Neoplasia

A lecture based on Chapter 7 of
Robbins Textbook of Pathology

Dr. Fred Maate

2021, 2022

CANCER STORIES

Cancer Stories

Rupiah diagnosed with colon cancer, asks for prayers

By Ernest Chanda on October 18, 2020

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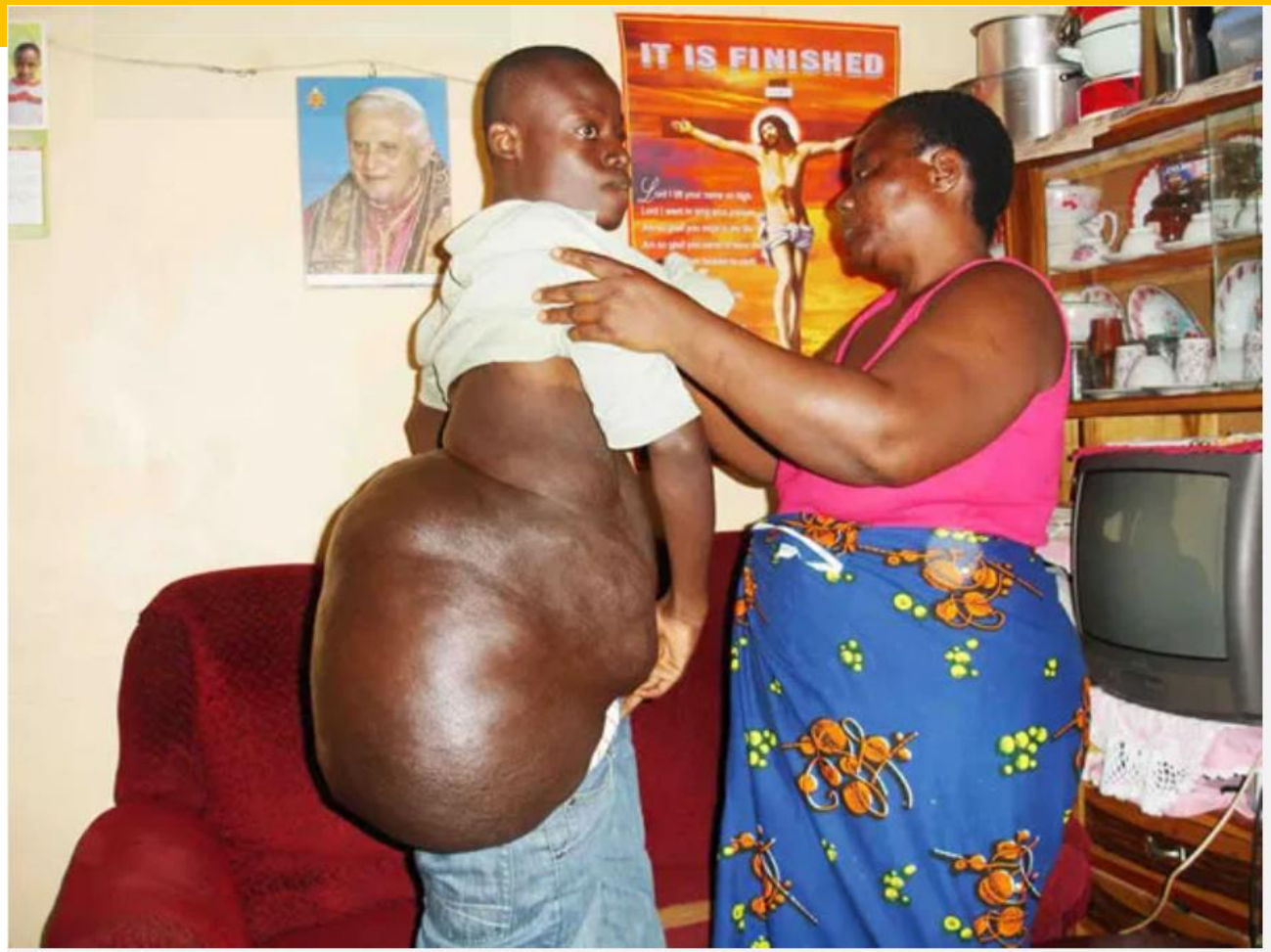
Mpali Actress Narrates How She Was Cured Of Cancer

By Editor01 on January 24, 2020 · Comments Off on Mpali Actress Narrates How She Was Cured Of Cancer

Is this cancer?



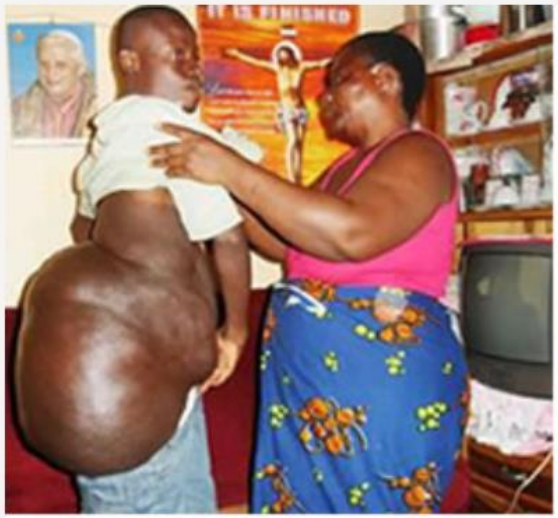
Sata Orders Evacuation Of Robiana Muteka

Successfully removed?

Doctors successfully remove 20Kg tumour off man's back

by

30 Mar 2012 at 07:26hrs | 1263 Views



Robiana Muteka has incurable cancer

June 6, 2012 | 43 views | 39

FILE: President Sata visits Robiana Muteka at the University Teaching hospital

University Teaching Hospital (UTH) Managing Director Lackson Kasonka has disclosed that the recent operation which resulted in the removal of a 14.5 kg tumour from the back of 24-year-old Robiana Muteka has not cured his problem.

Dr Kasonka said Robiana had been kept at UTH even after removal of the tumour because doctors

The Elephant in the house…

- What is *cancer*?
- Is every growth *cancer*?
- If not, how can one tell the difference?
- *Who* can give us the answer?

HENCE OUR LECTURE TODAY!

Lecture Outline

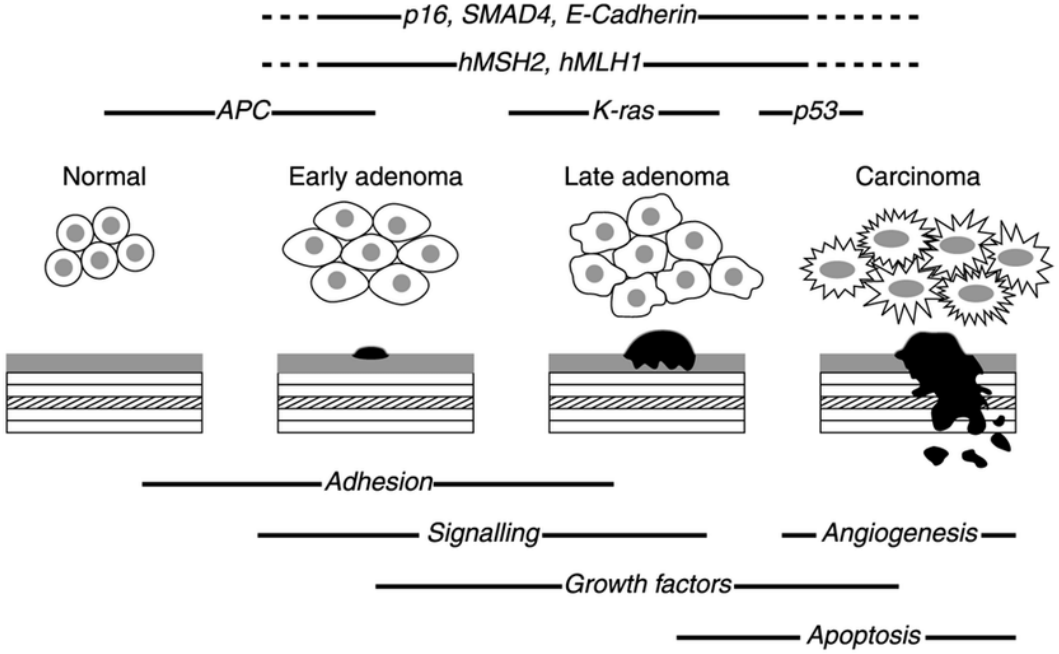
- Definitions
- Nomenclature
- Telling the difference between benign and malignant neoplasms
- Methods of tumour spread
- Epidemiology of cancer

History of definitions of neoplasia

- In the pre-molecular era, the eminent British oncologist Willis came closest:
- “A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.”

Current definition of neoplasia

- In the modern era, neoplasm: **a disorder of cell growth that is triggered by a series of acquired mutations affecting a single cell and its clonal progeny**.



Definition of *Neoplasia*

- Neo=new
- Plasia=growth
- Oncology-
  - Neoplasm= tumour
  - Oncos=tumour, logos= study

- Cancer- Crab in Latin

Two components of a neoplasm

- Parenchyma- name and biology of the tumour
- Stroma- support, blood supply

NOMENCLATURE

Meaning of benign and malignant

Benign-

- gross and microscopic features are considered *innocent*
- Remains *localized* and is amenable to surgery

Malignant-

- Can *invade* and *destroy* adjacent structures and *spread* to distant sites and cause death
- Collectively called ***cancer-*** crab

Benign tumours

- Designated by attaching the suffix ***-oma*** to the cell type from which the tumor arises
- fibrous tissue-***fibroma***;
- cartilaginous tumor-***chondroma***

Benign Epithelial Tumours

- More varied and complex nomenclature
- ***Adenoma***-
  - benign epithelial neoplasms that produce gland like structures, but also to
  - benign epithelial neoplasms that are derived from glands but lack a glandular growth pattern.
- ***Papillomas*** are benign epithelial neoplasms, growing on any surface, that produce microscopic

  or macroscopic fingerlike fronds.
- A ***polyp*** is a mass that projects above a mucosal surface, as in the gut, to form a macroscopically visible structure

- ***Cystadenomas*** are hollow cystic masses that typically arise in the ovary

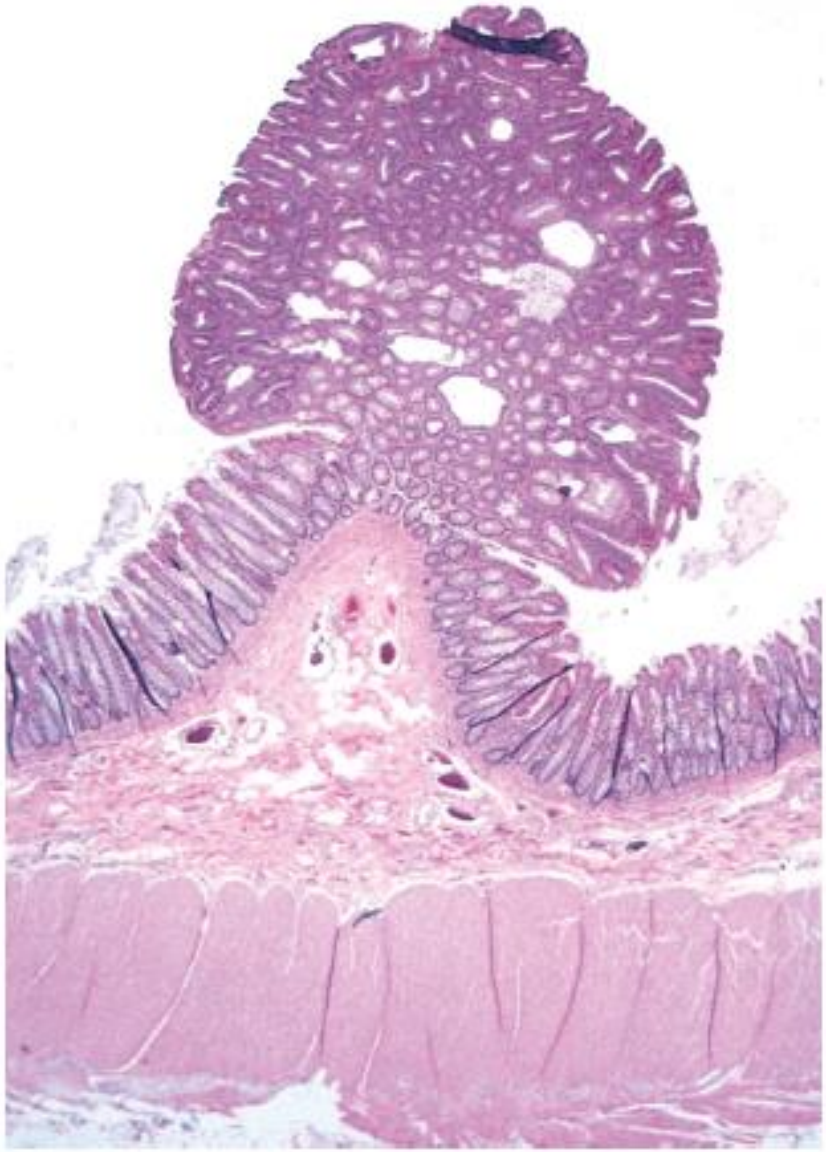


Fig. 6.1 Colonic polyp. This glandular tumor is seen projecting into the colonic lumen. The polyp is attached to the mucosa by a distinct stalk.

Malignant Tumours

- ***Sarcomas-*** Malignant neoplasms arising in "solid" mesenchymal tissues or its derivatives
  - Designated based on their cell-type composition
    - fat-like cells- *lipo*sarcoma,
    - chondrocyte-like cells- *chondro*sarcoma
- **leukemias** or **lymphomas: -** mesenchymal cells of the blood
- ***Carcinomas:*** malignant neoplasms of epithelial cells
  - Further subdivided- gland formation/ squamous cells
  - Poorly differentiated ones

Mixed Tumours

- Mixed tumour of salivary glands- pleomorphic adenoma
- Mixed tumour of the breast- fibroadenoma
- Teratoma- three germ layers

Table 6.1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Endothelium and related cell types		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cell types		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Skin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Lung	Bronchial adenoma	Bronchogenic carcinoma
Kidney	Renal tubular adenoma	Renal cell carcinoma
Liver	Liver cell adenoma	Hepatocellular carcinoma
Bladder	Urothelial papilloma	Urothelial carcinoma
Placenta	Hydatidiform mole	Choriocarcinoma
Testicle		Seminoma Embryonal carcinoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived From One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived From More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Beware of outlaws!

- *lymphoma,*
- *mesothelioma,*
- *melanoma,* and
- *seminoma.*

You shouldn't be confused!!!

- ***Hamartoma***- is a mass of disorganized tissue indigenous to the particular site, such as the lung or the liver-
  - Monoclonal= neoplastic
- ***Choristoma***- congenital anomaly consisting of a heterotopic nest of cells

CAN WE TELL THE DIFFERENCE BETWEEN BENIGN AND MALIGNANT?

Characteristics of benign and malignant neoplasms

1. Differentiation and anaplasia
2. local invasion
3. Metastasis
4. Rate of growth

Differentiation-

- refers to the extent to which neoplasms resemble their parenchymal cells of origin, both morphologically and functionally;
- lack of differentiation is called *anaplasia*
- *Benign- closely resemble parent cell of origin and lack atypical mitoses.*

Anaplasia

- Pleomorphism- size and shape
- Nuclear abnormalities
- Tumour giant cells
- Atypical mitoses
- Loss of polarity

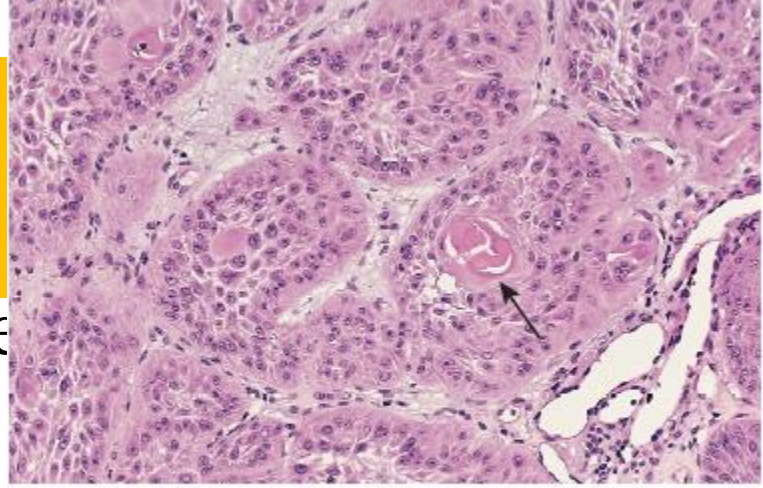


Fig. 6.3 Well-differentiated squamous cell carcinoma of the skin. The tumor cells are strikingly similar to normal squamous epithelial cells, with intercellular bridges and nests of keratin *(arrow)*. *(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

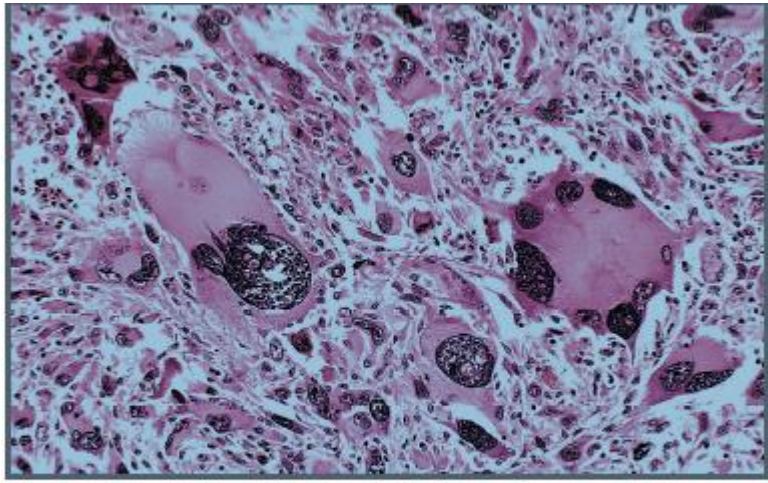


Fig. 6.4 Pleomorphic malignant tumor (rhabdomyosarcoma). Note the marked variation in cell and nuclear sizes, the hyperchromatic nuclei, and the presence of tumor giant cells. *(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

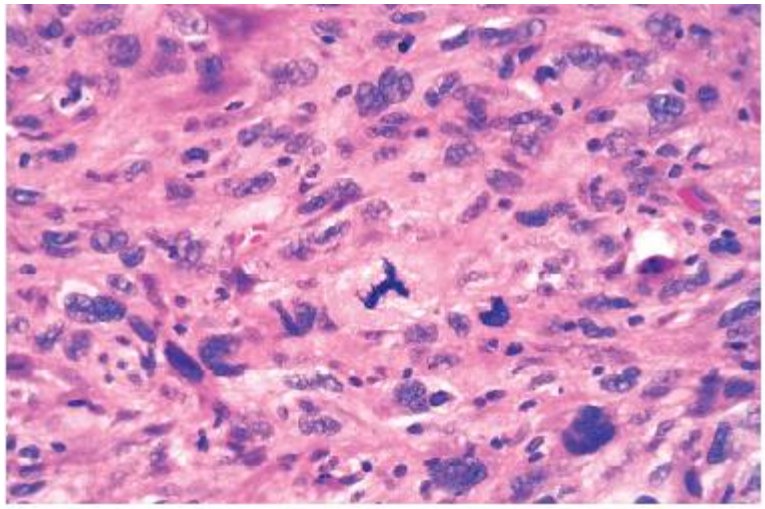


Fig. 6.5 High-power detailed view of anaplastic tumor cells shows cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

Dysplasia

- Disorderly proliferation

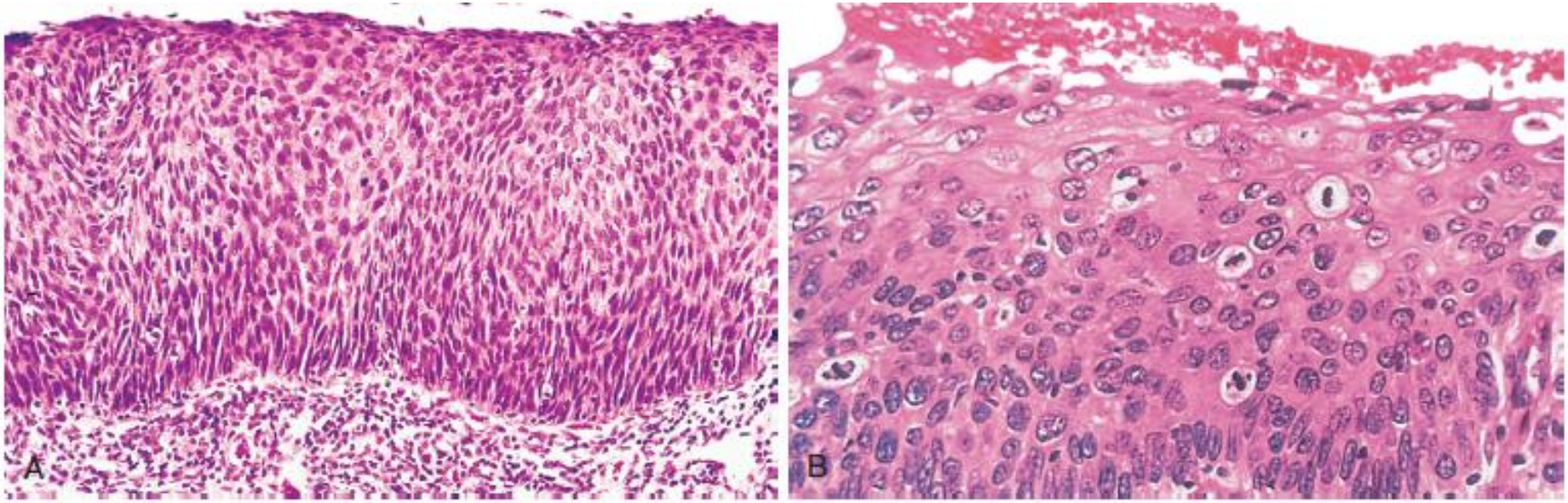


Fig. 6.6 Carcinoma in situ. (A) Low-power view shows that the entire thickness of the epithelium is replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma. (B) High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface. The intact basement membrane (below) is not seen in this section.

Local Invasion

- Growth pattern-
  - infiltrative or pushing border
  - Capsule vs no capsule

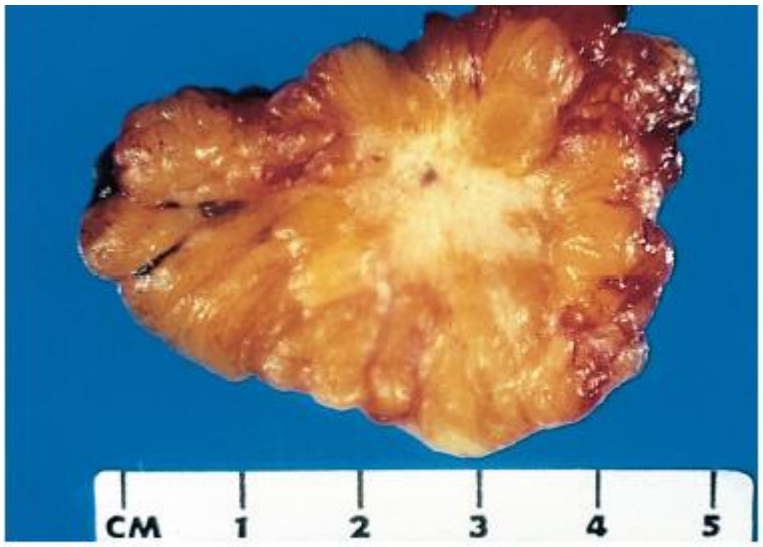


Fig. 6.9 Cut section of invasive ductal carcinoma of the breast. The lesion is retracted, infiltrating the surrounding breast substance, and was stony-hard on palpation.

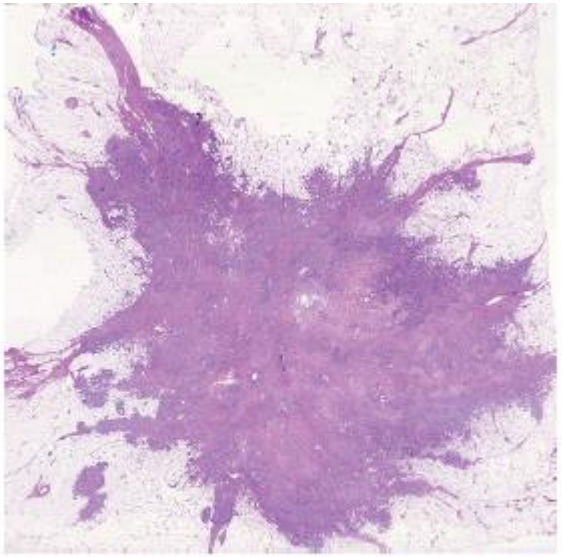


Fig. 6.10 Microscopic view of breast carcinoma seen in Fig. 6.9 illustrates the invasion of breast stroma and fat by nests and cords of tumor cells (compare with Fig. 6.8). Note the absence of a well-defined capsule. *(Courtesy of Dr. Susan Lester, Brigham and Women's Hospital, Boston, Massachusetts.)*

Metastasis

- Defined by the spread of a tumor to sites that are physically discontinuous with the primary tumor
- unequivocally marks a tumor as malignant, as by definition benign neoplasms do not metastasize

Example of metastatic deposit in the liver

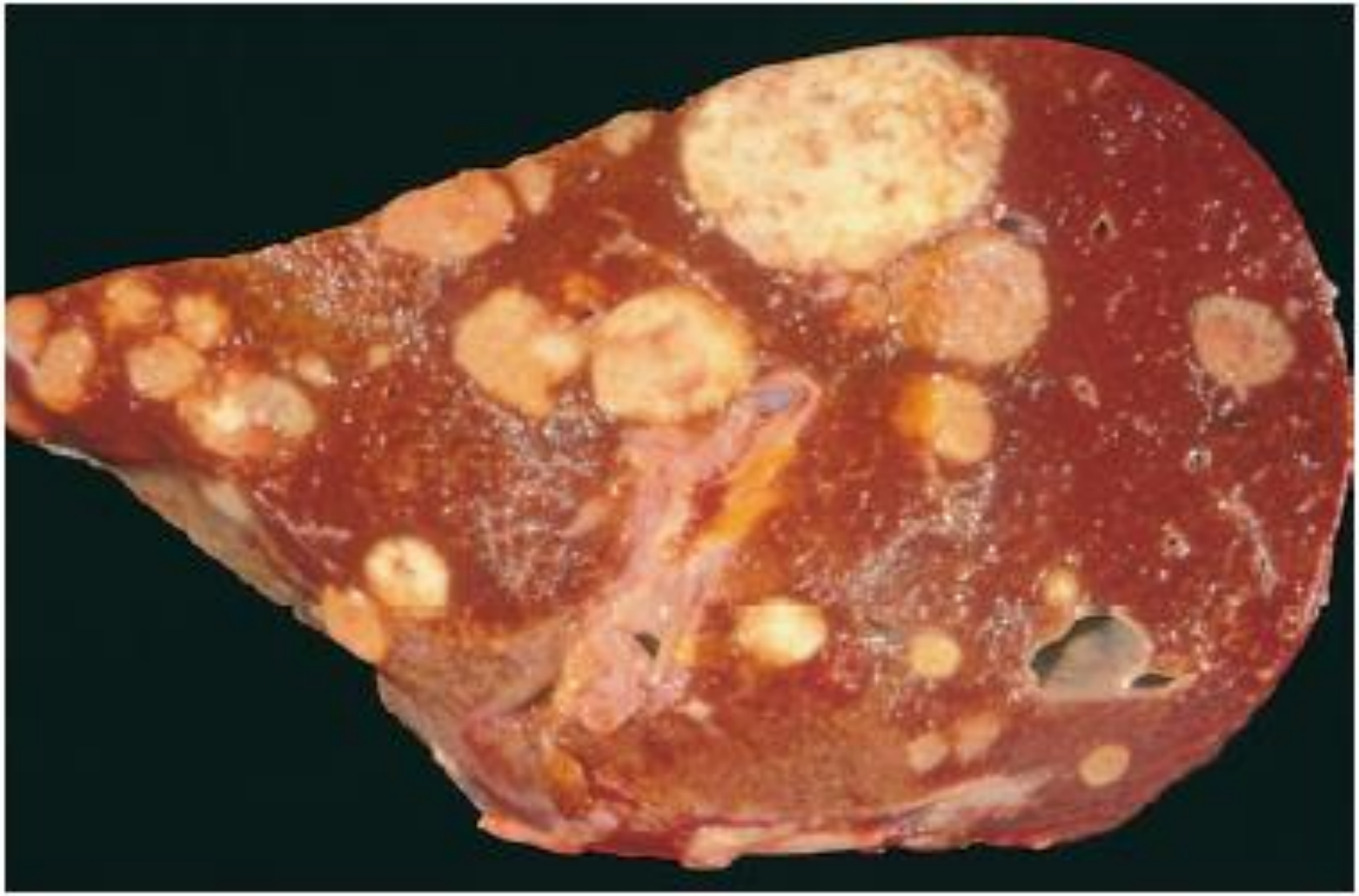


Fig. 6.11 A liver studded with metastatic cancer.

For blood derived cancers

- with only rare exceptions, leukemias and lymphomas are taken to be disseminated diseases at diagnosis and are always considered to be malignant

Methods of tumour spread

1. Seeding of body cavities
2. Lymphatic spread
3. Hematogenous spread

- *Lymphatic spread is more typical of carcinomas, whereas hematogenous spread is favored by sarcomas.*
- A “sentinel lymph node” is the first regional lymph node that receives lymph flow from a primary tumor

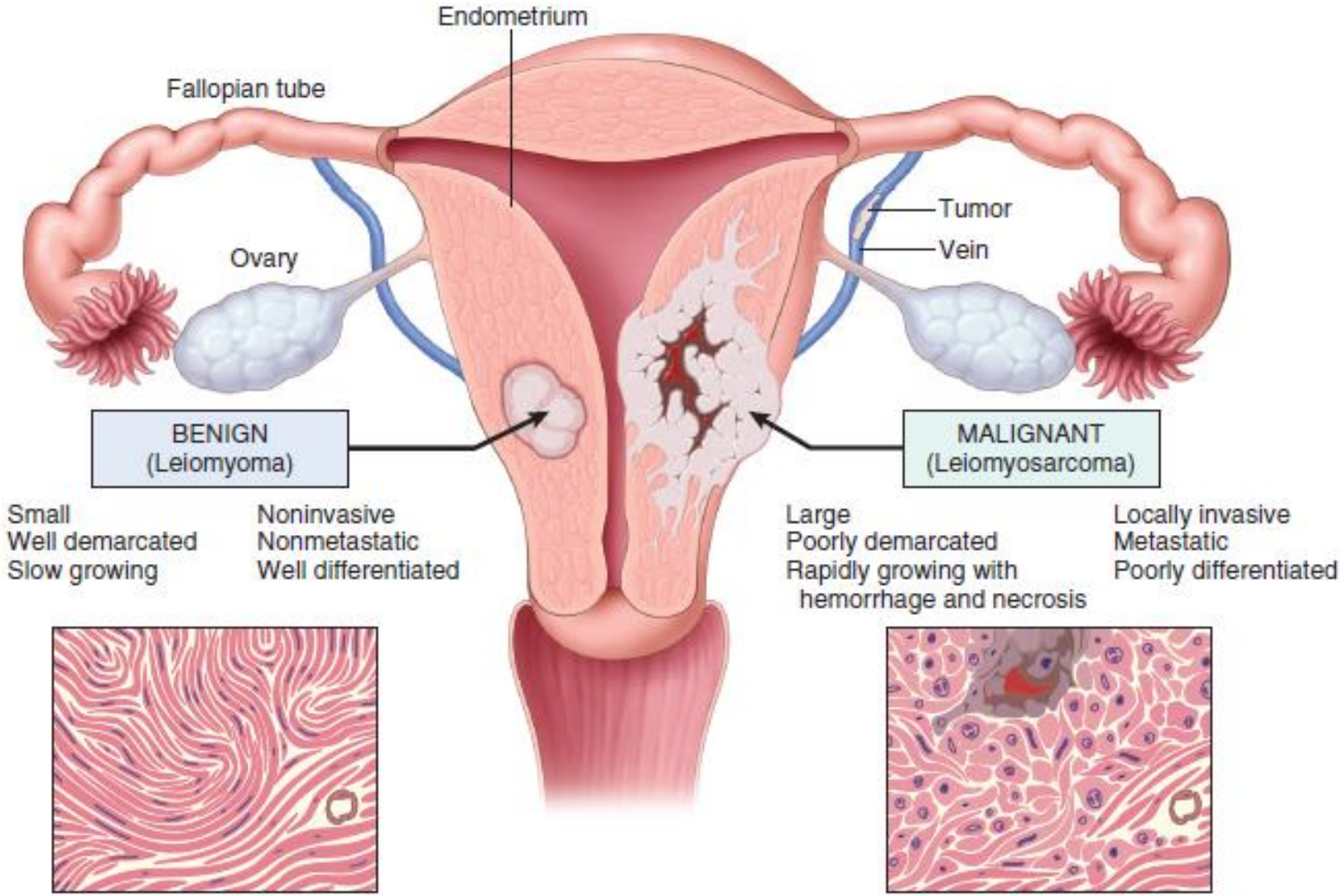


Fig. 6.12 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of similar origin (leiomyosarcoma).

Table 7-2 Comparisons Between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/ anaplasia	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation (anaplasia); structure often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures rare and normal	Erratic, may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive, expansile, well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating surrounding tissue; sometimes may be misleadingly cohesive and expansile
Metastasis	Absent	Frequent; more likely with large undifferentiated

EPIDEMIOLOGY OF CANCER

Cancer incidence

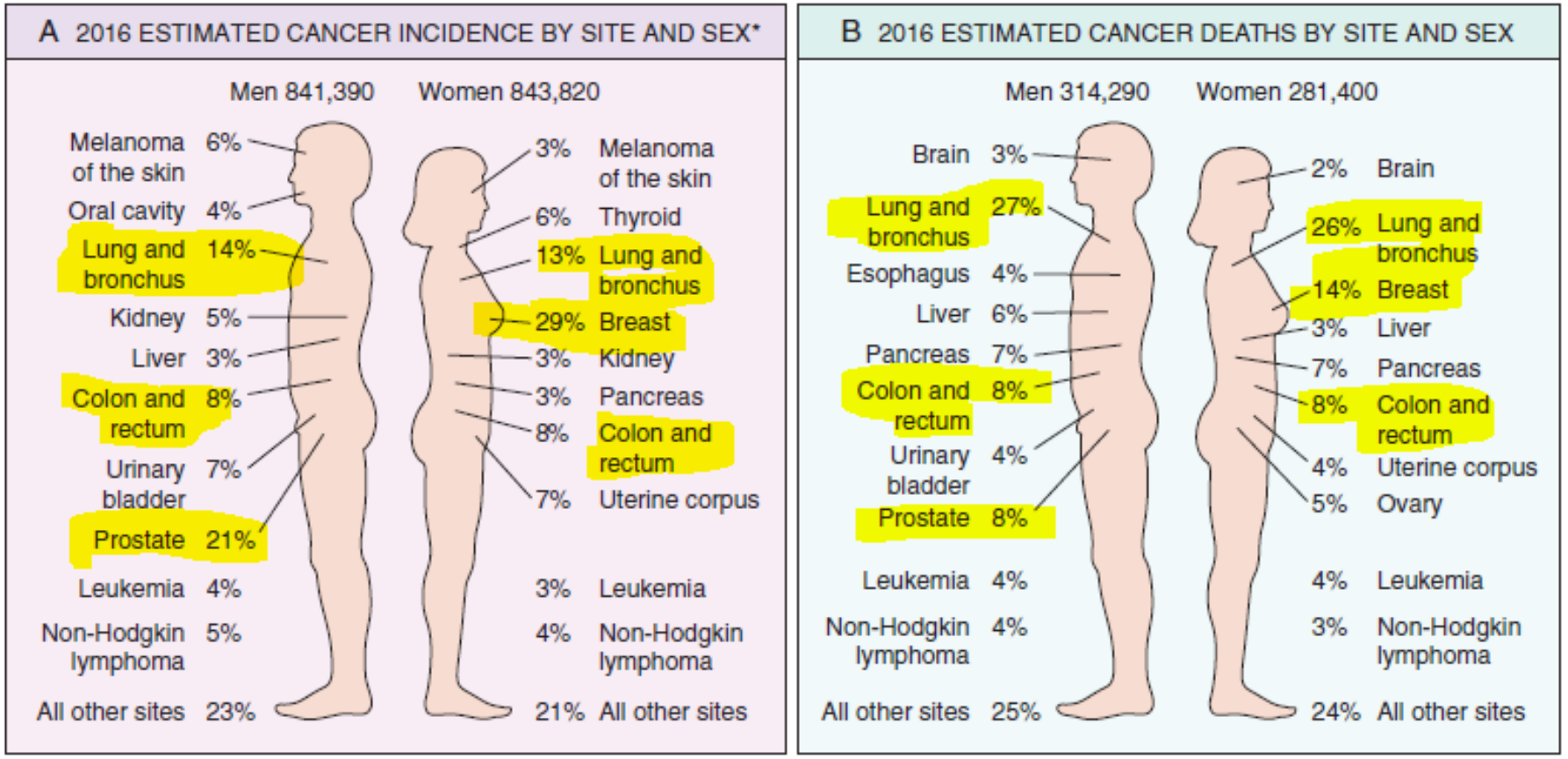


Fig. 6.13 Estimated cancer incidence and mortality by site and sex in the United States. Excludes basal cell and squamous cell skin cancers and in situ carcinomas, except urinary bladder. *(Adapted from* Cancer facts & figures 2016. *American Cancer Society. www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html.)*

Environmental factors

- Environmental exposures- dominant risk factors for many common cancers
- high fraction of cancers are potentially preventable.

Environmental factors

- **Diet**
- **Smocking**
  - *mouth, pharynx, larynx, esophagus, pancreas, bladder, and, most significantly, the **lung**, as 90% of lung cancer deaths are related to smoking*.
- **Alcohol consumption**
  - oropharynx, larynx, esophagus, and (due to alcoholic cirrhosis) liver
- **Reproductive history-** lifelong exposure to estrogen- endometrium and breast ca
- **Infectious agents-** *approx.* 15% of cancers worldwide.

Age and Cancer

- In general, the frequency of cancer increases with age
- responsible for slightly more than 10% of all deaths among children younger than 15 years of age

Acquired *Predisposing* Conditions

- Disorders associated with *chronic inflammation*,
- *immunodeficiency states*, and
- *precursor lesions*

Table 6.3 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, germ line 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* 1:119, 2006.

PRECURSOR LESIONS

Precursor lesions

- *Squamous metaplasia and dysplasia of bronchial mucosa,* seen in in habitual smokers—a risk factor for lung carcinoma
- *Endometrial hyperplasia and dysplasia,* seen in women with unopposed estrogenic stimulation—a risk factor for endometrial carcinoma

ENVIRONMENT AND CANCER

Interactions Between Environmental and Genetic Factors

- breast cancer risk in females who inherit mutated copies of the *BRCA1* or *BRCA2* tumor suppressor genes is almost three-fold higher for women born after 1940 than for women born before that year, perhaps because of changes in reproductive behavior or increases in obesity in more recent times.

CANCER GENES

Cancer genes

- Oncogenes
- Tumour suppressor genes
- *Genes that regulate apoptosis*
- *genes that regulate interactions between tumor cells and host cells*

Cancer genes

- ***Oncogenes*** are genes that induce a transformed phenotype when expressed in cells by **promoting increased cell growth**
  - mutated or overexpressed versions of normal cellular genes, which are called *proto-oncogenes*.
  - encode transcription factors, factors that participate in pro-growth signaling pathways, or factors that enhance cell survival.
  - Usually dominant genes

Tumour suppressor genes

- genes that *normally prevent uncontrolled growth* and, when mutated or lost from a cell, allow the transformed phenotype to develop
- Usually both alleles have to be mutated
- ***"governors"*** = brakes on cellular proliferation, and ***"guardians"*** =responsible for sensing genomic damage.

Acquired or germline mutations

Genetic Lesions In Cancer

- The genetic changes found in cancers vary from point mutations involving single nucleotides to abnormalities large enough to produce gross changes in chromosome structure

Driver and Passenger Mutations

- Driver mutations are mutations that alter the function of cancer genes and thereby directly contribute to the development or progression of a given cancer.
- passenger mutations are acquired mutations that are neutral in terms of fitness and do not affect cellular behavior

- *Point Mutations*
  - *Gain of function mutation- RAS*
  - *Deletion or insertion- TP 53- loss of function*
- *Gene Rearrangements*
  - Chromosomal translocations or inversion– hematopoetic and mesenchymal tumours---
  - *Burkitt lymphoma t(8,14) MYC, IgH*
  - *follicular lymphoma t(14, 18) IgH, BCL- 2*

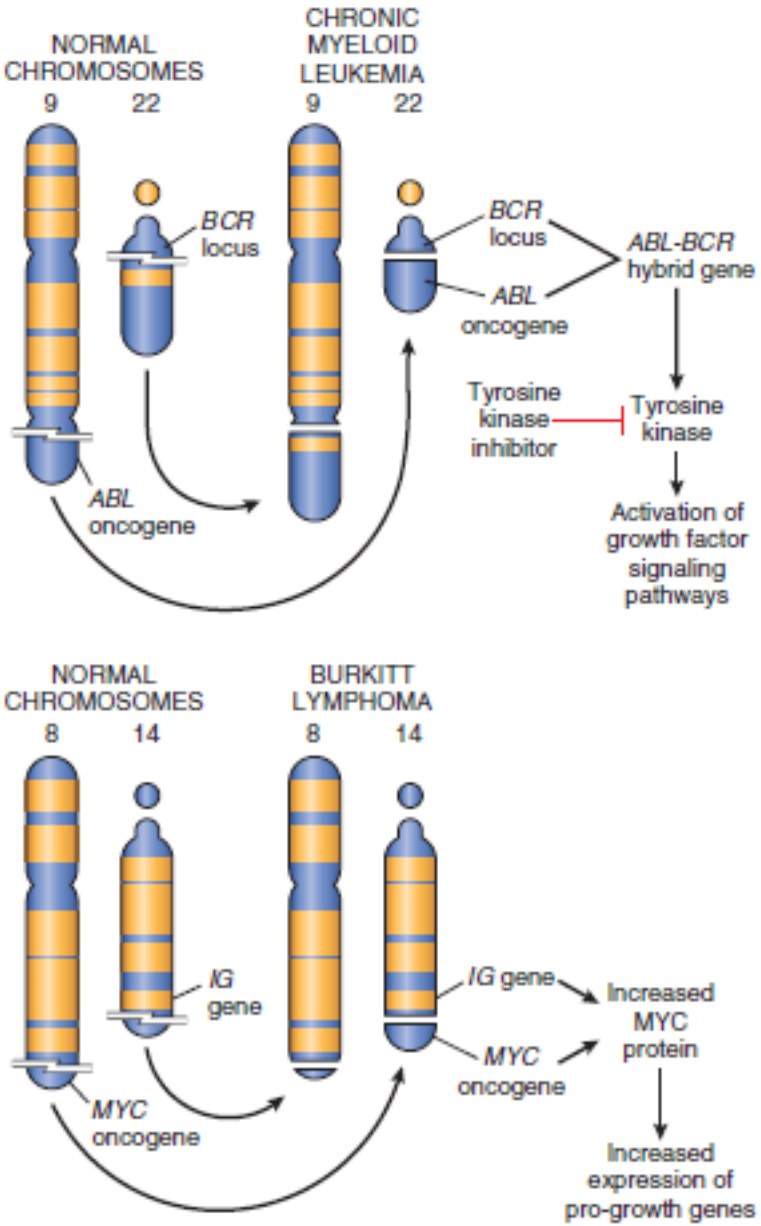


Fig. 6.14 The chromosomal translocations and associated oncogenes in chronic myelogenous leukemia and Burkitt lymphoma.

- *Deletions*
  - Deletion of specific regions of chromosomes may result in the loss of particular tumor suppressor genes
- *Gene Amplifications*
  - *Nmyc*
  - *Her 2*

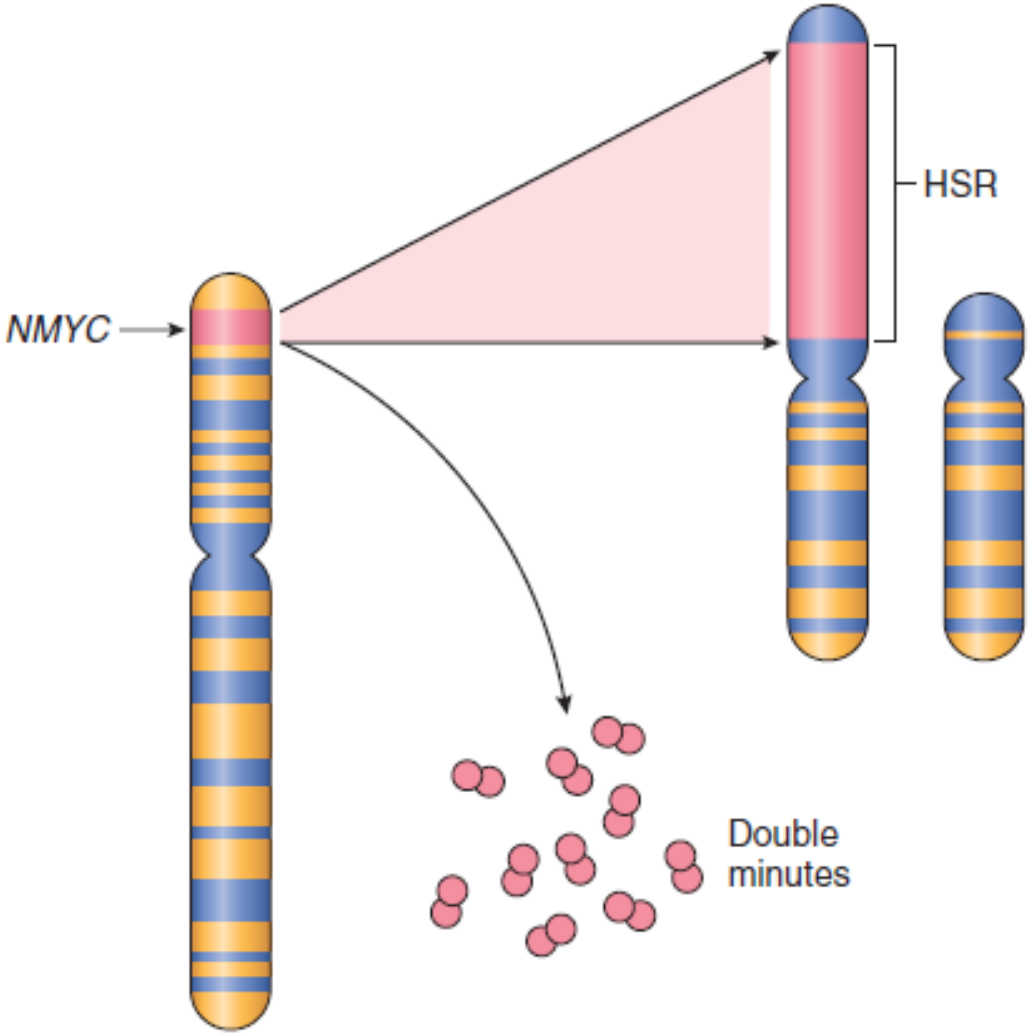


Fig. 6.15 Amplification of the *NMYC* gene in human neuroblastoma. The *NMYC* gene, present normally on chromosome 2p, becomes amplified and is seen either as extrachromosomal double minutes or as a chromosomally integrated homogeneous-staining region (HSR). The integration involves other autosomes, such as 4, 9, or 13. *(Modified from Brodeur GM, Seeger RC, Sather H, et al: Clinical implications of oncogene activation in human neuroblastomas.* Cancer *58:541, 1986. Reprinted by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.)*

- *Aneuploidy*
  - aneuploidy tends to increase the copy number of key oncogenes and decrease the copy number of potent tumor suppressors
- *MicroRNAs and Cancer*

CARCINOGENESIS

Carcinogenesis A Multistep Process

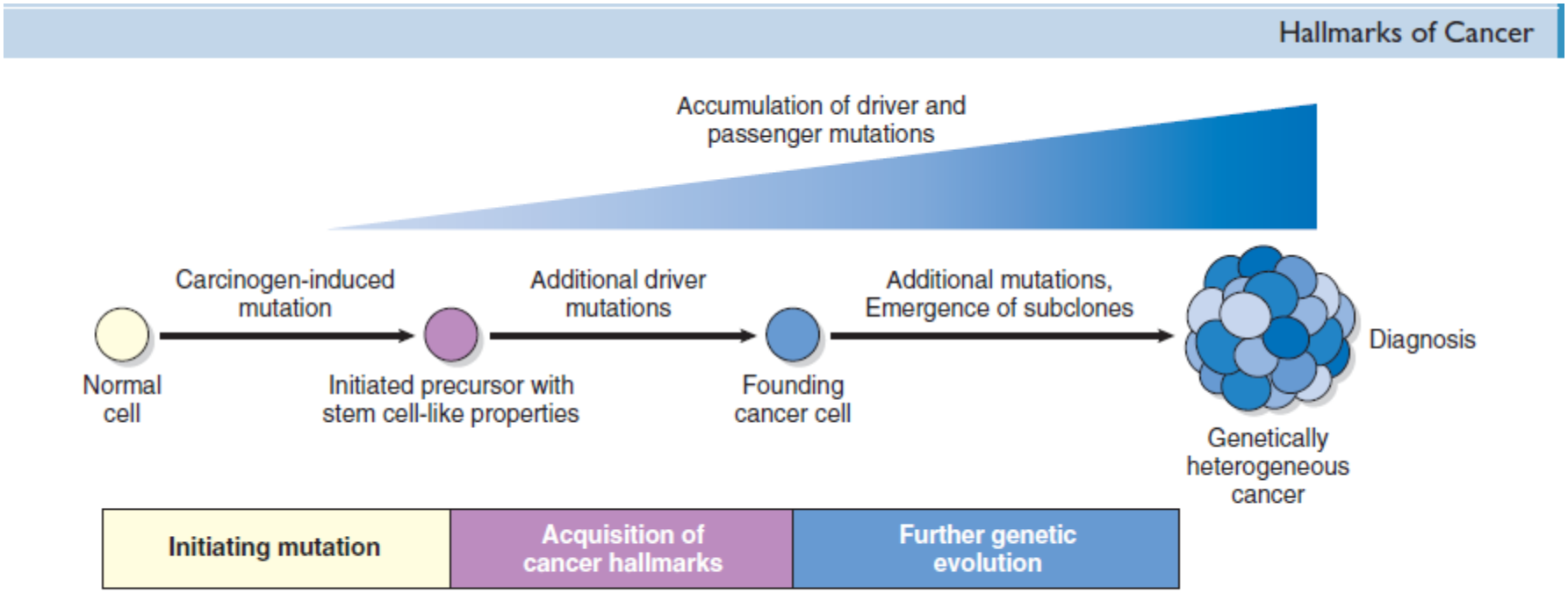


Fig. 6.16 Development of cancer through stepwise accumulation of complementary driver mutations. The order in which various driver mutations occur is usually unknown and may vary from tumor to tumor.

Hallmarks Of Cancer

1. *Self-sufficiency in growth signals*
2. *Insensitivity to growth-inhibitory signals*
3. *Altered cellular metabolism*
4. *Evasion of apoptosis*
5. *Limitless replicative potential (immortality)*
6. *Sustained angiogenesis*
7. *Invasion and metastasis*
8. *Evasion of immune surveillance*

- The acquisition of the genetic and epigenetic alterations that confer these hallmarks may be accelerated by *cancer promoting inflammation* and by *genomic instability*.
- These are considered enabling characteristics because they promote cellular transformation and subsequent tumor progression

ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

- (1) chemicals,
- (2) radiant energy, and
- (3) microbial products

Chemicals

- Direct acting
- Indirect acting

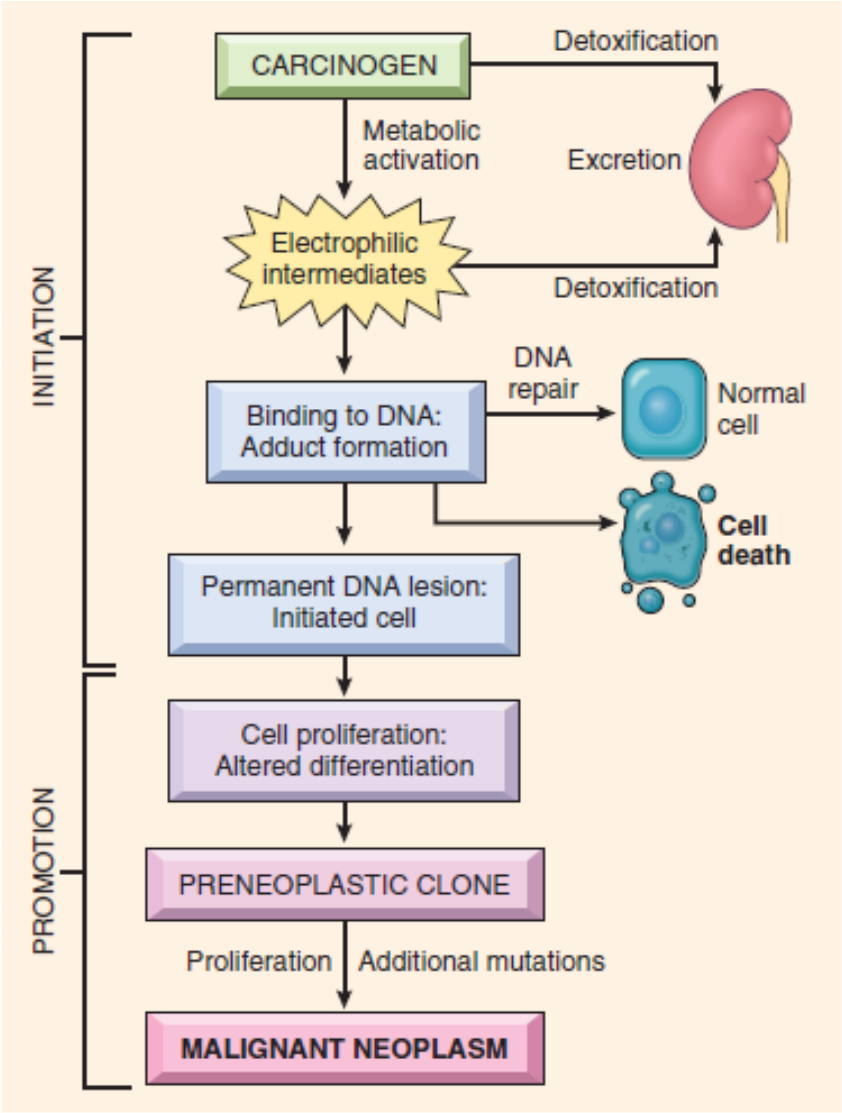


Fig. 6.32 General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter or other factors causes accumulation of additional mutations and emergence of a malignant tumor.

Radiation

- Hiroshima Nagasaki
- Chernobil in Soviet union
- Ionizing radiation to the head and neck
- Tsunami
- UV light and skin cancer

- Mutations- pt. , breaks, inversions…

- Excision repair-xeroderma pigmentosa, melanoma

Viral and Microbial Oncogenesis

- *Oncogenic RNA Viruses*
  - **HTLV-1 causes *adult T-cell leukemia/lymphoma***
- *Oncogenic DNA Viruses*
  - HPV, Epstein-Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8]), a polyoma virus called Merkel cell virus, and hepatitis B virus (HBV)

CLINICAL ASPECTS OF NEOPLASIA

- Site
- Cancer cachexia
- Paraneoplastic syndromes

Grading and staging of cancer

- Grade
- Stage

Laboratory diagnosis of cancer

- Morphologic methods
  - Excision, biopsy, FNAB, cytology, immunohistochemistry, flow cytometry
- Tumour markers
  - PSA, alpha fetoprotein, CEA, etc
- Molecular methods

Assignment- Discussion

- What is the role of the pathologist in the diagnosis of neoplasia?
- What is the role of a clinician in the diagnosis of cancer?
- How can doctors diagnose cancer?
- what are the differences between benign and malignant tumours?
- What are the routes of metastasis?
- What is the role of genetic predisposition in causation of cancer? Give examples.
- What are oncogenic viruses?
- Give an example of an oncogenic retrovirus
- Give examples of DNA oncogenic viruses.
- List the hallmarks of cancer
- What are the common causes of cancer (general classification)?
- What are the risk factors for cancer?
- What are cancer stem cells?
- What is the warburg effect?
- Discuss TP53
- Discuss Retinoblastoma (Rb) gene and Knudson's two hit hypothesis
- What are paraneoplastic syndromes and what is their importance? Give two examples of paraneoplastic syndromes.