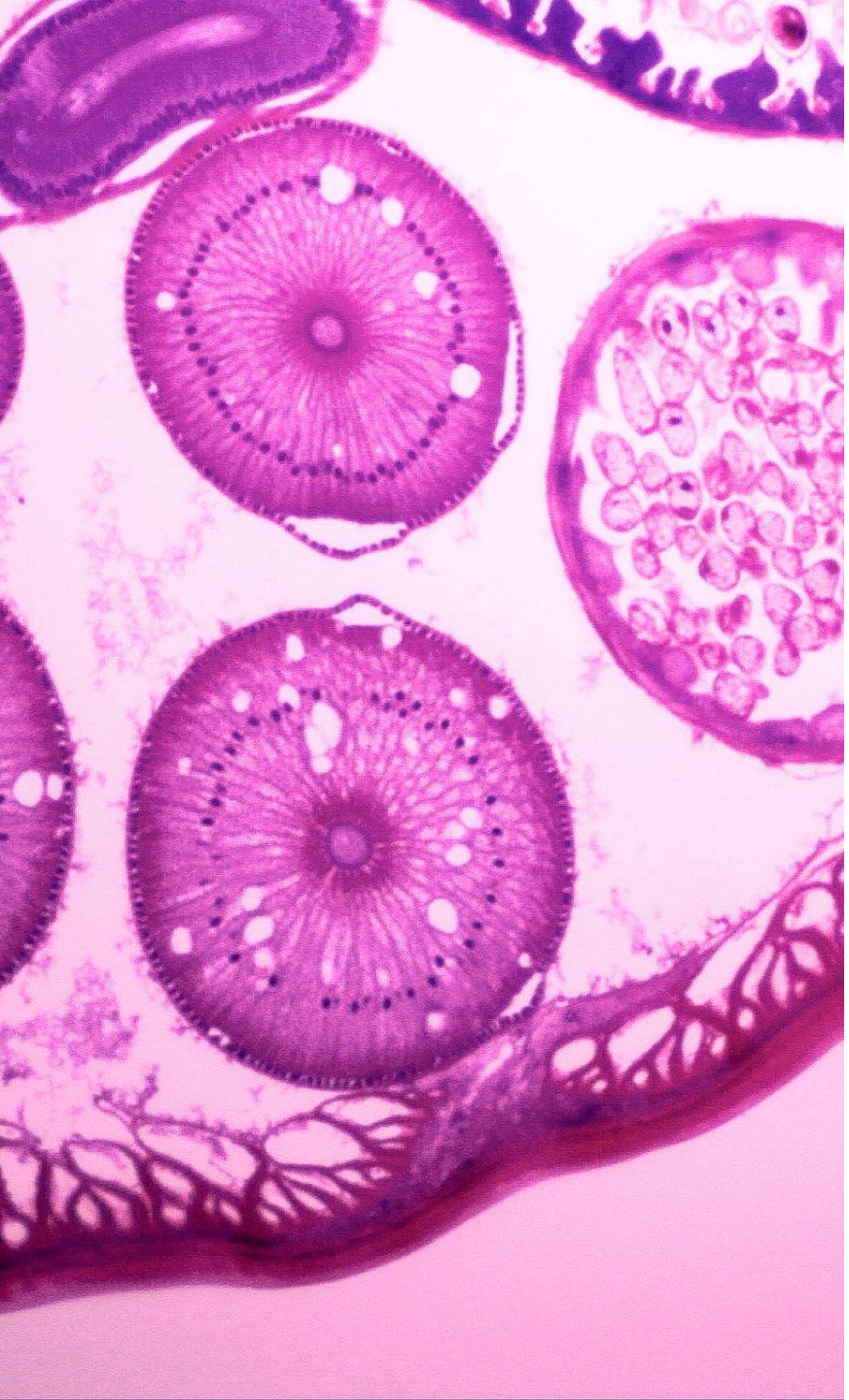
LOCAL INVASION

- This commonly occurs in carcinomas of the skin, breast, and certain other sites and is best illustrated by carcinoma of the uterine cervix .
- In situ epithelial cancers display the cytologic features of malignancy without invasion of the basement membrane.
- They may be considered one step removed from invasive cancer; with time, most penetrate the basement membrane and invade the sub-epithelial stroma.



METASTASIS

- Metastasis is defined by the spread of a tumor to sites that are physically discontinuous with the primary tumor.
- All malignant tumors can metastasize, but some do so very infrequently.
- Examples include malignant neoplasms of the glial cells in the central nervous system, called gliomas, and basal cell carcinomas of the skin. Both of these cancers invade early in their course, but rarely metastasize. It is evident then that the properties of invasion and metastasis are separable.



METASTASIS

- In general, the likelihood of a primary tumor metastasizing correlates with lack of differentiation, aggressive local invasion, rapid growth, and large size.
- There are innumerable exceptions, however. Small, well-differentiated, slowly growing lesions sometimes metastasize widely; conversely, some rapidly growing, large lesions remain localized for years.

METASTASIS

- Approximately 30% of newly diagnosed solid tumors (excluding skin cancers other than melanomas) present with metastases.
- Metastatic spread strongly reduces the possibility of cure; hence, short of prevention of cancer, no achievement would be of greater benefit to patients than an effective means to block metastasis.

- Blood cancers (the leukemias and lymphomas, sometimes called liquid tumors) are derived from blood-forming cells that normally have the capacity to enter the bloodstream and travel to distant sites; as a result, leukemias and lymphomas are often disseminated at diagnosis and are always taken to be malignant.

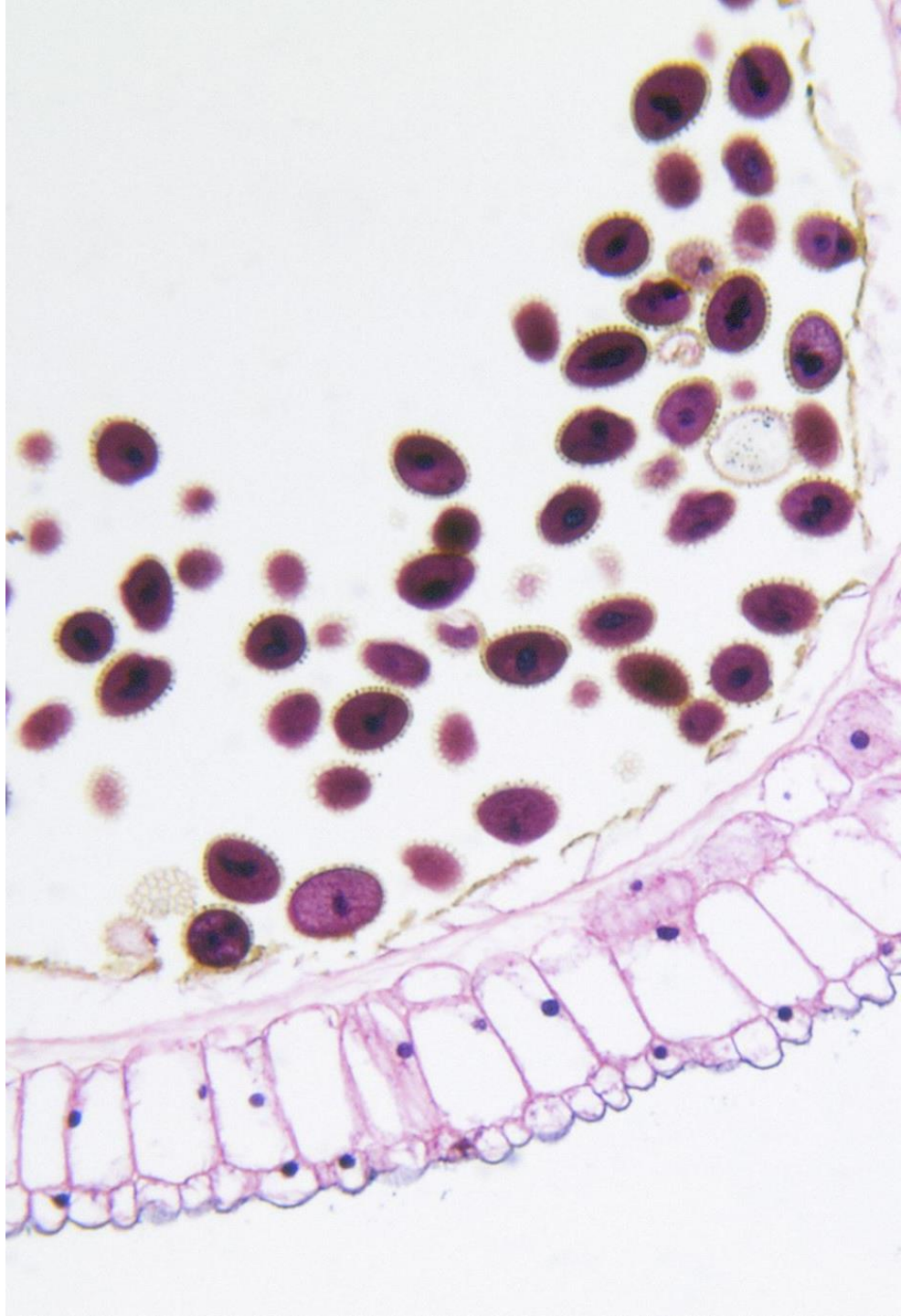
PATHWAYS OF SPREAD

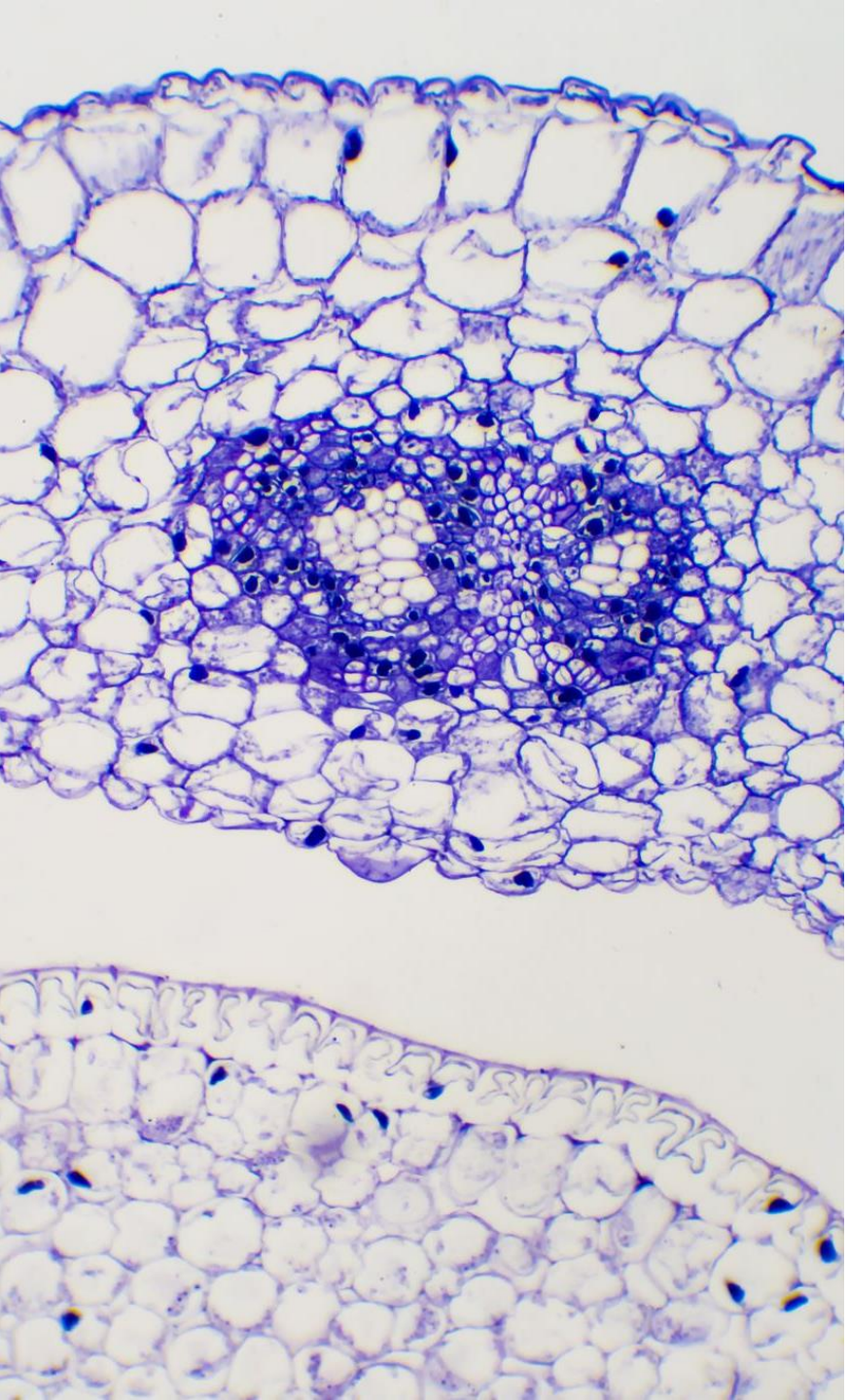
- Dissemination of cancers may occur through one of three pathways:

(1) direct seeding of body cavities or surfaces

(2) lymphatic spread

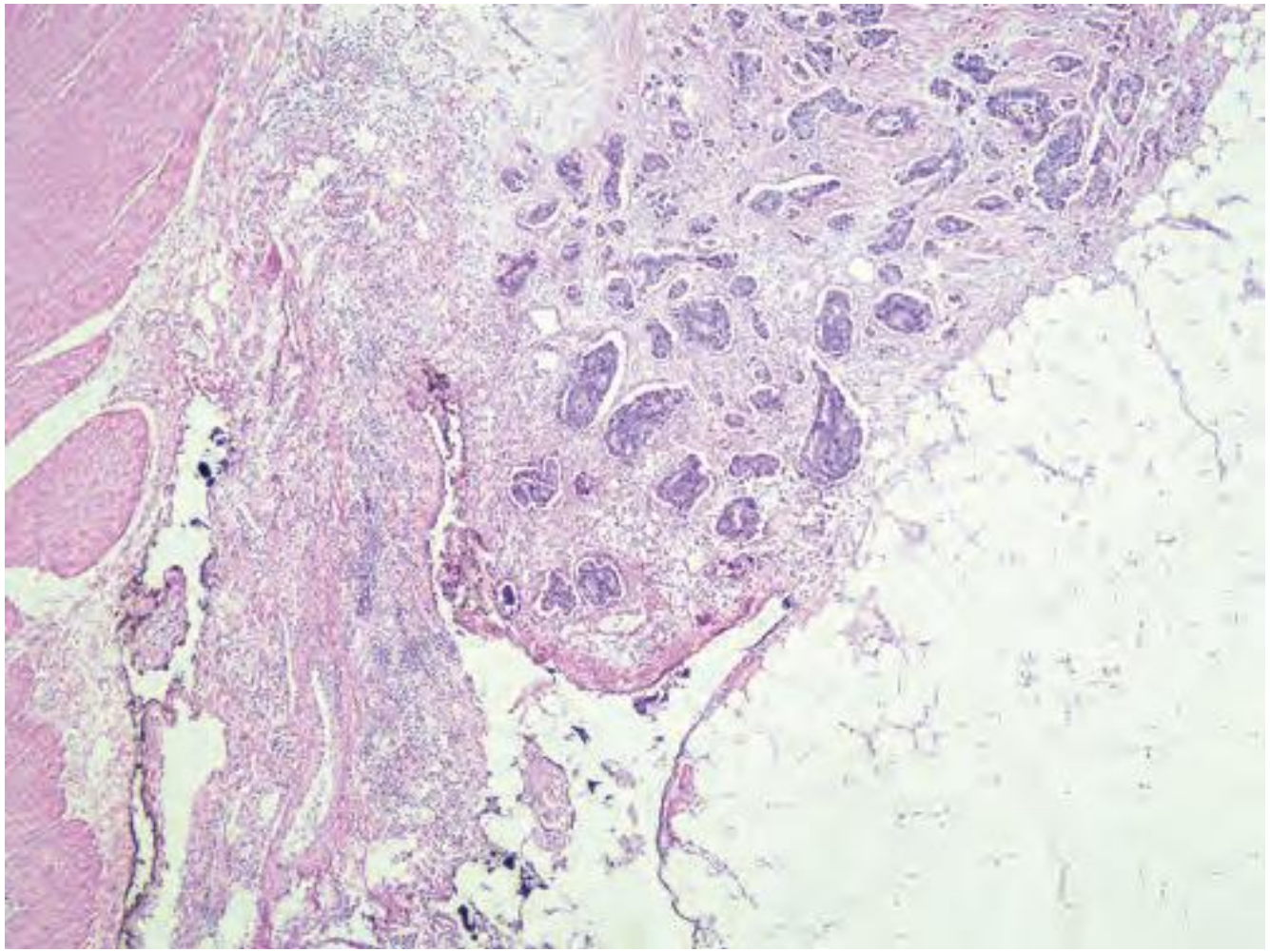
(3) hematogenous spread.

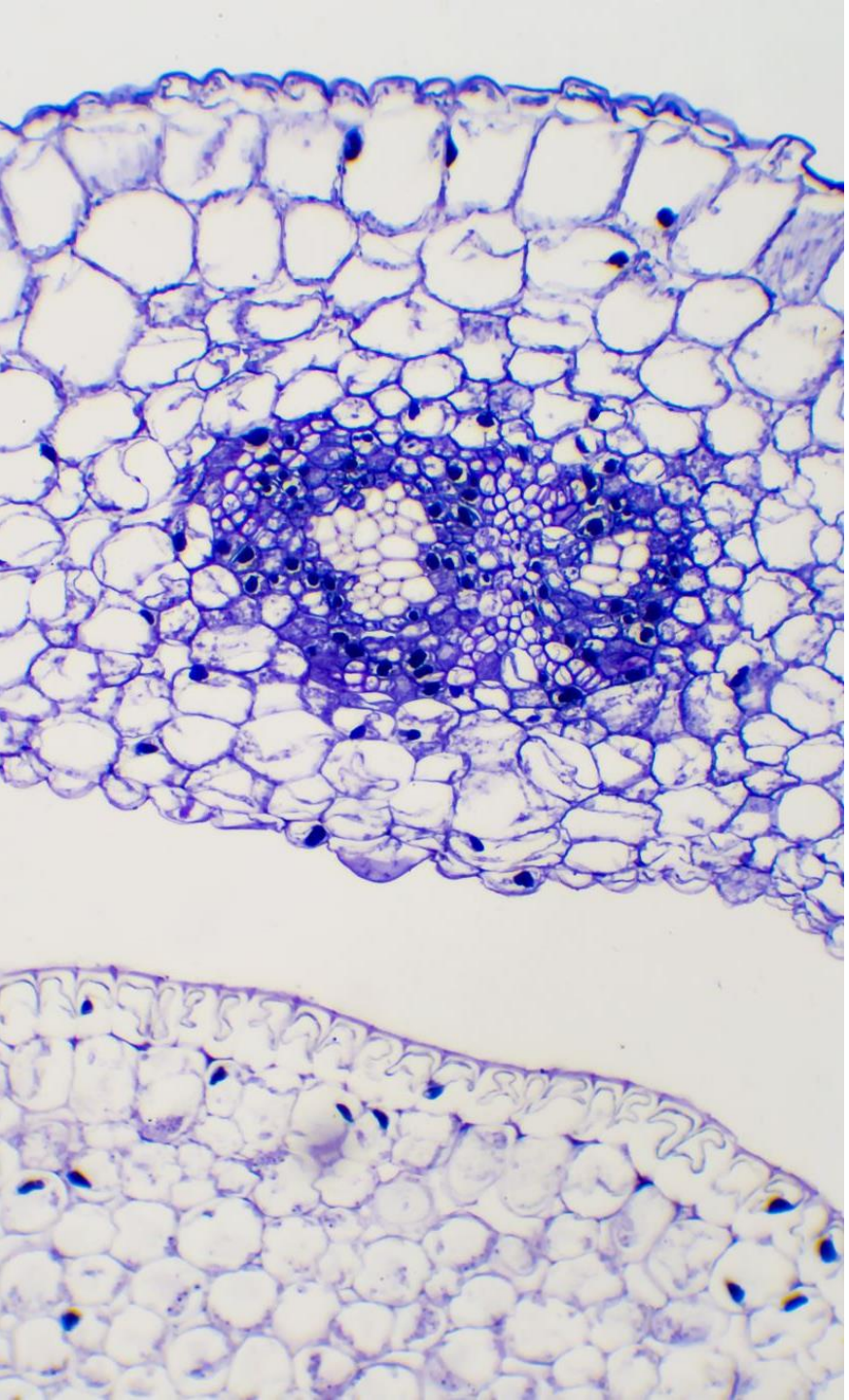




SEEDING OF BODY CAVITIES AND SURFACES.

- May occur whenever a malignant neoplasm penetrates into a natural "open field" lacking physical barriers.
- Most often involved is the peritoneal cavity , but any other cavity—pleural, pericardial, subarachnoid, and joint spaces—may be affected.
- Seeding is characteristic of carcinomas arising in the ovaries, which, spread to peritoneal surfaces. Remarkably, the tumor cells may remain confined to the surface of the abdominal viscera without penetrating into the substance.
- Mucus-secreting appendiceal carcinomas or ovarian carcinomas sometimes fill the peritoneal cavity with a gelatinous neoplastic mass referred to as *pseudomyxoma peritonei.*





LYMPHATIC SPREAD

- **Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas .**

- Sarcomas may also use this route.
- Tumors do not contain functional lymphatics, but lymphatic vessels located at the tumor margins are apparently sufficient for the lymphatic spread of tumor cells.

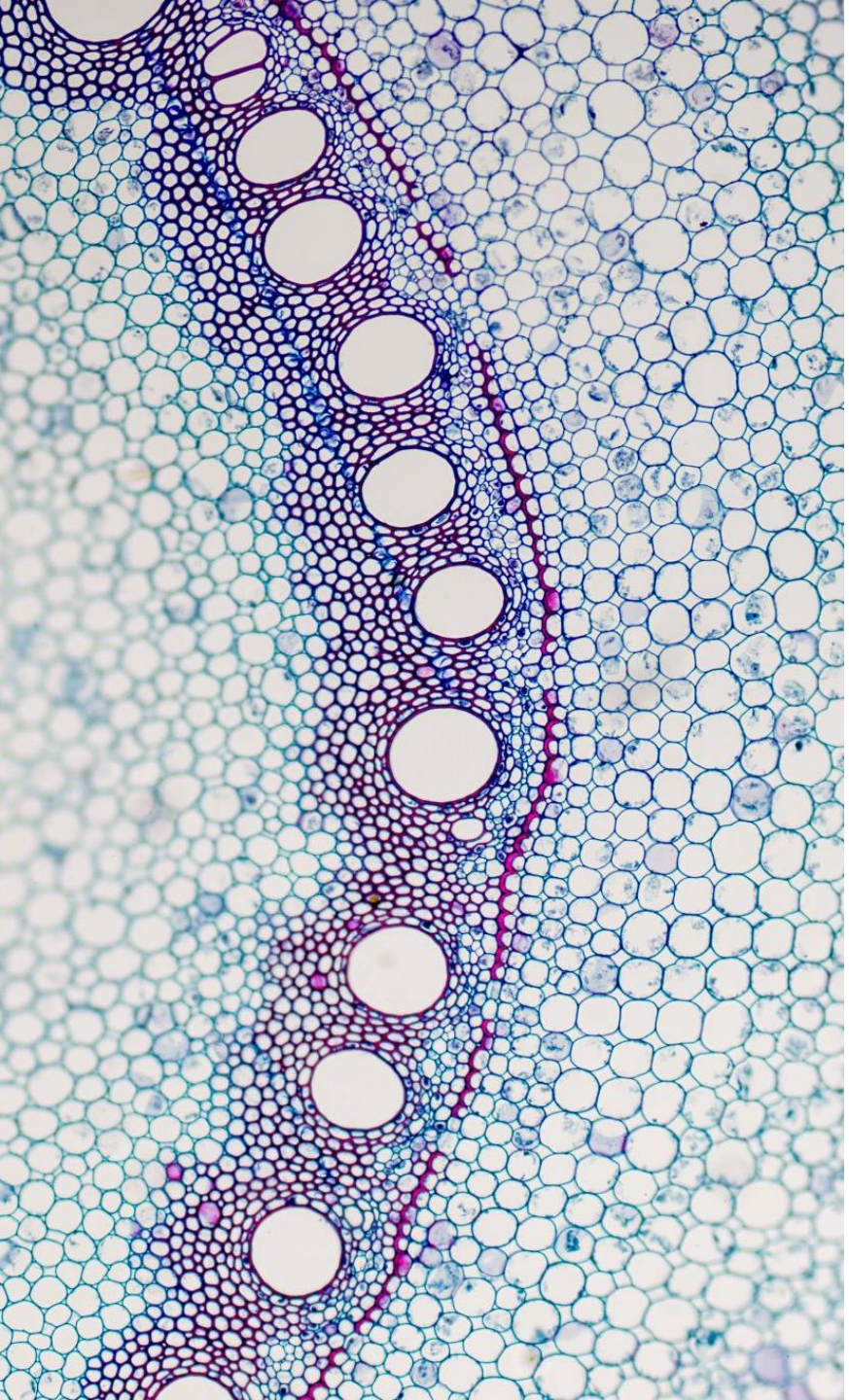
- The pattern of lymph node involvement follows the natural routes of lymphatic drainage. Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to the axillary lymph nodes.

LYMPHATIC SPREAD

- Cancers of the inner quadrants drain to the nodes along the internal mammary arteries. Thereafter, the infraclavicular and supraclavicular nodes may become involved.

- Carcinomas of the lung arising in the major respiratory passages metastasize first to the perihilar tracheobronchial and mediastinal nodes.

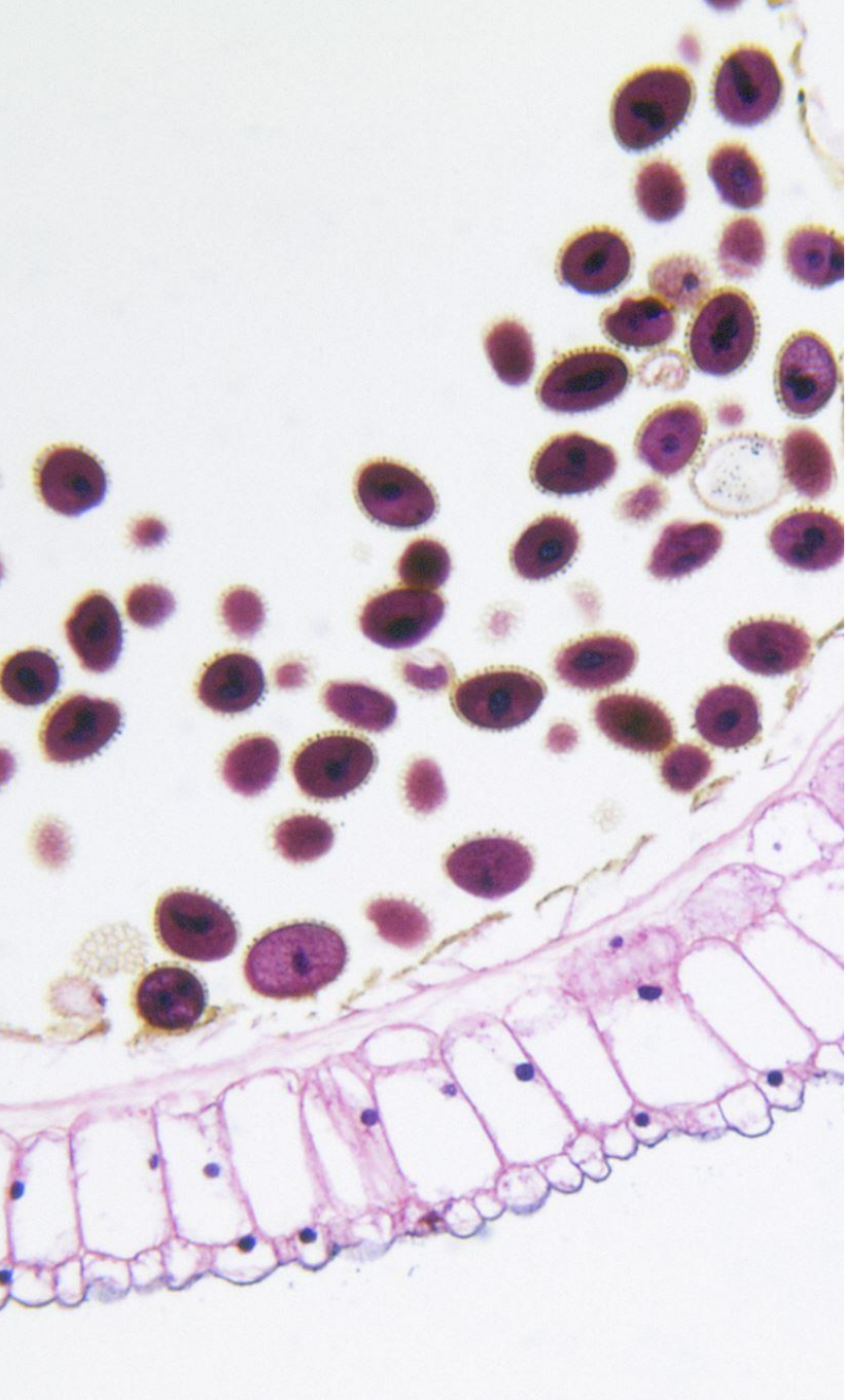
- Local lymph nodes may be bypassed—so-called skip metastasis—because of venous-lymphatic anastomoses or because inflammation or radiation has obliterated lymphatic channels.



SENTINEL NODE

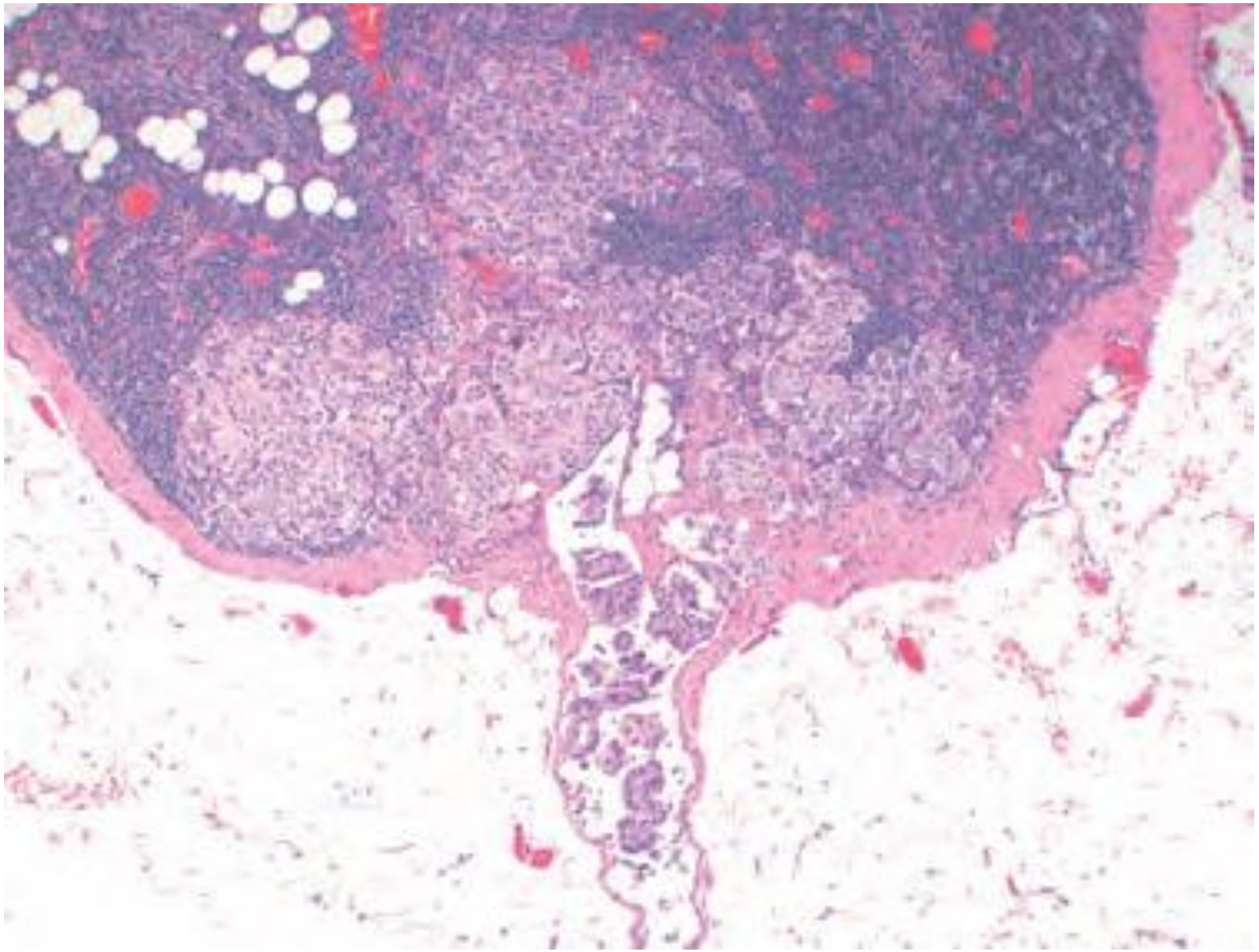
- In breast cancer, determining the involvement of axillary lymph nodes is important for assessing the future course of the disease and for selecting suitable therapeutic strategies.
- To avoid the considerable surgical morbidity associated with a full axillary lymph node dissection, *biopsy of sentinel nodes* is often used to assess the presence or absence of metastatic lesions in the lymph nodes .
- **A sentinel node is defined as "the first node in a regional lymphatic basin that receives lymph flow from the primary tumor."** Sentinel node mapping can be done by injection of radiolabeled tracers or colored dyes, and examination of frozen sections of the sentinel lymph node performed during surgery can guide the surgeon to the appropriate therapy.

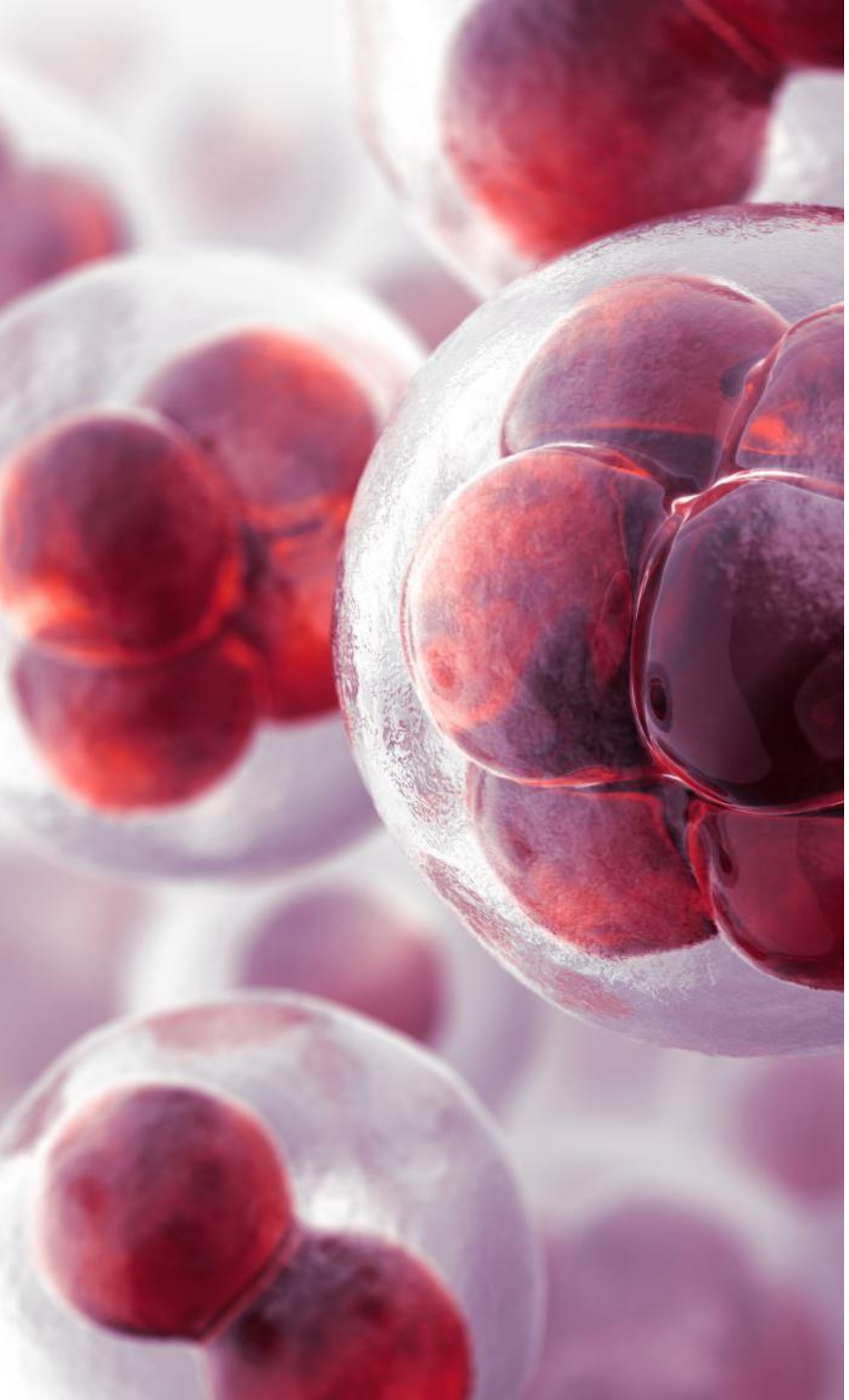
- Sentinel node examination has also been used for detecting the spread of melanomas, colon cancers, and other tumors.



LYMPHATIC SPREAD

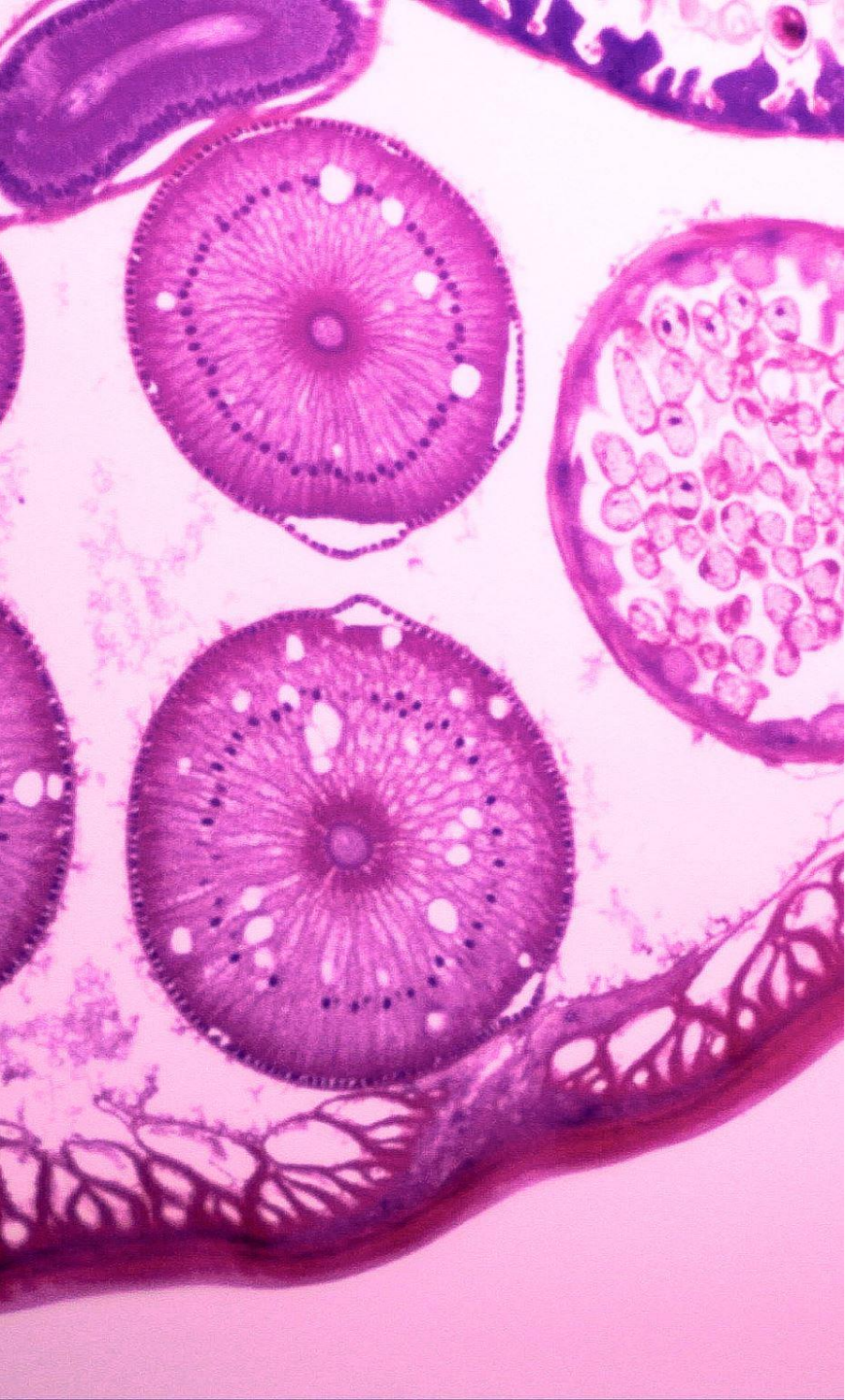
- Drainage of tumor cell debris or tumor antigens, or both, also induces reactive changes within nodes. Thus, enlargement of nodes may be caused by the spread and growth of **lymph** cancer cells or reactive hyperplasia.
- Nodal enlargement in proximity to a cancer, while it must arouse suspicion, does not necessarily equate with dissemination of the primary lesion.





HEMATOGENOUS SPREAD

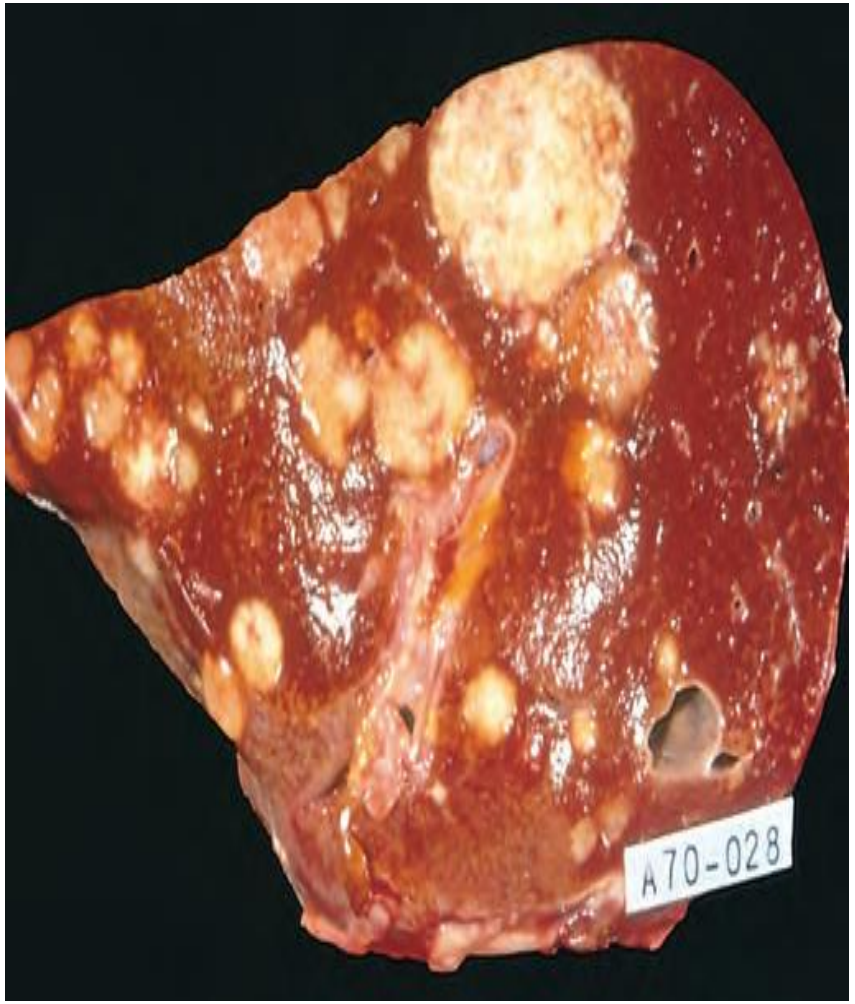
- Hematogenous spread is typical of sarcomas but is also seen with carcinomas.
- Arteries, with their thicker walls, are less readily penetrated than are veins.
- Arterial spread may occur when tumor cells pass through the pulmonary capillary beds or pulmonary arteriovenous shunts or when pulmonary metastases themselves give rise to additional tumor emboli.



HEMATOGENOUS SPREAD

- The liver and the lungs are most frequently involved in hematogenous dissemination, because all portal area drainage flows to the liver and all caval blood flows to the lungs.

- Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus, and this pathway is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate.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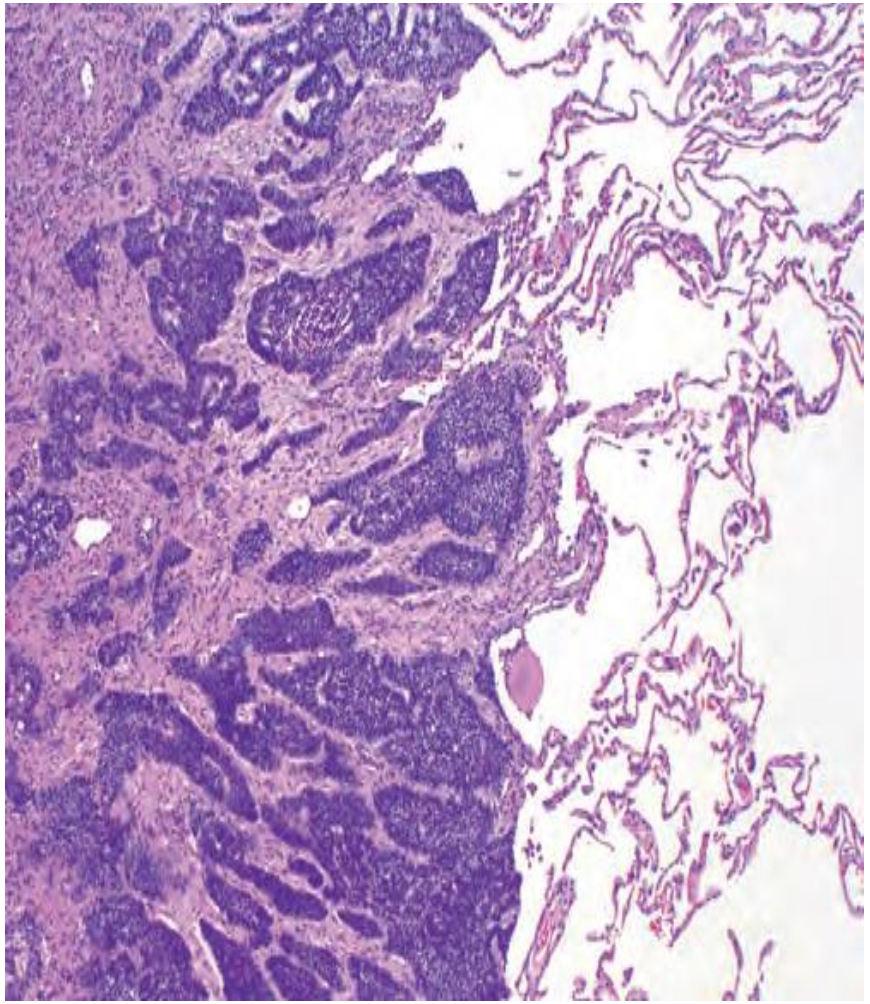
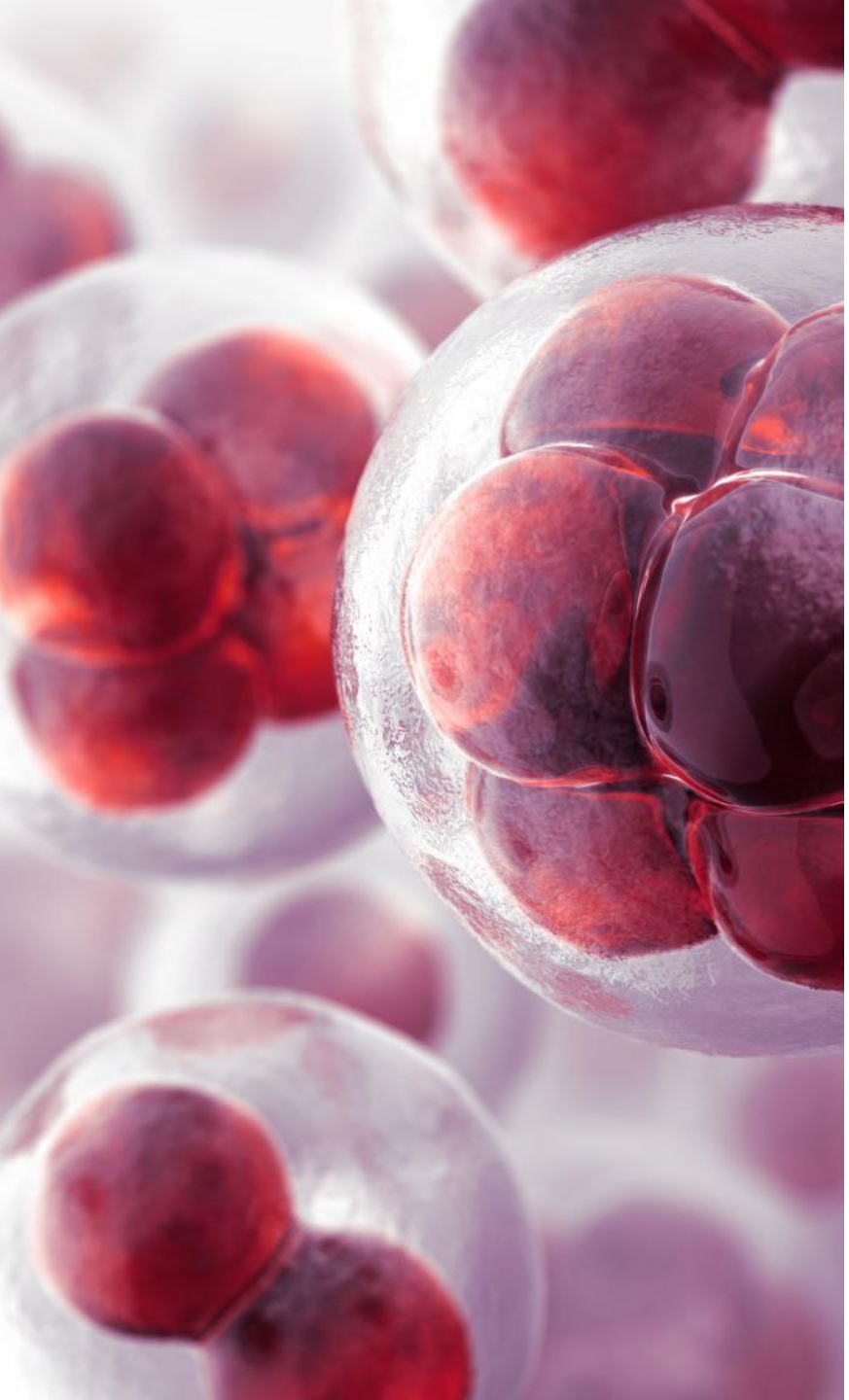




HEMATOGENOUS SPREAD

- Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself, from where it may grow up to the inferior vena cava, sometimes reaching the right side of the heart.
- Hepatocellular carcinomas often penetrate portal and hepatic radicles.
- Intravenous growth may not be accompanied by widespread dissemination.
- Histologic evidence of penetration of small vessels at the site of the primary neoplasm is obviously an ominous feature.

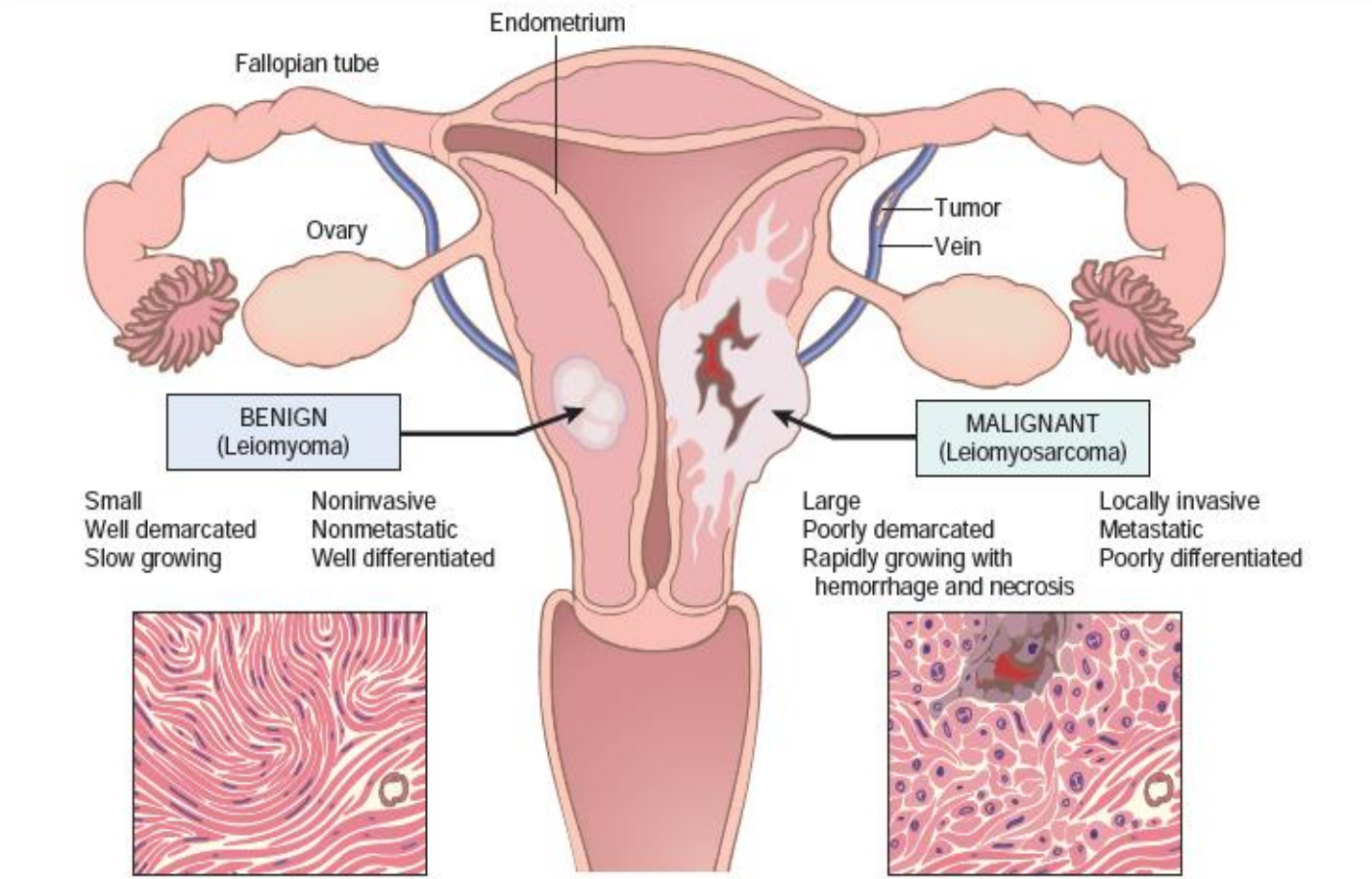
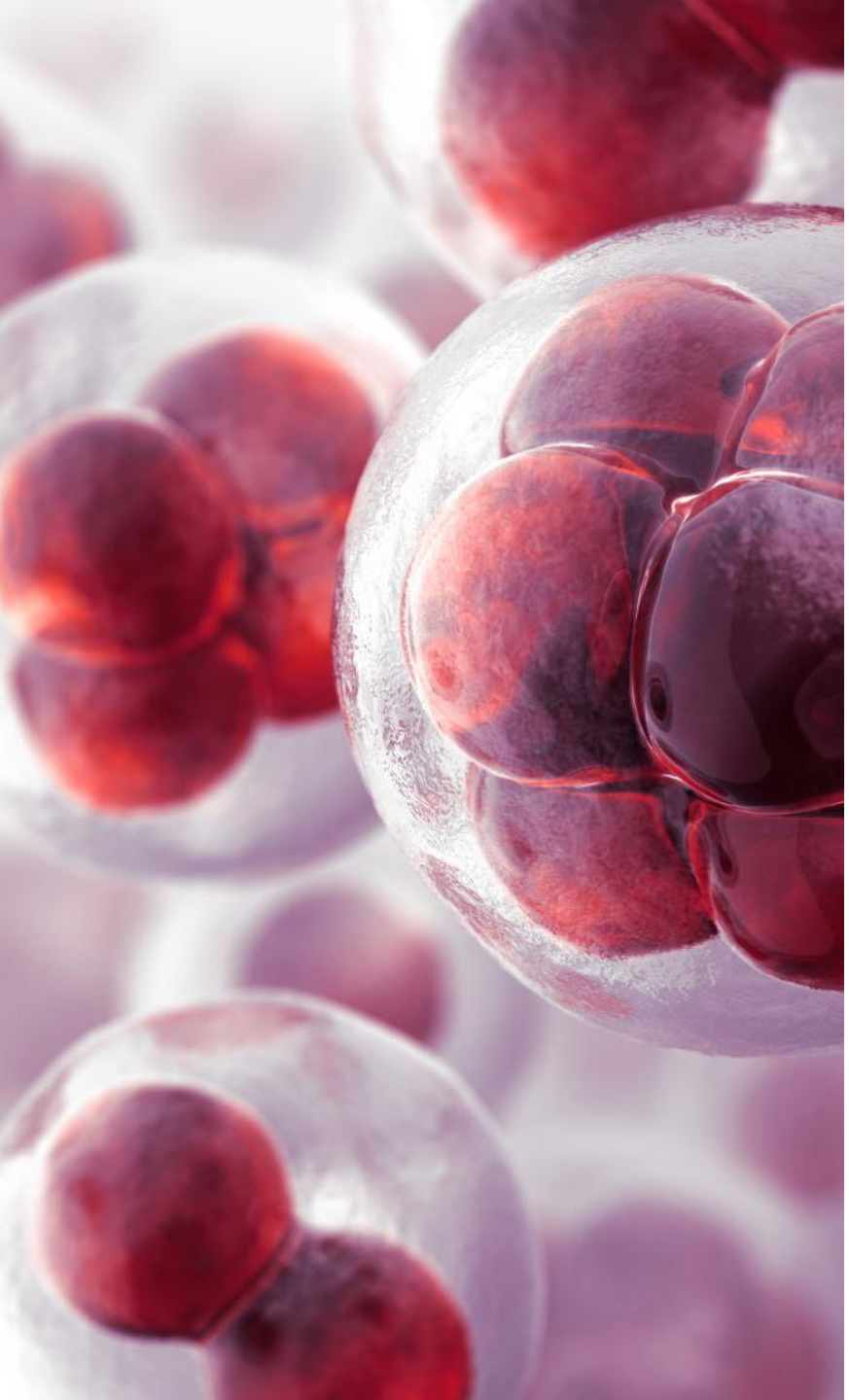


Figure 7-19 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of the same origin (leiomyosarcoma).



EPIDEMIOLOGY

- In USA The most common tumors in **men** arise in the prostate, lung, and colon/rectum. In **women,** cancers of the breast, lung, and colon/rectum are the most frequent.

- Cancers of the lung, female breast, prostate, and colon/ rectum constitute more than 50% of cancer diagnoses and cancer deaths in the United States.

- In the **developing world** the most common cancers involve the lung, stomach, and liver in **men** and the breast, cervix, and lung in **women.**

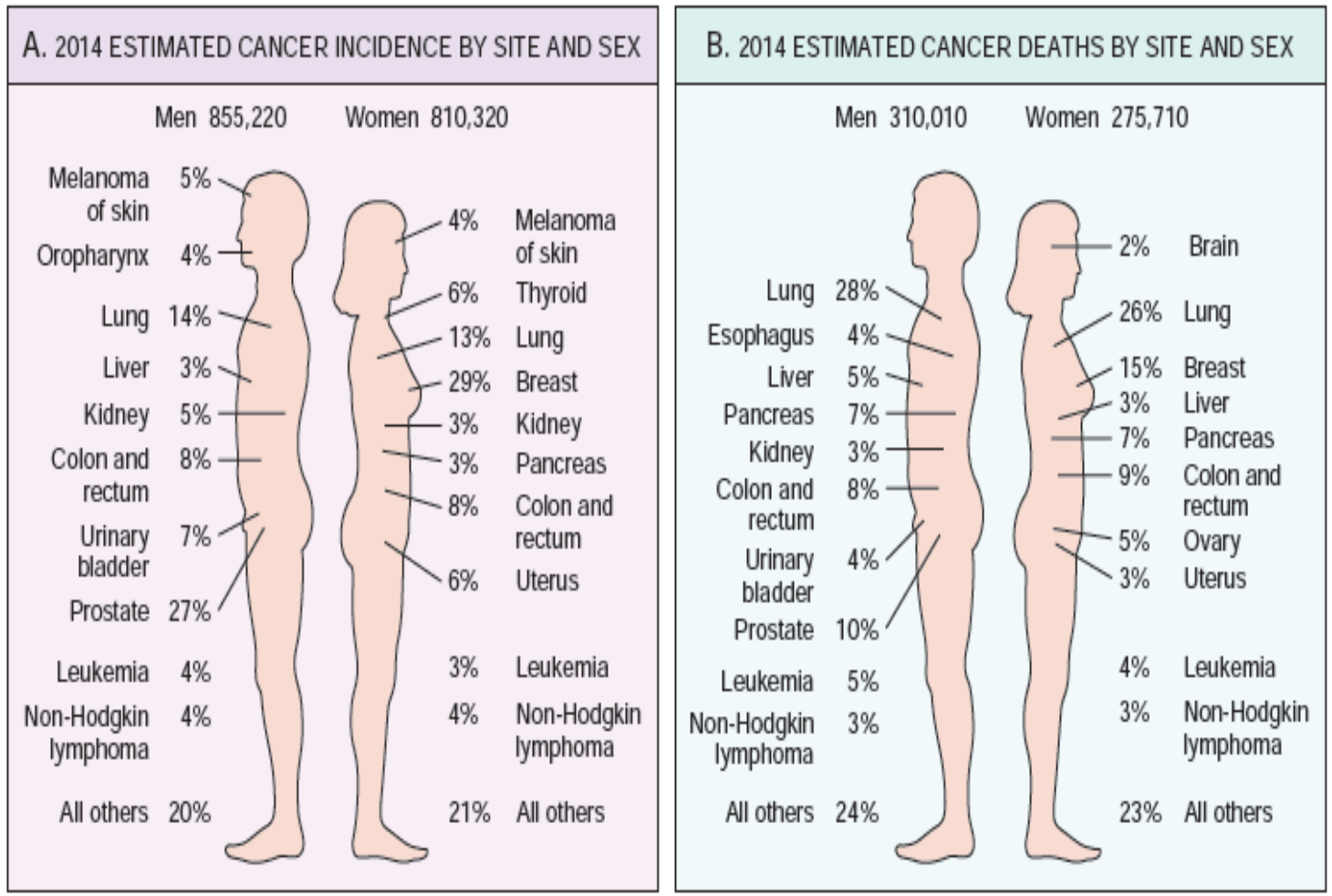


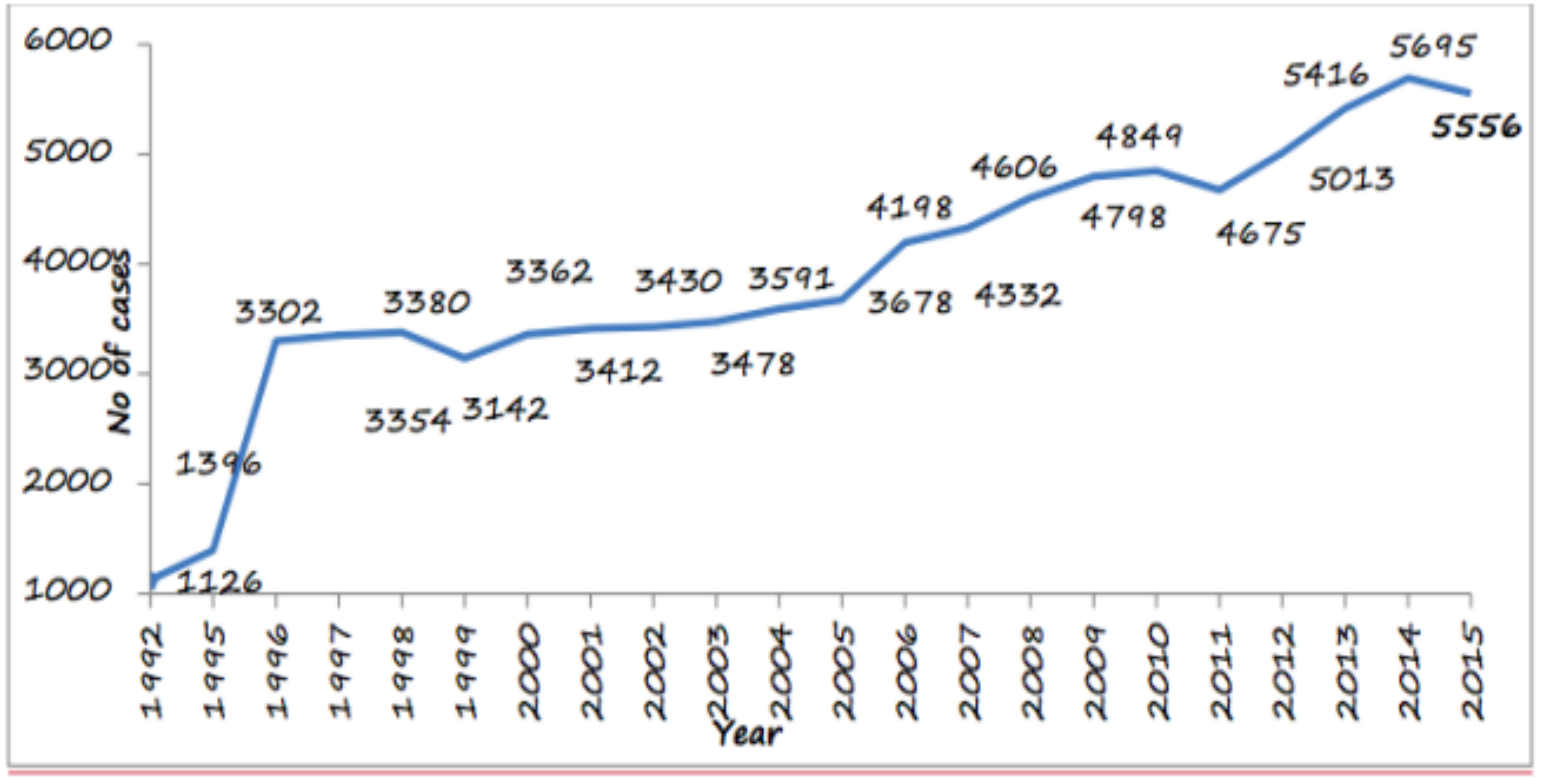
Figure 7-20 Cancer incidence **(A)** and mortality **(B)** by site and sex. Excludes basal cell and squamous cell skin cancers and in situ carcinomas, except urinary bladder. (Adapted from American Cancer Society. Cancer Statistics 2011.)

JORDAN

- National cancer registry collects data about cancer from ALL hospitals in the country.
- According to 2015 statistics the most common cancer among Jordanian males is colorectal cancer followed by lung cancer.
- According to 2015 statistics, the most common cancer among Jordanian females is breast followed by colorectal cancer.

- Jordanian cancer Registry (JCR) Published yearly, on the ministry of health website:https://www.moh.gov.jo/Echobusv3.0/SystemAssets/fbd82c46-6851-40d5-ae9f-651dfc9515ec.pdf

Figure (1)Trend of cancer in Jordan, 1992-2015



CANCER IN JORDAN IS INCREASING

Table (7) Ten most common cancers among Jordanians, Males, 2015

Rank	Site	Frequency	Percent
1	Colorectal	388	14.5
2	Lung	301	11.3
3	Urinary Bladder	269	10.1
4	Prostate	215	8.1
5	Non-Hodgkin lymphoma	137	5.1
6	Leukemia	120	4.5
7	Kidney	116	4.3
8	Brain	108	4.0
9	Stomach	101	3.8
10	Hodgkin disease	76	2.8

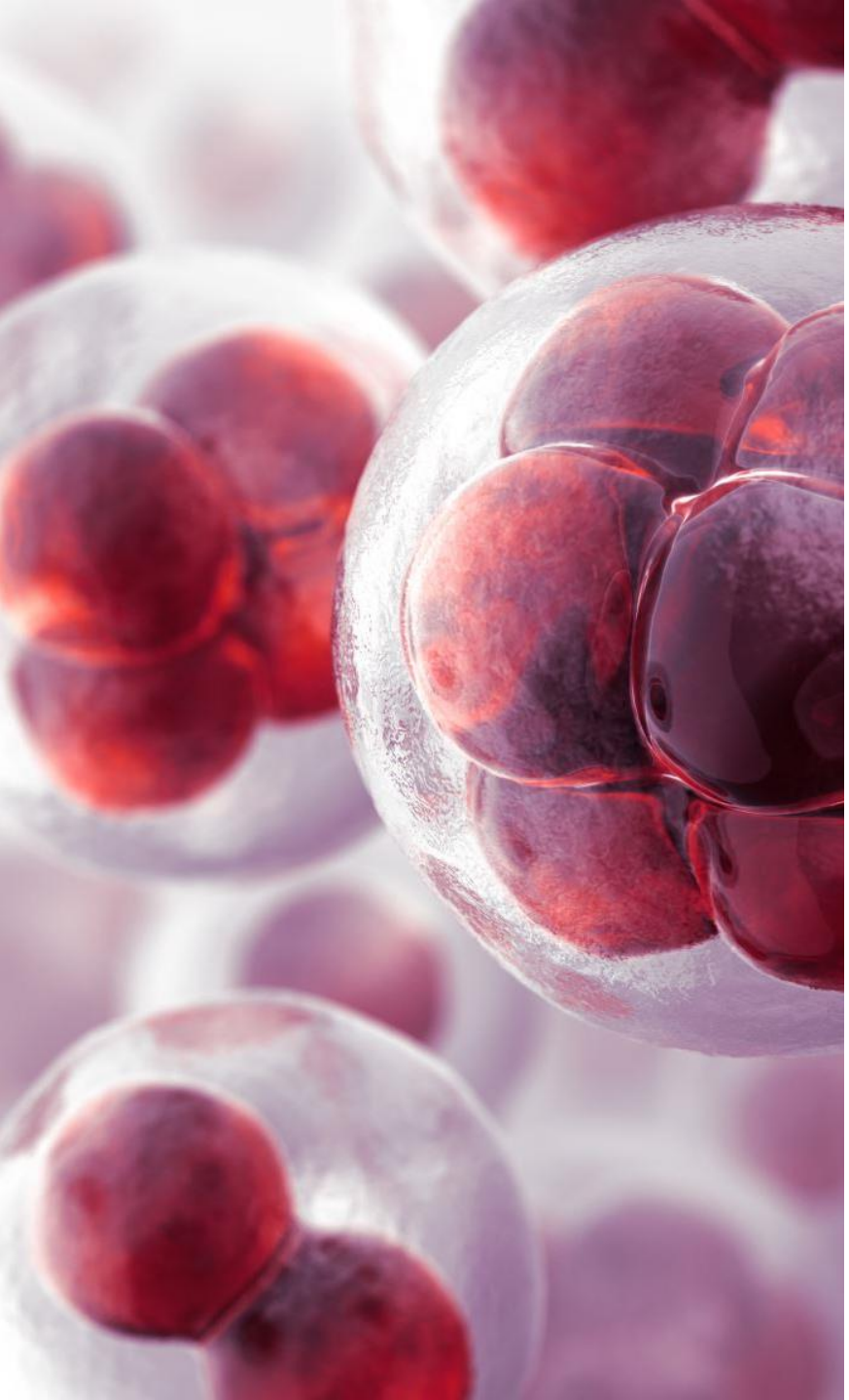
Table (8) Ten most common cancers among Jordanian Females , 2015

Rank	Site	Frequency	Percent
1	Breast	1138	39.4
2	Colorectal	280	9.7
3	Thyroid	170	5.9
4	Corpus Uteri, unspecified	156	5.4
5	Non-Hodgkin lymphoma	109	3.8
6	Ovary	86	3.0
7	Leukemia	80	2.8
8	Lung	77	2.7
9	Hodgkin disease	68	2.4
10	Brain, Nervous system	67	2.3

ENVIRONMENTAL FACTORS

- Both genetic and environmental factors contribute to the development of cancer, but **environmental influences** appear to be the dominant risk factors for most cancers.

- Evidence supporting a central role for environmental factors can be found in the wide geographic variation that exists in the incidence of specific forms of cancer .



ENVIRONMENTAL FACTORS

- For example, the most common tumor of men in the United States and most of the developed world is prostate cancer, but in certain countries or regions (most located in the developing world), cancers of the liver, stomach, esophagus, bladder, lung, oropharynx, and the immune system rise to the top of the list.
- The incidence of breast cancer is generally much higher in women in developed countries than in most parts of the developing world.
- Although racial predispositions cannot be ruled out, it is believed that environmental influences— some known, some not— underlie most of these differences in cancer incidence.

CHANGING TRENDS

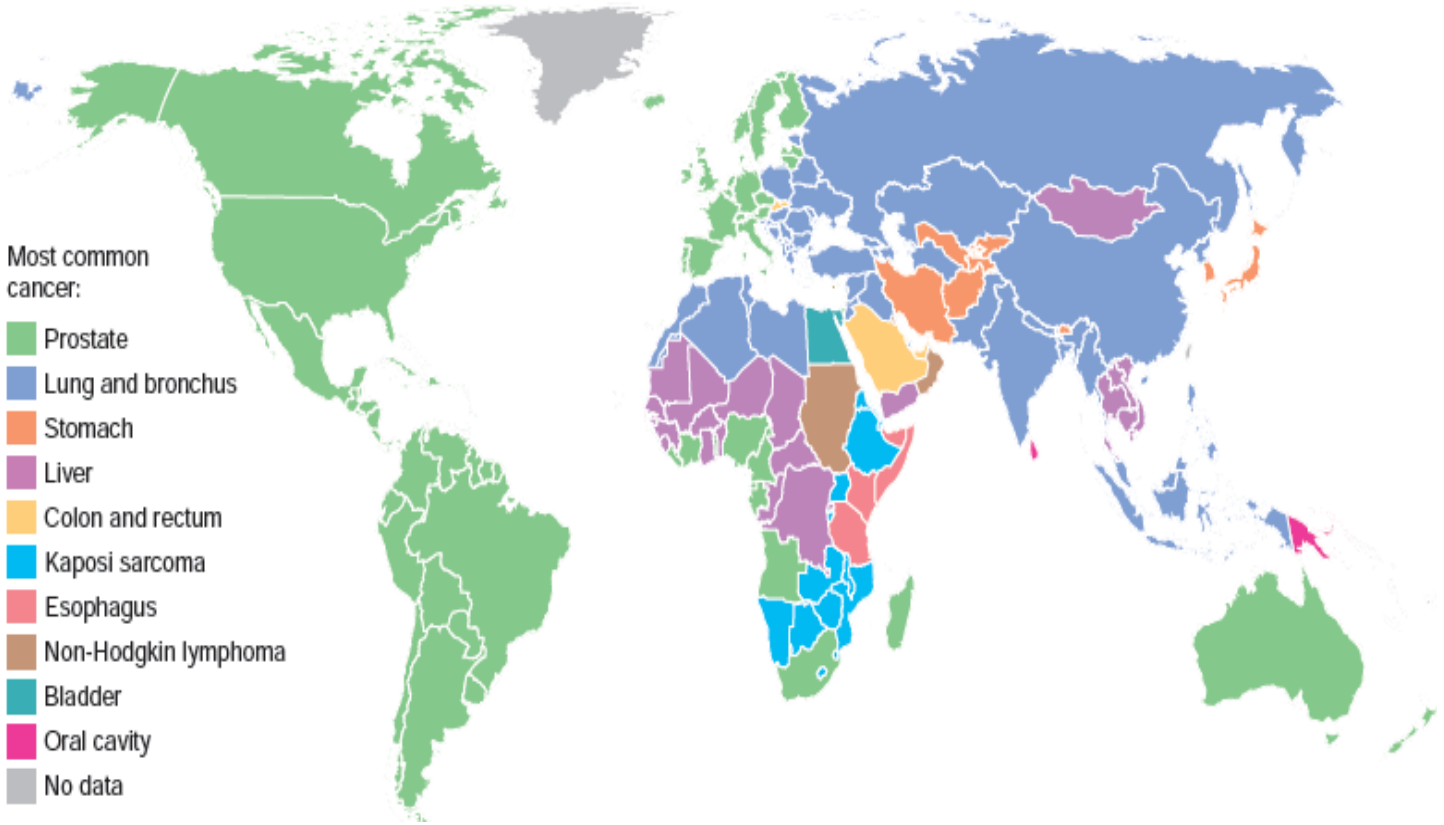
• Cancer incidence and mortality can change according to treatments or to changes in environmental factors.

• Example 1: Colorectal cancer incidence has decreased in USA during the last decade due to awareness of risk factors and to screening programs. However in Jordan, Colorectal carcinoma is increasing.

• Example 2: Cervical cancer has decreased in the West due to screening (cervical smear tests).

• Example 3: Lung cancer was uncommon among women worldwide. But when more women started to smoke, lung cancer increased among them.

A. Worldwide variation of cancer incidence in males



B. Worldwide incidence of breast cancer

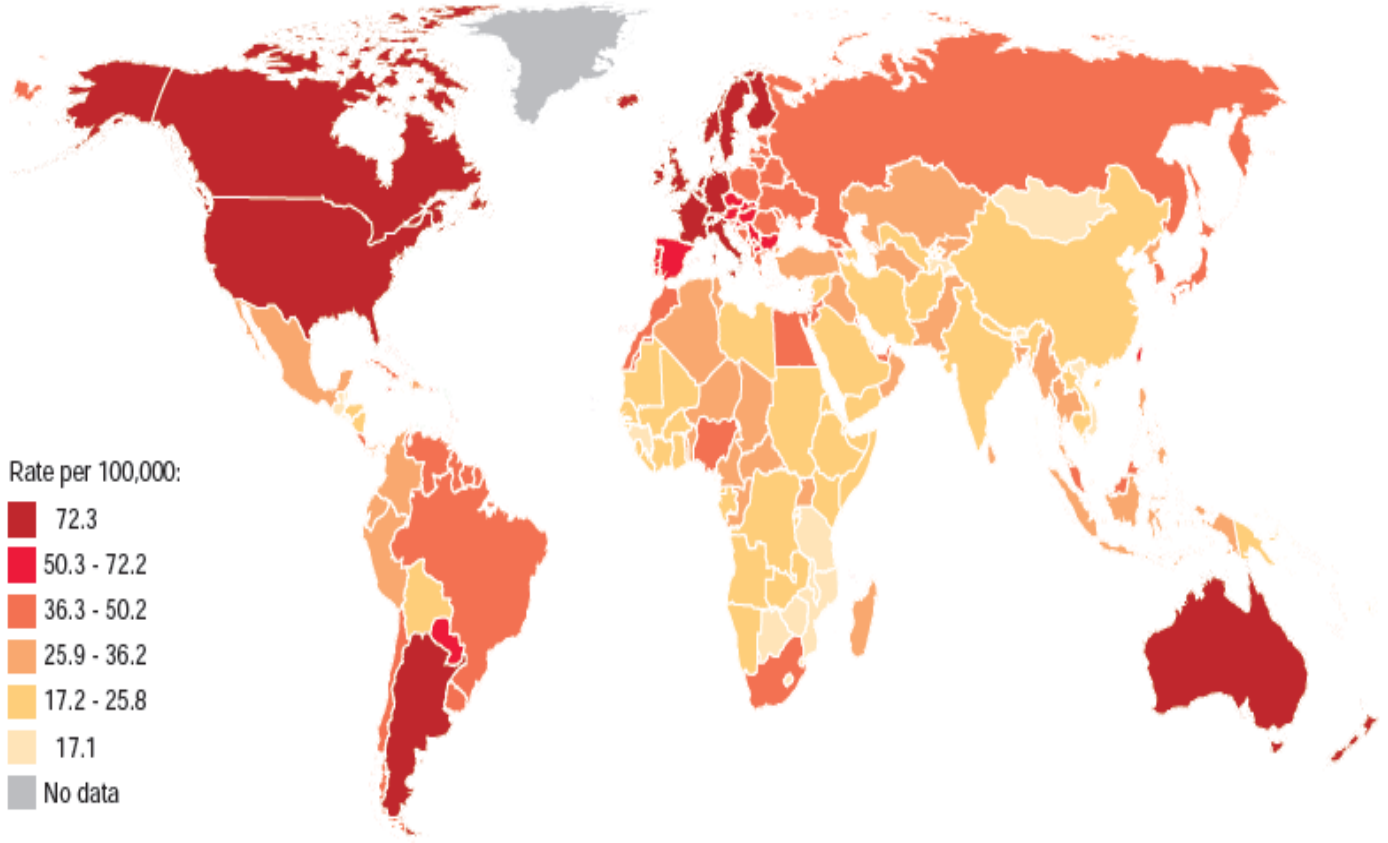


Figure 7-21 Geographic variation in cancer incidence. **A,** Most common cancers in males by country. **B,** Variation in breast cancer incidence in women by country. (Adapted from Global Cancer Facts & Figures, 2nd ed. Atlanta, American Cancer Society, 2011.)

GEOGRAPHIC AND ENVIRONMENTAL FACTORS

- Environmental factors are the predominant cause of cancer.
- Geographic variations in cancer incidence are due to different life styles and to environmental factors.
- When people move from one geographic area to another, subsequent generations acquire the same risk of cancer development as original population.
- Why subsequent generations: because it takes time for migrants to fully adapt the new country's life style!
- Example: Stomach cancer is common in Japan. Japanese who migrate to USA have lower incidence of gastric cancer than Japanese in Japan.

ETIOLOGY (**INFECTIOUS AGENTS**)

- About 15% of all cancers are believed to be caused directly or indirectly by infectious agents, with the burden of cancers linked to infections being roughly three times higher in the developing world than in the developed world.
- For example, *human papilloma virus* (HPV), an agent that is spread through sexual contact, is responsible for a large majority of cases of cervical carcinoma and an increasing fraction of head and neck cancers.

ETIOLOGY (SMOKING)

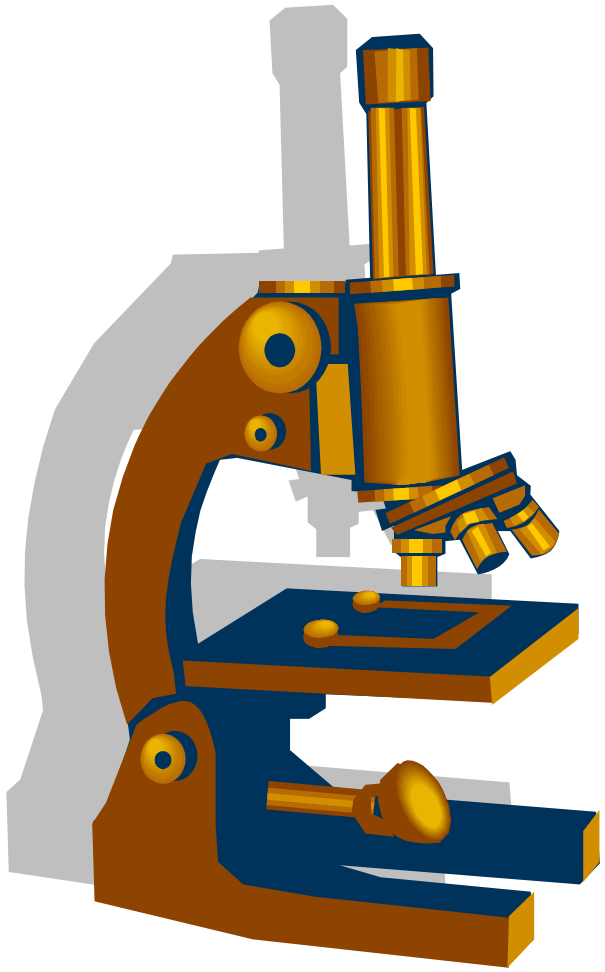
- The single most important environmental factor contributing to premature death in the United States. Smoking cigarettes has been implicated in cancer of the mouth, pharynx, larynx, esophagus, pancreas, bladder, and about 90% of lung cancer deaths.

ETIOLOGY (ALCOHOL CONSUMPTION)

- It increases the risk of carcinomas of the oropharynx (excluding lip), larynx, and esophagus and the development of alcoholic cirrhosis, hepatocellular carcinoma.
- Alcohol and tobacco together synergistically increase the risk of cancers.

ETIOLOGY (DIET)

Although the precise dietary factors that affect cancer risk remain a matter of debate, wide geographic variation in the incidences of colorectal carcinoma, prostate carcinoma, and breast carcinoma has been ascribed to **differences in diet.**



ETIOLOGY (OBESITY)

Overall, the most overweight individuals in the U.S. population have 52% (men) to 62% (women) higher death rates from cancer.

ETIOLOGY (REPRODUCTIVE FACTORS)

- There is strong evidence that lifelong cumulative exposure to estrogen stimulation, particularly if unopposed by progesterone, increases the risk of cancers of the breast and endometrium.
- Some of the differences in breast cancer incidence that are seen across the world are affect the timing and number of pregnancies a woman has during her lifetime.

ETIOLOGY (ENVIRONMENTAL CARCINOGENS)

- Individuals may be exposed to carcinogenic factors when they go outside (e.g., ultraviolet [UV] rays, smog), drink well water (e.g., arsenic, particularly in Bangladesh), take certain medications (e.g., methotrexate), go to work (e.g., asbestos), or even while lounging at home (e.g., grilled meat, high-fat diet, alcohol).

Table 7-3 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

Modified from Stellman JM, Stellman SD: Cancer and workplace. CA Cancer J Clin 1996;46:70.

ETIOLOGY (AGE)

- **Age has an important influence on the likelihood of being afflicted with cancer**.
- Most carcinomas occur in the later years of life (>55 years).
- Cancer is the main cause of death among women aged 40 to 79 and among men aged 60 to 79; the decline in deaths after age 80 is due to the lower number of individuals who reach this age.
- The rising incidence of cancer with age is likely explained by the accumulation of somatic mutations .
- The decline in immune competence that accompanies aging may also be a factor.

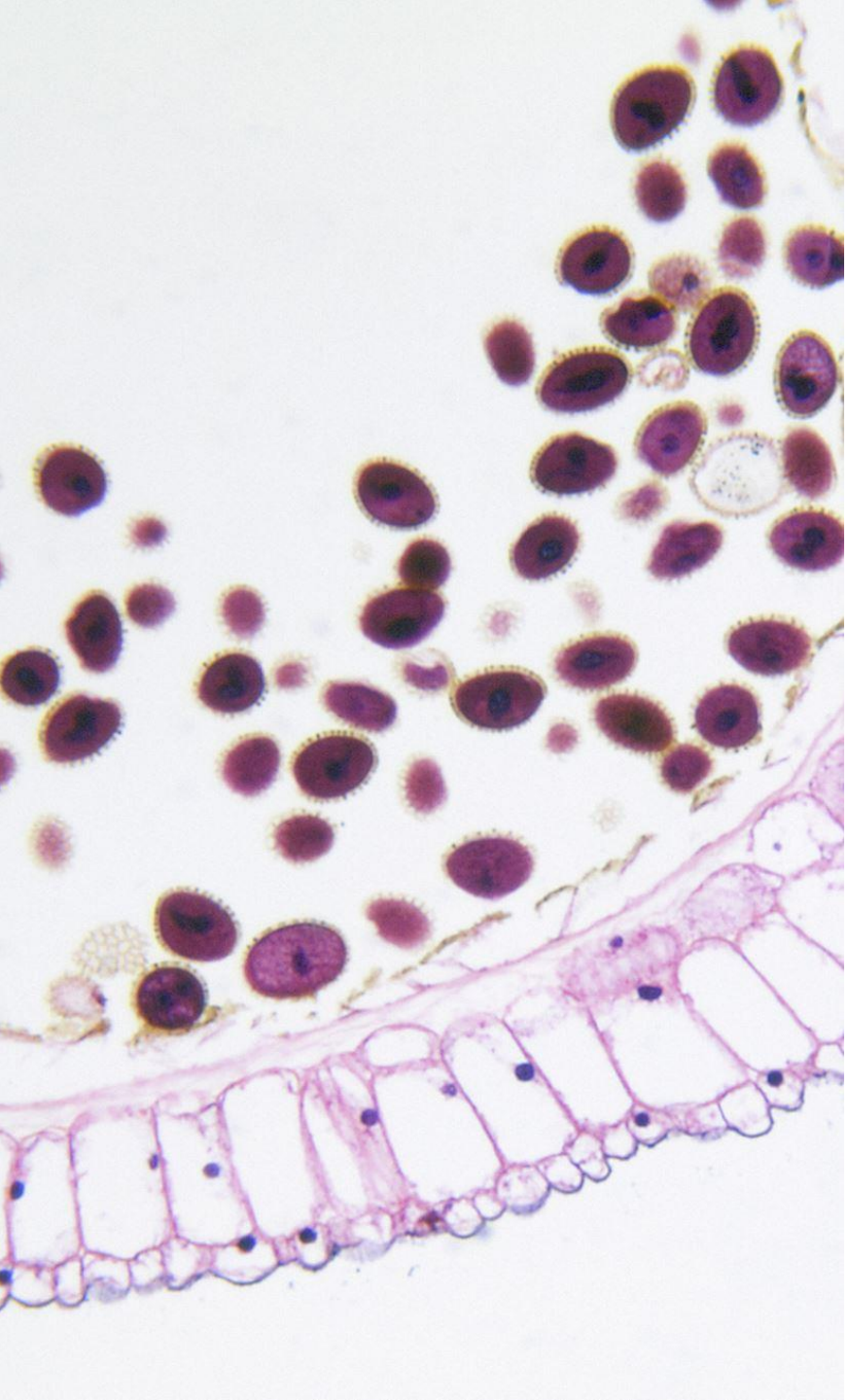
ETIOLOGY (AGE)

- Children are not spared; cancer accounts for slightly more than 10% of all deaths in children younger than age 15 in the United States, second only to accidents.
- The types of cancers that predominate in children are significantly different from those seen in adults, acute leukemia and neoplasms of the central nervous system are responsible for approximately 60% of childhood cancer deaths.

- The common neoplasms of infancy and childhood include small round blue cell tumors such as neuroblastoma, Wilms tumor, retinoblastoma, acute leukemias, and rhabdomyosarcomas.

ACQUIRED PREDISPOSING CONDITIONS

- **Acquired conditions that predispose to cancer can be divided into chronic inflammations, precursor lesions, and immunodeficiency states.**
- Chronic inflammatory disorders and precursor lesions span a diverse set of conditions that are all associated with increased cellular replication, which appears to create a "fertile" soil for the development of malignant tumors. Indeed, repeated rounds of cell division may be required for neoplastic transformation, in that proliferating cells are the most at risk for accumulating the genetic lesions that lead to carcinogenesis.
- Tumors arising in the context of chronic inflammation are mostly carcinomas, but also include mesothelioma and several kinds of lymphoma. Immunodeficiency states predispose to virus-induced cancers.



PRECURSOR LESIONS

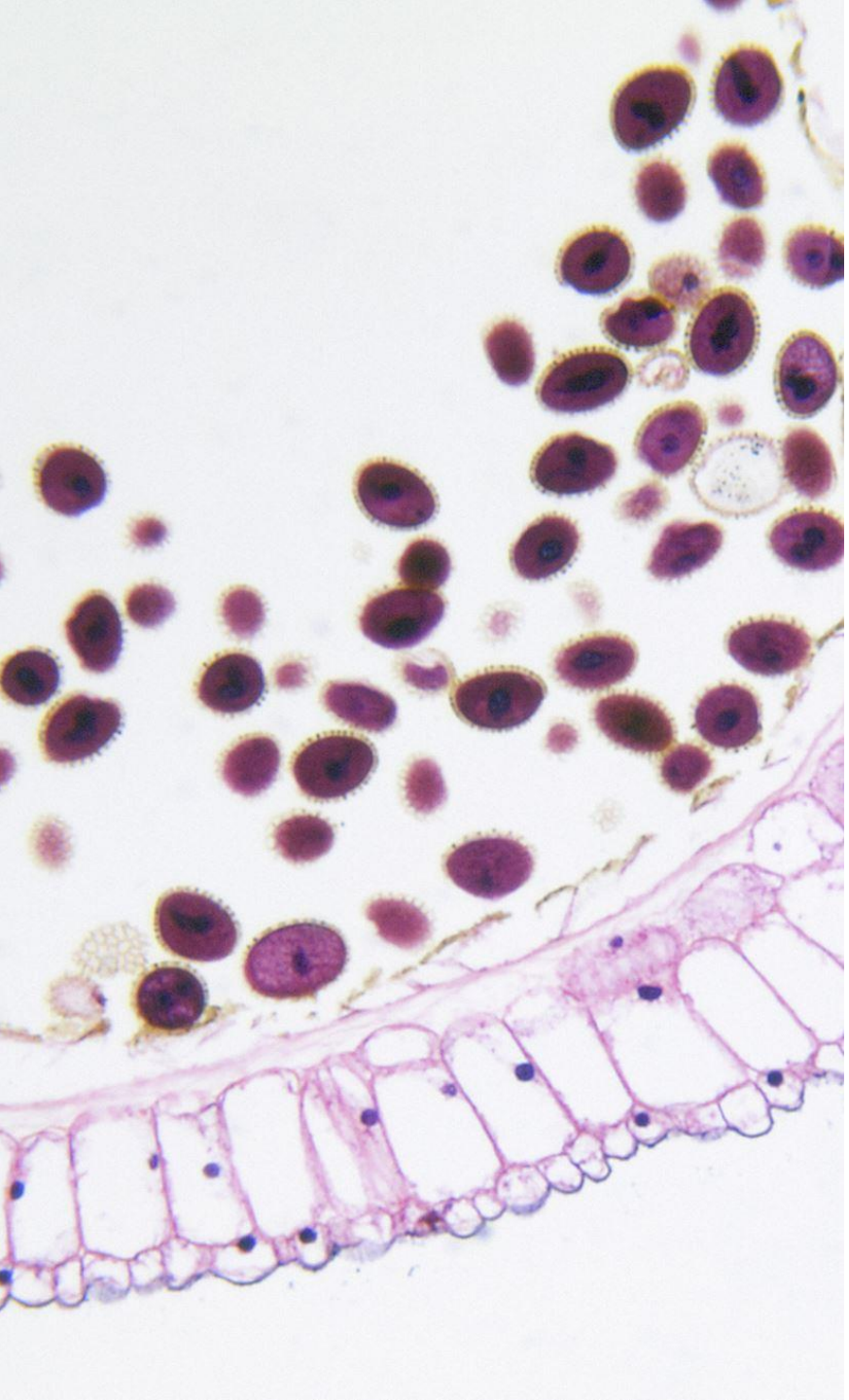
- Precursor lesions can be defined as localized morphologic changes that are associated with a high risk of cancer.

- Virtually all precursor lesions arise in epithelial surfaces and are associated with an increased risk of various forms of carcinoma.

PRECURSOR LESIONS

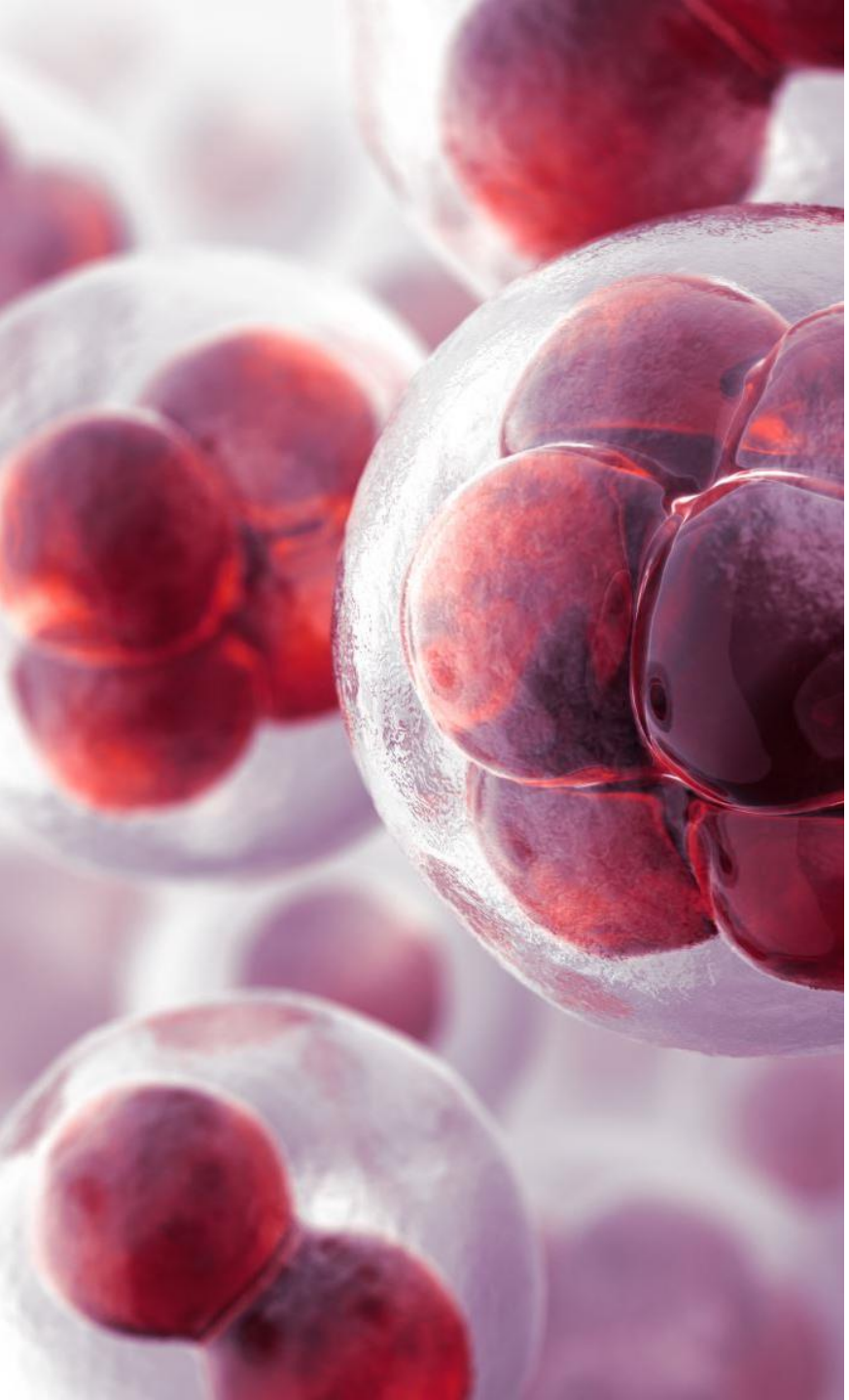
- Precursor lesions do not inevitably progress to cancer; nevertheless, they are important to recognize because some precursor lesions can be detected by screening procedures and treated, thereby reducing the risk of developing cancer.

- Many precursor lesions arise in the setting of chronic inflammation and can be recognized by the presence of metaplasia: examples include *Barrett esophagus* (gastric and colonic metaplasia of the esophageal mucosa in the setting of gastric reflux); *squamous metaplasia* of the bronchial mucosa (in response to smoking) and the bladder mucosa (in response to schistosomiasis infection); and *colonic metaplasia* of the stomach (in the setting of pernicious anemia and chronic atrophic gastritis).



PRECURSOR LESIONS

- Other precursor lesions are **non-inflammatory hyperplasias.**
- One of the most common precursor lesions of this type is ***endometrial hyperplasia*****,** which is caused by sustained estrogenic stimulation of the endometrium
- Another relatively frequent precursor lesion is ***leukoplakia***, a thickening of squamous epithelium that may occur in the oral cavity or on the penis or vulva and give rise to squamous carcinoma.



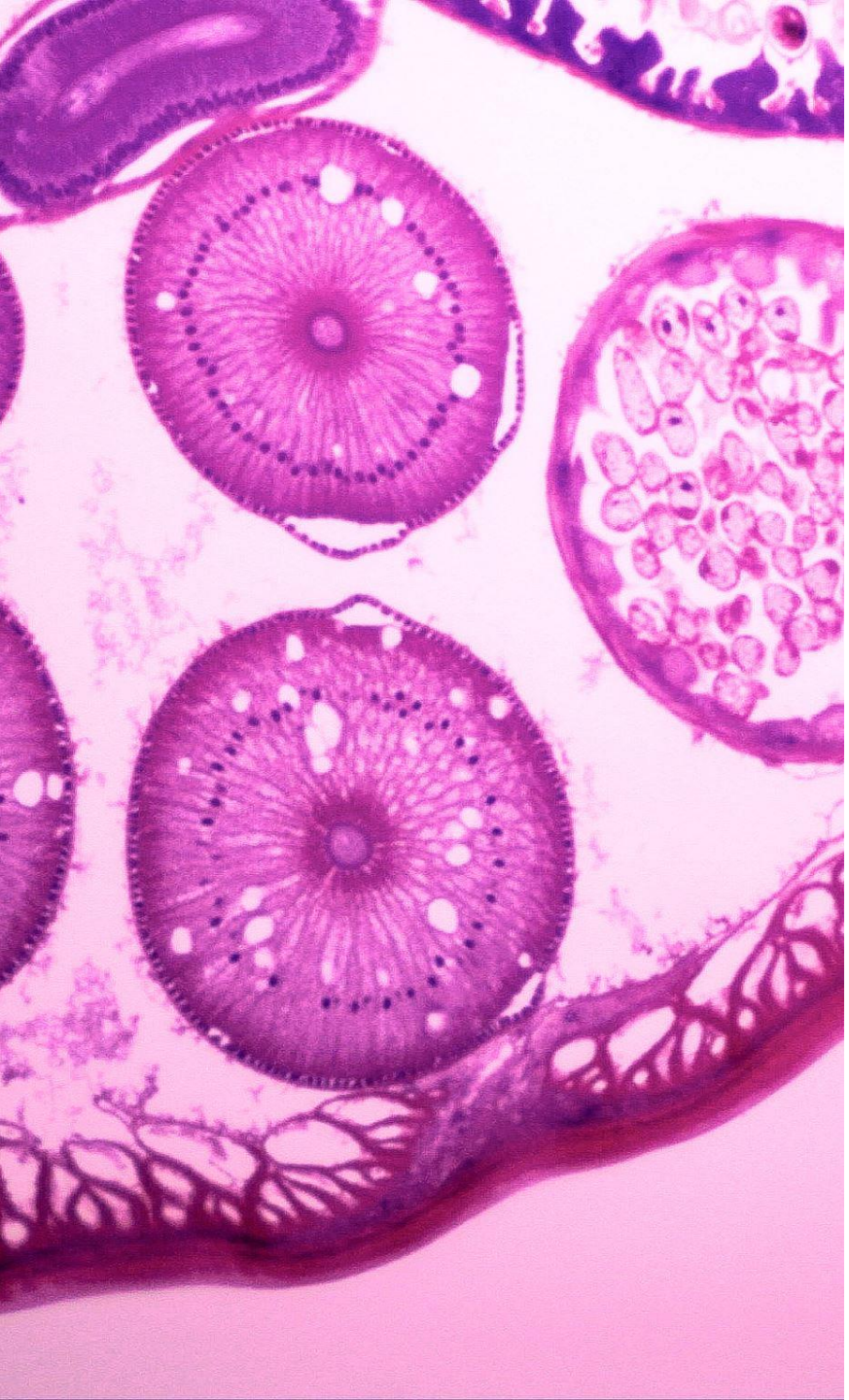
PRECURSOR LESIONS

- The final group of precursor lesions is **benign neoplasms** that are at risk for malignant transformation.
- The classic example of a neoplastic precursor lesion is the colonic *villous adenoma*, which if left untreated progresses to cancer in about 50% of cases. It should be emphasized, however, that most benign tumors transform rarely (e.g., uterine leiomyomas, pleomorphic adenoma) and others not at all (e.g., lipomas).
- Why many benign tumors have a negligible risk of malignant transformation is an unsettled question; one possibility is that benign tumors at high risk for malignant transformation possess the cancer-enabling property of genomic instability , whereas truly benign tumors do not.

Table 7-4 Chronic Inflammatory States and Cancer

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germline mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes (*Opisthorchis viverrini*)
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

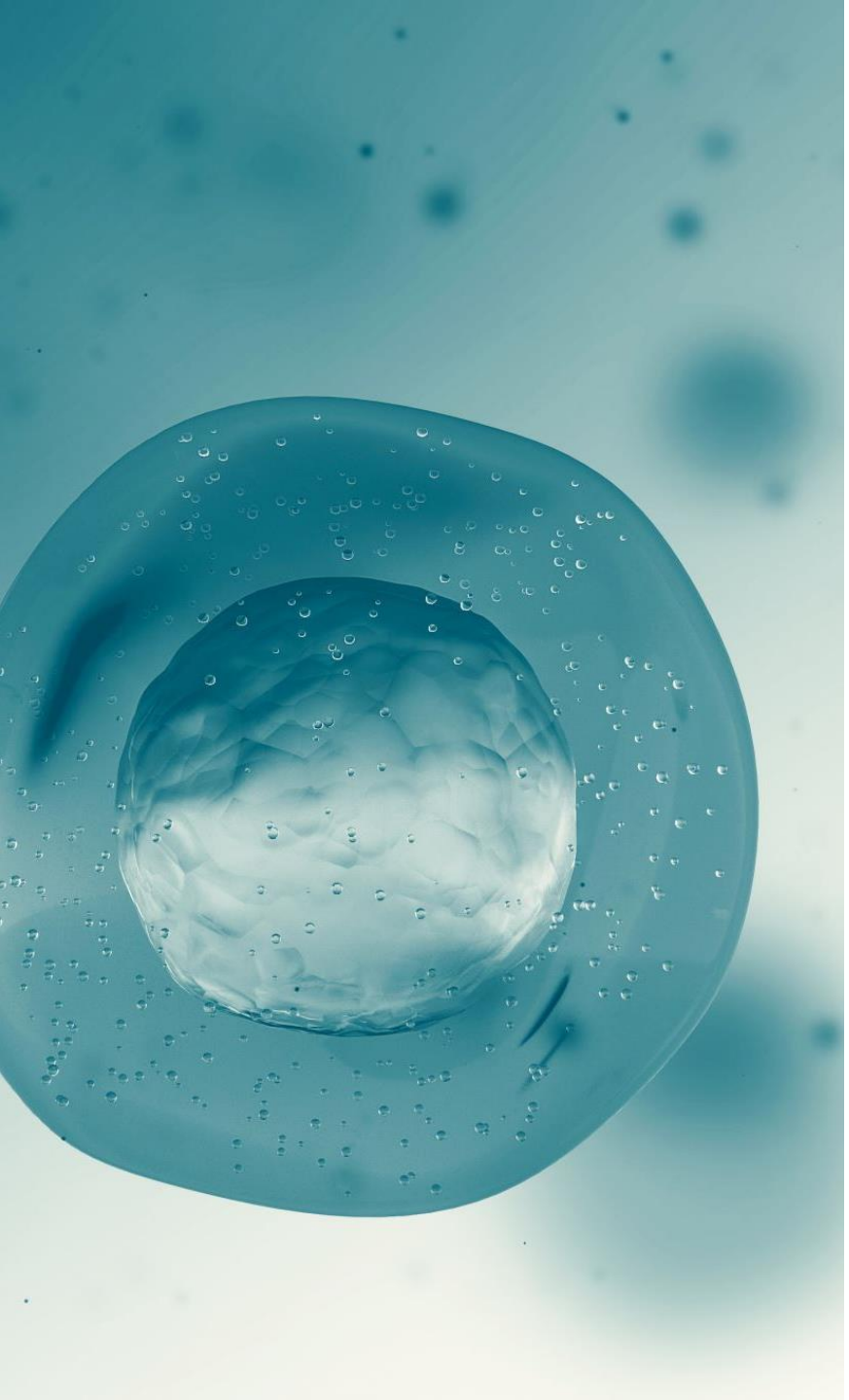
Adapted from Tlsty TD, Coussens LM: Tumor stroma and regulation of cancer development. Ann Rev Pathol Mech Dis 2006;1:119.



CHRONIC INFLAMMATION AND CANCER.

- A cause-and-effect relationship between chronic inflammation and cancer was first proposed by Virchow in 1863, and it is now appreciated that cancer risk is increased in individuals affected by a variety of chronic inflammatory diseases, including those with infectious and noninfectious etiologies

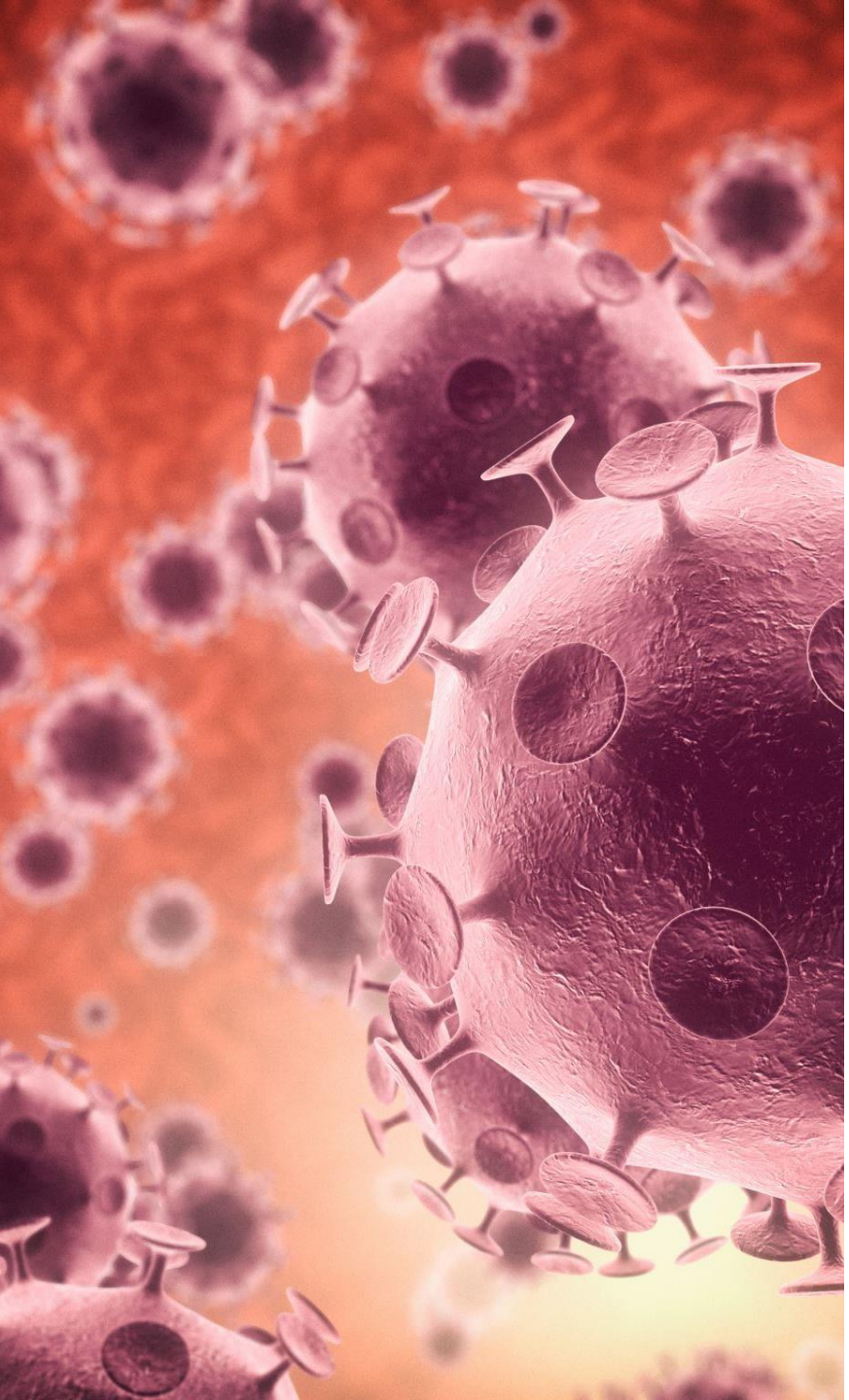
- As with any cause of tissue injury, each of these disorders is accompanied by a compensatory proliferation of cells that serves to repair the damage. In some cases, chronic inflammation may increase the pool of tissue stem cells, which may be particularly susceptible to transformation.



CHRONIC INFLAMMATION AND CANCER.

- Additionally the activated immune cells produce reactive oxygen species that are directly **genotoxic**. as well as inflammatory mediators that may promote bystander cell survival, even in the face of genomic damage.

- Chronic epithelial injury often leads to metaplasia, the replacement of one cell type with a second that is better able to survive the ongoing insult. In the short term, these changes can be adaptive; the organism must survive, and the damaged cells can be repaired or eliminated.



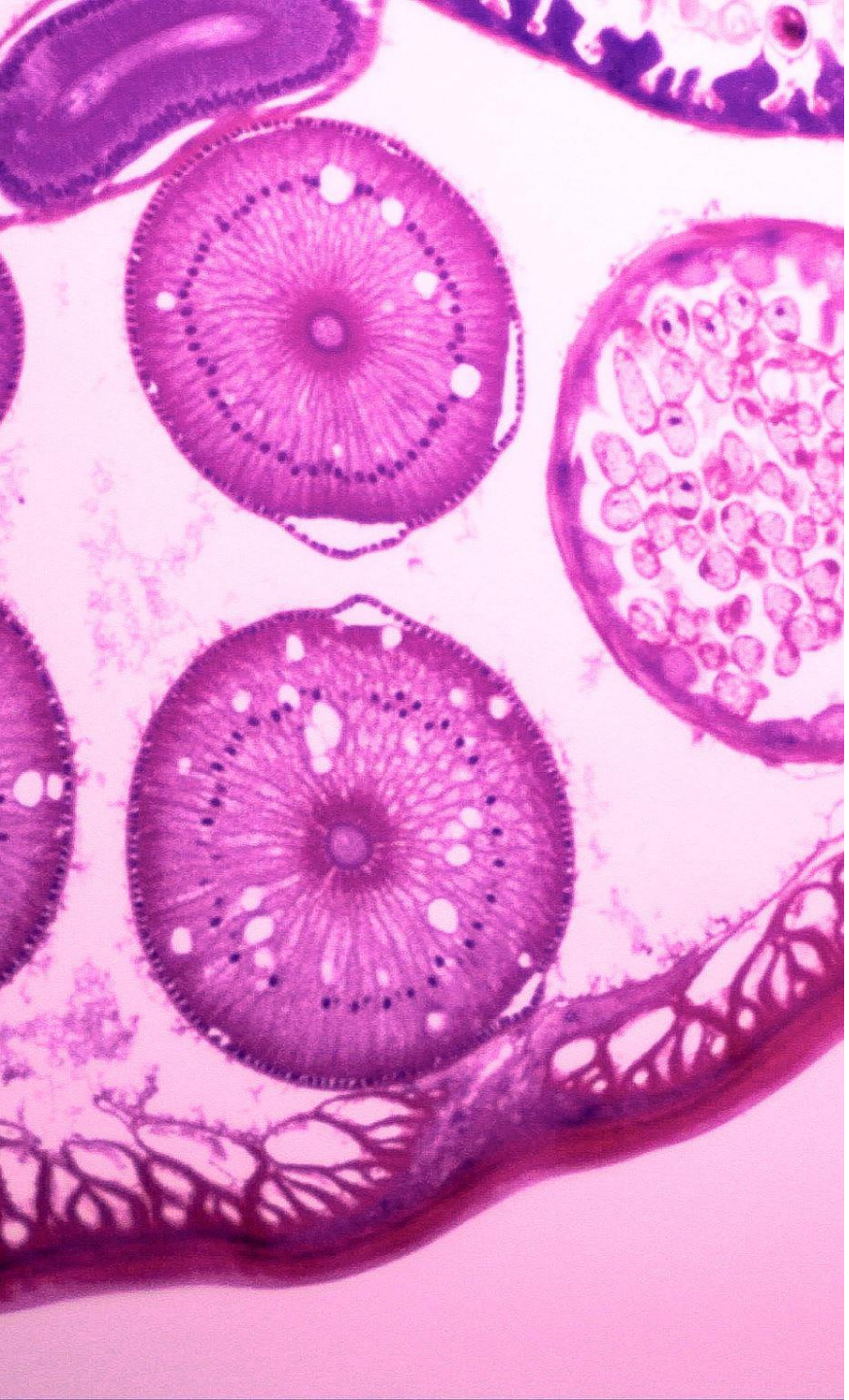
IMMUNODEFICIENCY STATES AND CANCER

- Patients who are immunodeficient, and particularly those who have deficits in T-cell immunity, are at increased risk for cancers, especially those caused by oncogenic viruses. These virally associated tumors include mainly lymphomas, but also certain carcinomas and even some sarcomas and sarcoma-like proliferations.

CLINICAL ASPECTS OF NEOPLASIA

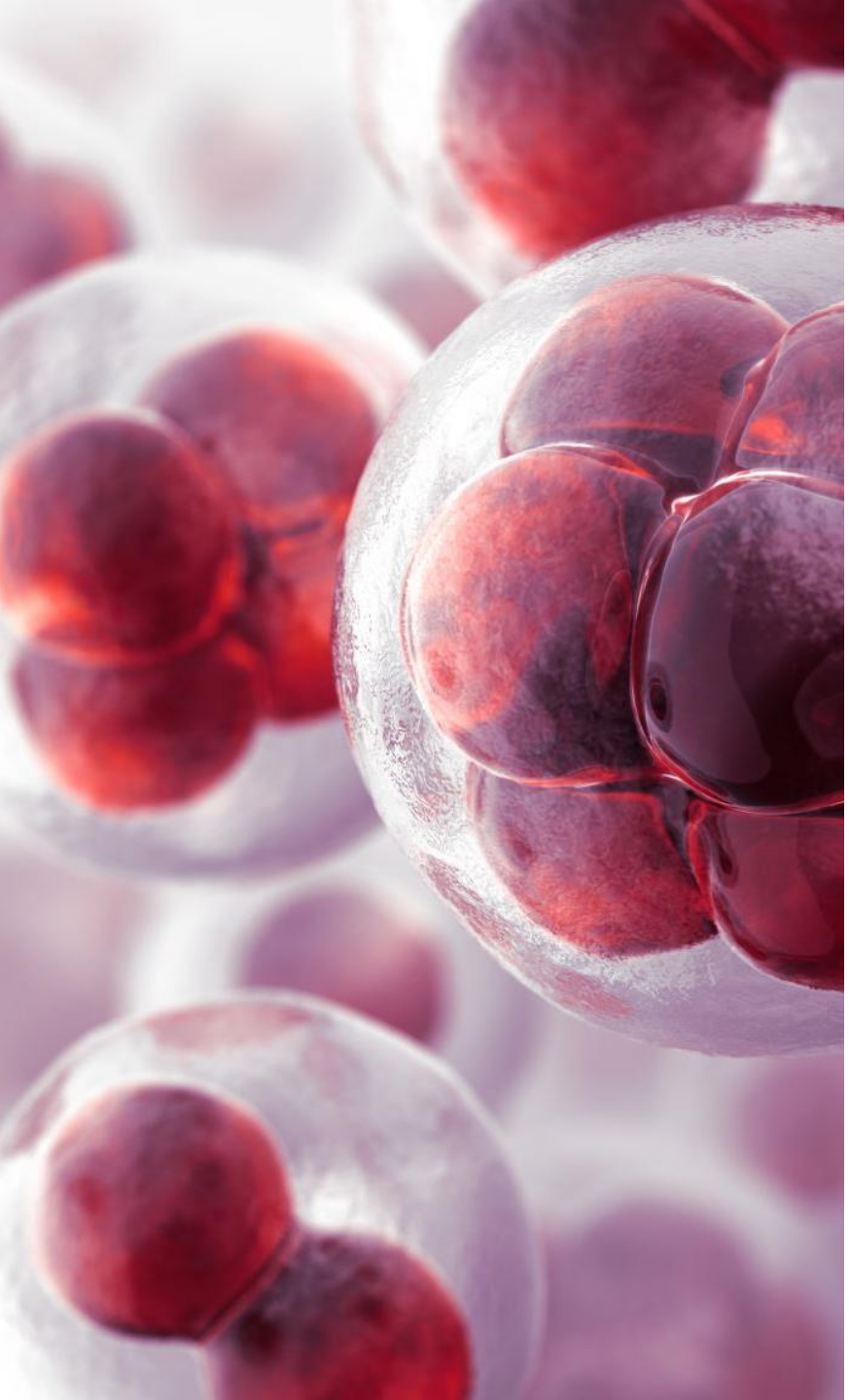
- Although malignant tumors are more threatening than benign, both can cause problems because of:

- Location and impingement on adjacent structures
- Functional activity such as hormone production
- Bleeding and infection
- Symptoms from tumor rupture or infarction
- Cachexia (wasting)



LOCAL AND HORMONAL EFFECTS

- Location: Intracranial tumors (e.g., pituitary adenoma) can expand and destroy the remaining pituitary gland, giving rise to an endocrine disorder; tumors of the gastrointestinal tract may cause obstruction of the bowel or may ulcerate and cause bleeding
- Hormone production: These may cause paraneoplastic syndromes such as hypoglycemia (insulin production) or hypercalcemia (parathyroid hormone-producing tumors)



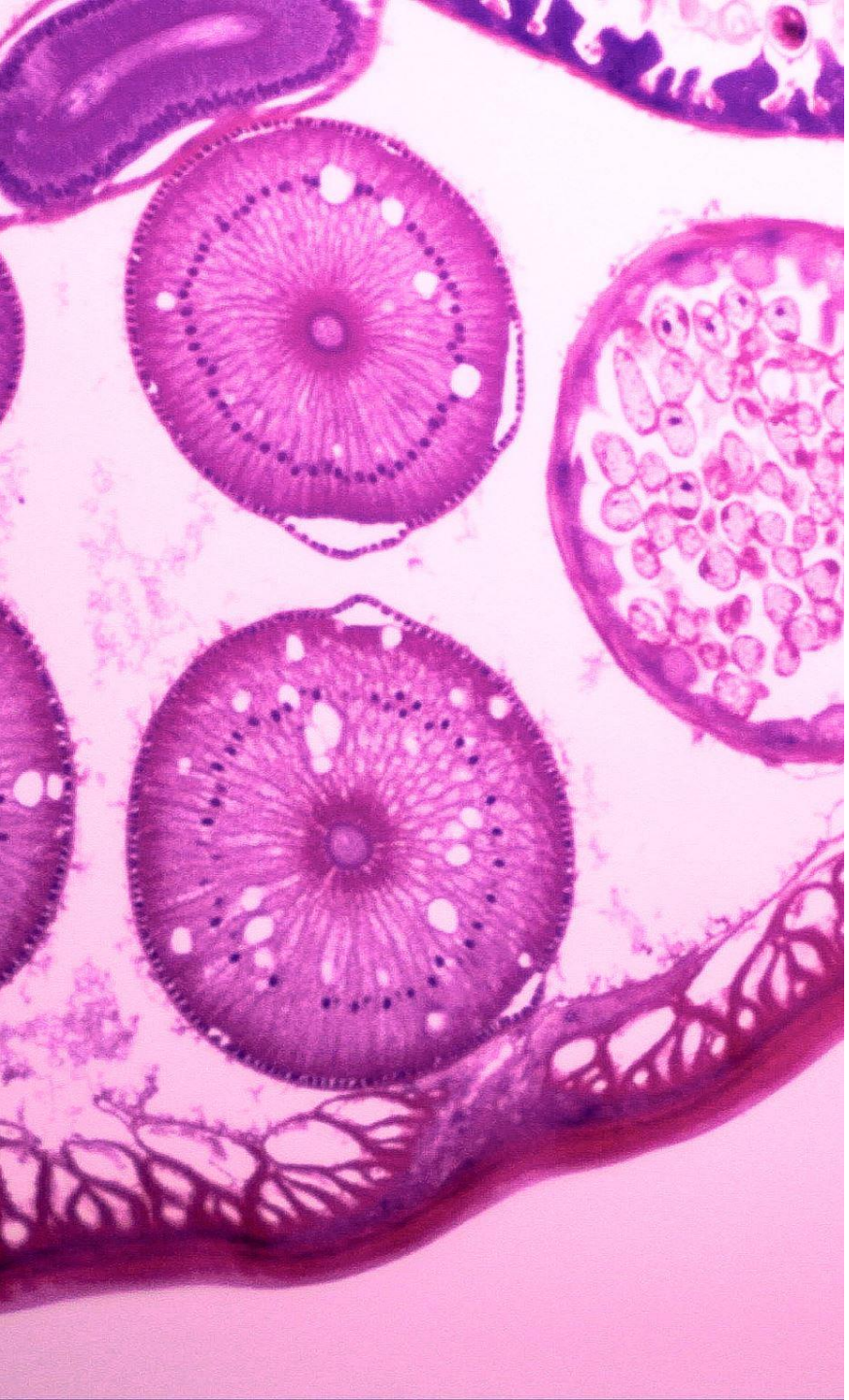
CANCER CACHEXIA

- Loss of body fat, lean body mass, and profound weakness are referred to as cancer cachexia. Its cause is multifactorial, but is largely driven by interferon gamma, interleukin one, tumor necrosis factor, leukemia inhibitory factor elaborated by inflammatory cells in response to tumors:

• Loss of appetite.

• Metabolic changes causing reduced synthesis and storage of fat and increased mobilization of fatty acids from adipocytes.

• Increase catabolism of muscle and adipose tissue by ubiquitin proteasome pathways.



PARANEOPLASTIC SYNDROMES

- These are tumor-associated syndromes where the symptoms are not directly related to the spread of the tumor or to the elaboration of hormones indigenous to the tumor tissue. Paraneoplastic syndromes may be the earliest clinical manifestations of a neoplasm and can mimic distant spread

TABLE 7-5 Paraneoplastic Syndromes		
Clinical Syndromes	**Major Forms of Underlying Cancer**	**Causal Mechanism**
Endocrinopathies		
Cushing syndrome	Small-cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small-cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T-cell leukemia/ lymphoma	Parathyroid hormone–related protein (PTHRP), TGF-α, TNF, IL-1
Hypoglycemia	Ovarian carcinoma Fibrosarcoma Other mesenchymal sarcomas	Insulin or insulin-like substance
Carcinoid syndrome	Hepatocellular carcinoma Bronchial adenoma (carcinoid) Pancreatic carcinoma	Serotonin, bradykinin

Polycythemia	Gastric carcinoma Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndromes		
Myasthenia	Bronchogenic carcinoma	Immunological
Disorders of the central and peripheral nervous system	Breast carcinoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunological; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic, breast carcinoma	
Osseous, Articular, and Soft-Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown

TABLE 7-5 Paraneoplastic Syndromes—cont'd

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanism
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	
Red cell aplasia	Thymic neoplasms	Unknown
Others		
Nephrotic sundrome	Various cancers	Tumor antigens, immune complexes

ACTH, Adrenocorticotropic hormone; *IL,* interleukin; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor.

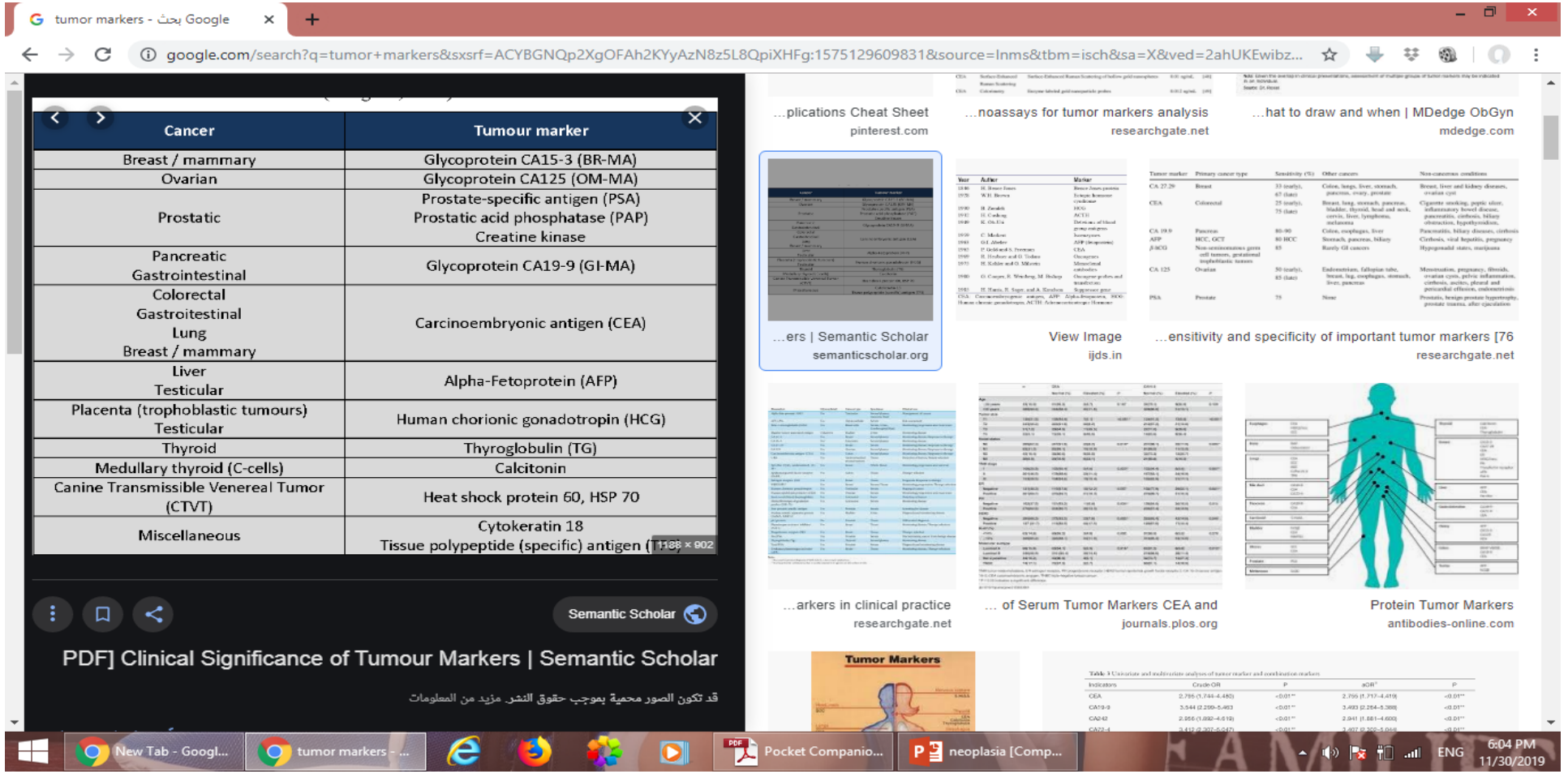
GRADING AND STAGING OF TUMOR

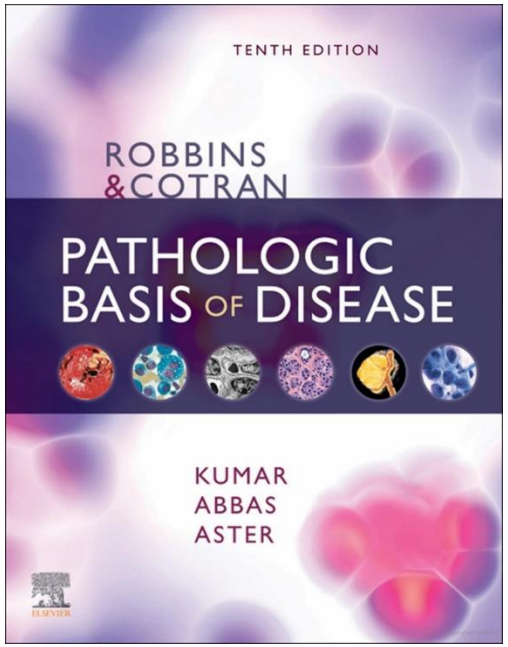
- Grading is based primarily on the degree of differentiation (how well the tumor resembles its normal counterpart), and, occasionally, architectural features or number of mitoses. In general, higher-grade tumors (more poorly differentiated) are more aggressive than lower-grade tumors.

GRADING AND STAGING OF TUMOR

- Staging is based on the size of the primary tumor and the extent of local and distant spread. The major system currently used is the American Joint Committee on Cancer (AJCC) staging; the classification involves a TNM designation—T for tumor (i.e., size and local invasion), N for regional lymph node involvement, and M for distant metastases.

LABORATORY DIAGNOSIS OF CANCER





THANK YOU

ANY QUESTIONS ??