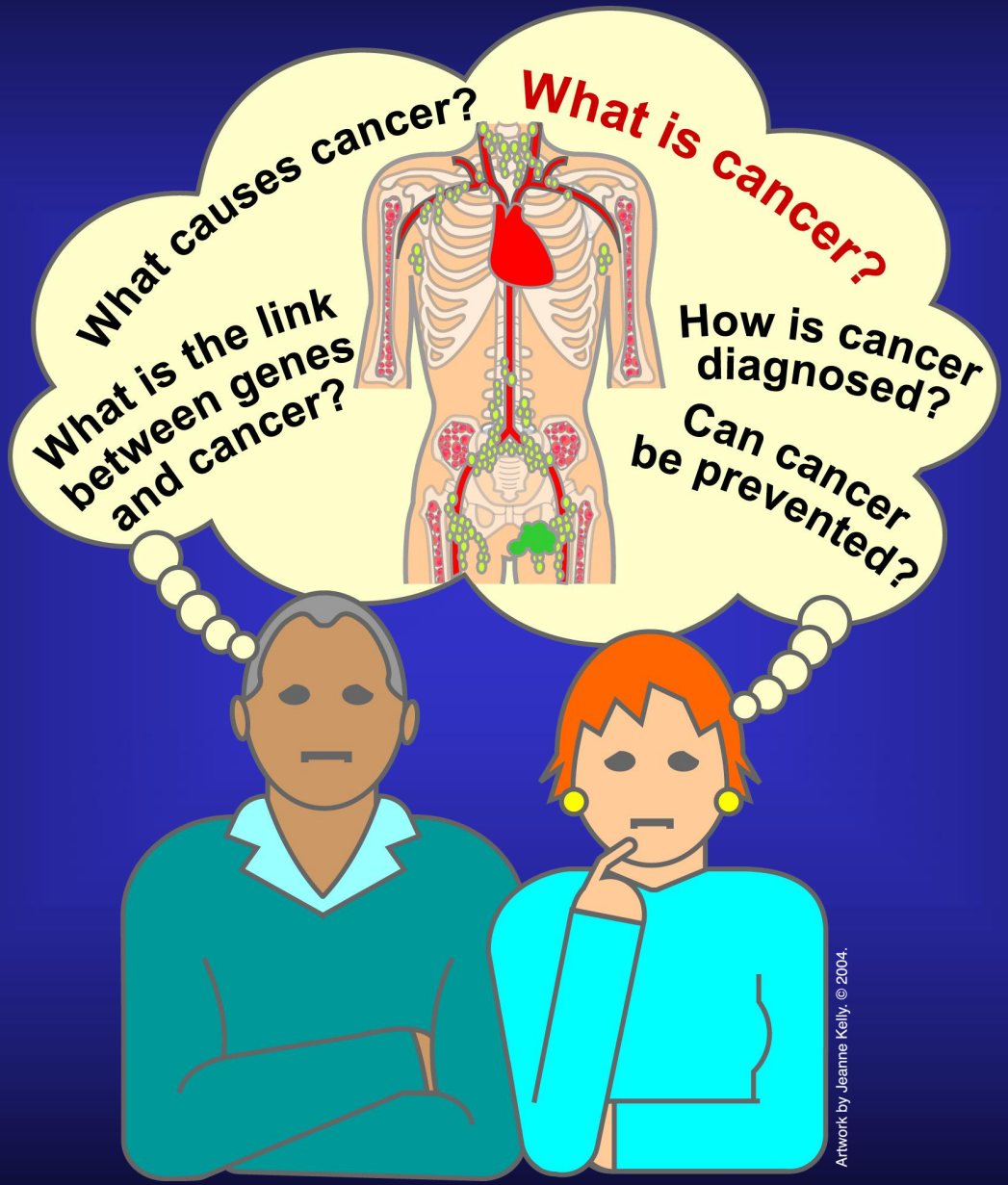
SBL100-Lecture

Introduction to Cancer

Part I

What Is Cancer?

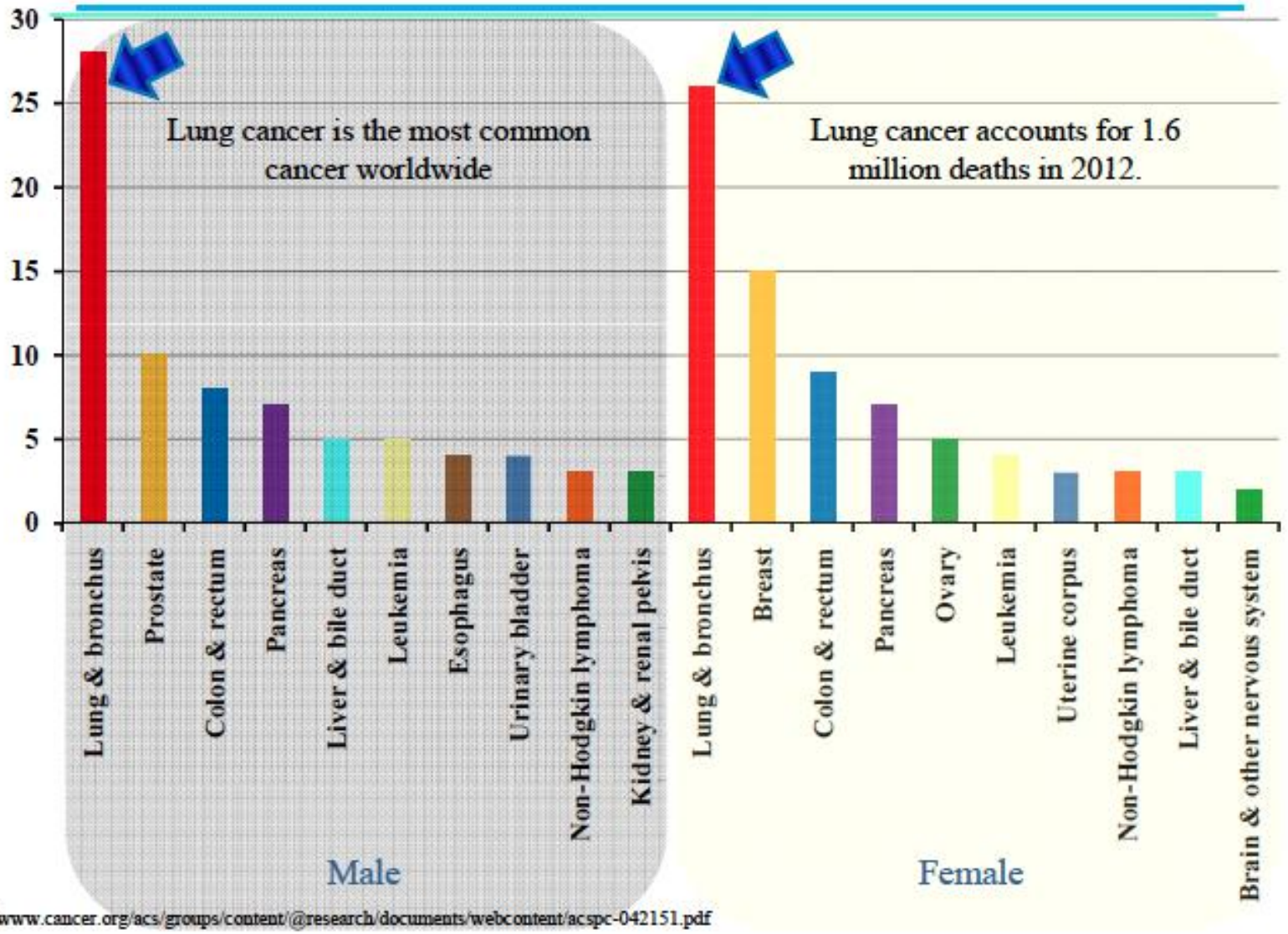


Cancer

- Cancer is one of the most common diseases in the world after heart disease.
- 1 in 4 deaths are due to cancer
- Lung cancer is the most common cancer in men
- Lung and Breast cancer is common in women
- There are over 100 different forms of cancer
- Every year 18 million people are diagnosed.
- More than 22 million peoples are living with cancer
- An estimated 9.6 million deaths in 2018.
- The most common cancers are:
- Lung (2.09 million cases)
- Breast (2.09 million cases)
- Colorectal (1.80 million cases)
- Prostate (1.28 million cases)
- Skin cancer (non-melanoma) (1.04 million cases)
- Stomach (1.03 million cases)
- **$200 billion: The overall costs of cancer, according to the National Institutes of Health (NIH).**

http://www.who.int/mediacentre/factsheets/fs297/en/

Most dangerous Cancer



http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf

WHO-2018

	Incident cases	
Lung	1 368 524	**14.5%**
Prostate	1 276 106	**13.5%**
Colorectum	1 026 215	**10.9%**
Stomach	683 754	**7.2%**
Liver	596 574	**6.3%**
Bladder	424 082	**4.5%**
Oesophagus	399 699	**4.2%**
Non-Hodgkin lymphoma	284 713	**3%**
Kidney	254 507	**2.7%**
Leukaemia	249 454	**2.6%**
Other cancers	2 892 790	**30.6%**
Total Cases	**9 456 418**	**100%**

Male

	Incident cases	
Breast	2 088 849	**24.2%**
Colorectum	823 303	**9.5%**
Lung	725 352	**8.4%**
Cervix uteri	569 847	**6.6%**
Thyroid	436 344	**5.1%**
Corpus uteri	382 069	**4.4%**
Stomach	349 947	**4.1%**
Ovary	295 414	**3.4%**
Liver	244 506	**2.8%**
Non-Hodgkin lymphoma	224 877	**2.6%**
Other cancers	2 482 031	**28.8%**
Total Cases	**8 622 539**	**100%**

Female

file:///Users/ashokkumarpatel/Downloads/9789240001299-eng.pdf

Fig. 1.2. Distribution of cases and deaths by the leading 10 cancer types in 2018 for both sexes.

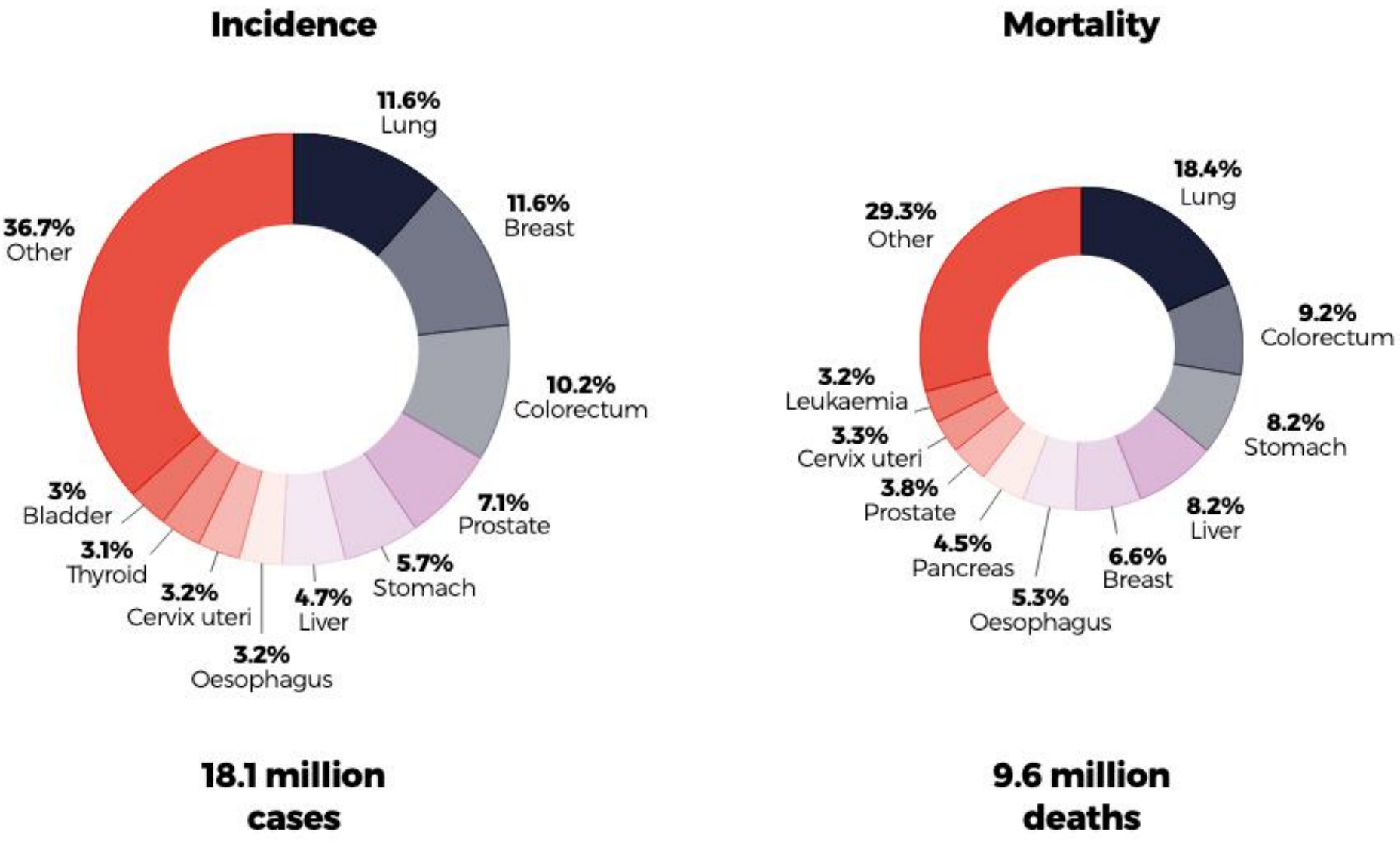
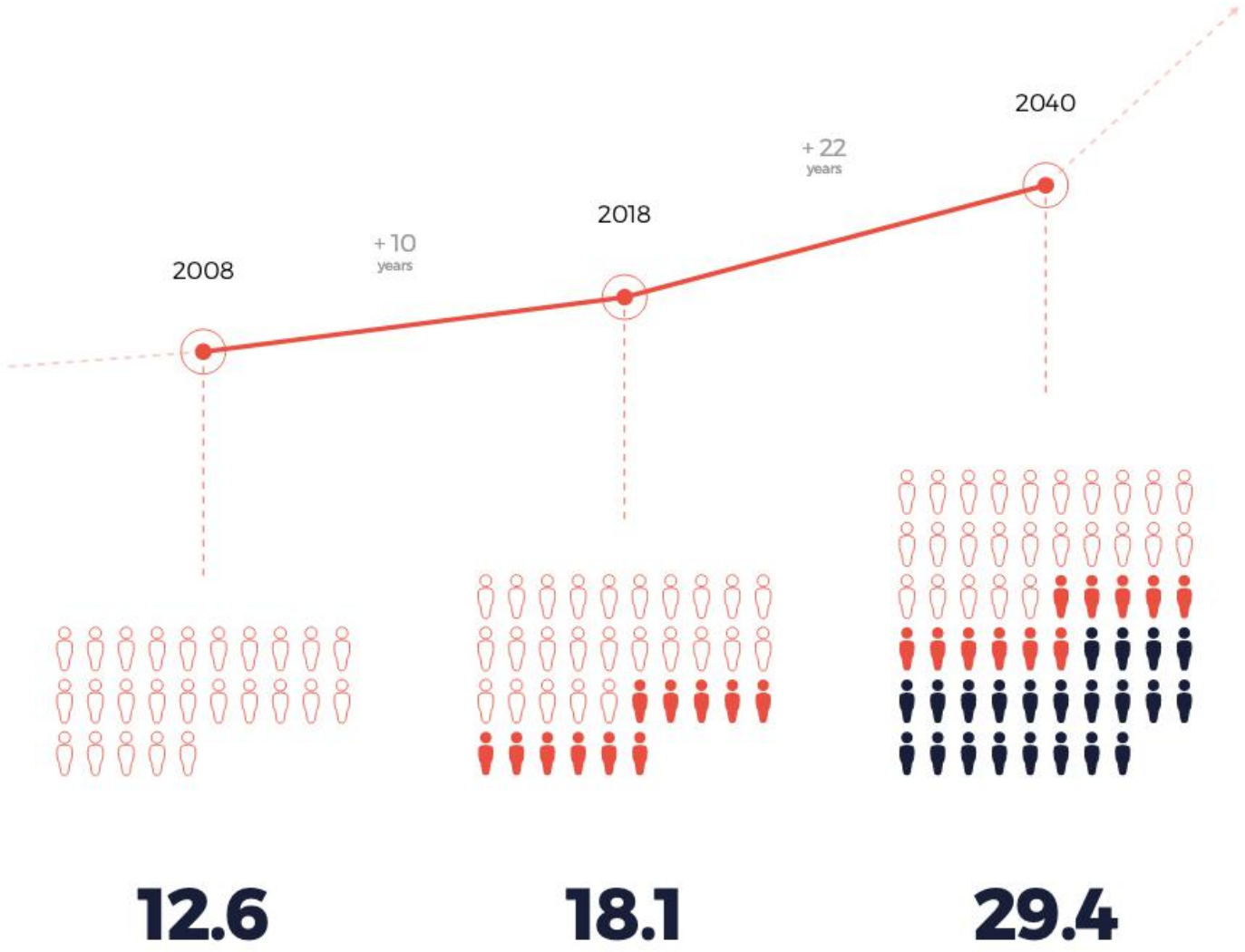


Fig. 1.6. Estimated global burden of cancer in 2018 and that in 2040 according to United Nations population projections.



Cancer scenario in India

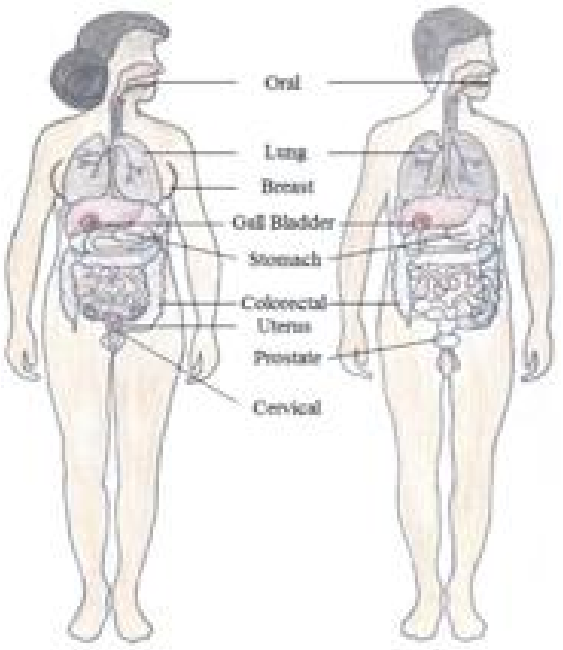
•Estimated number of people living with the disease: around 2.25 million

•Every year, new cancer patients registered: Over 11,57,294 lakh

•Cancer-related deaths: 7,84,821

Risk of developing cancer before the age of 75 years
Male: 9.81%
Female: 9.42%

Total deaths due to cancer in 2018
•Total: 7,84,821
•Men: 4,13,519
•Women: 3,71,302
Risk of dying from cancer is 7.34% in males and 6.28% in females.



	MEN	WOMEN
1	ORAL	BREAST
2	LUNG	ORAL
3	STOMACH	CERVIX
4	COLORECTAL	LUNG
5	ESOPHAGUS	GASTRIC

The top five cancers in men and women account for 47.2% of all cancers; these cancers can be prevented, screened for and/or detected early and treated at an early stage.
ICMR-2018

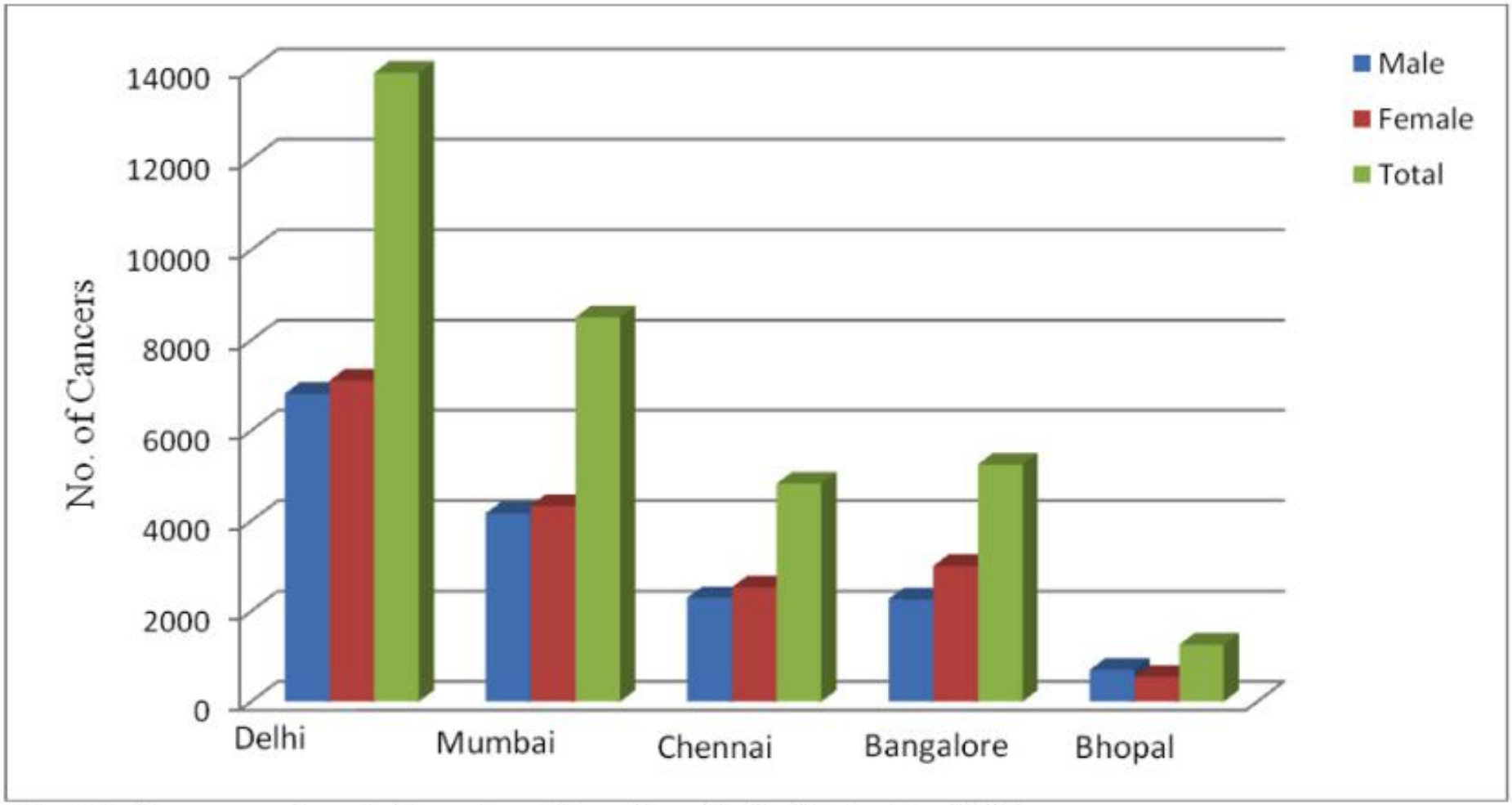


Figure 2: Cancer prevalence in five metropolitan cities of India [Marimuthu, 2008].

Cancer

- **Cancer** is a disease of multicellular organisms in which there is an uncontrolled proliferation of cells.
- The cardinal features of cancer are growth, invasion and metastasis.
- The term metastasis is given to the formation of secondary tumors at sites distant from the primary tumor.
- No morphological or biochemical change has been identified that is present in all cancer cells and has not been seen in any normal cell.

What is Cancer?

Cancer is a disease that begins when a single cell escapes from the regulation of its own division.

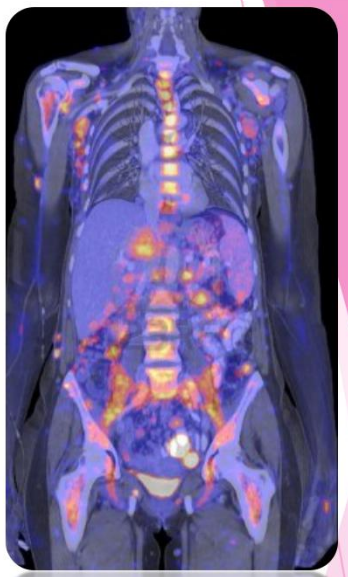
Cell division is the process a cell undergoes in order to make copies of itself. This division is normally regulated so that a cell divides only when more cells are required, and when conditions are favorable for division.

A cancerous cell is a rebellious cell that divides without instructions from the body.

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. it can result in death.

- As genes switch on and off, they determine when and how fast the cell will grow and divide, when it will stop dividing, and even when it will die. Cancer can result when controls over cell division are lost…

WHY IS CRAB (♋)THE SYMBOL OF CANCER?

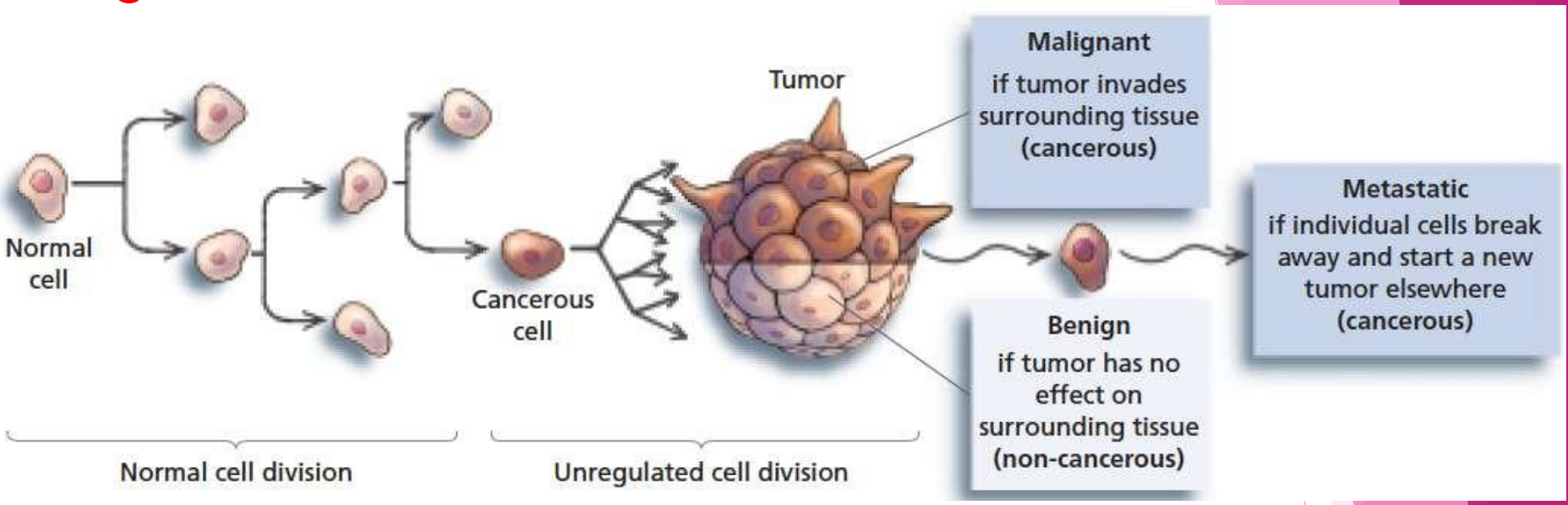


- **"Cancer"** is the Latin word for crab.
- In its natural habitat, a crab is a fast, resilient decapod crustacean that springs to action and moves in multiple directions.
- Similarly **cancer** spreads from the place at which it first arose as a primary tumor to distant locations in the body.

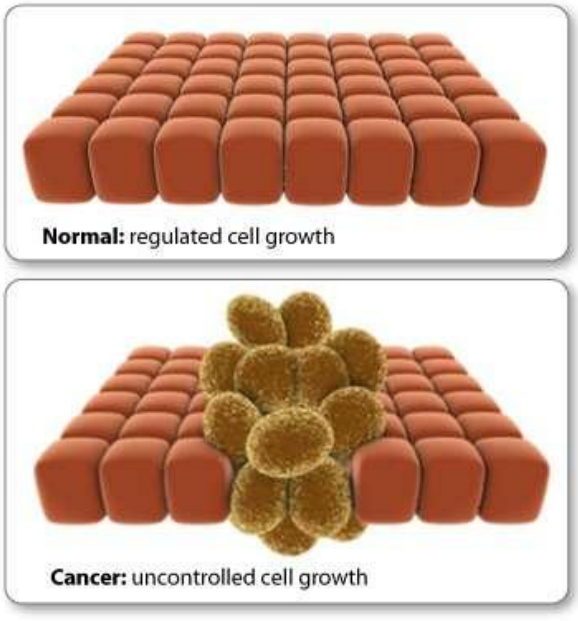
Cancer - incurable suffering?

www.dylanmatthews.com/images/cancer.jpg

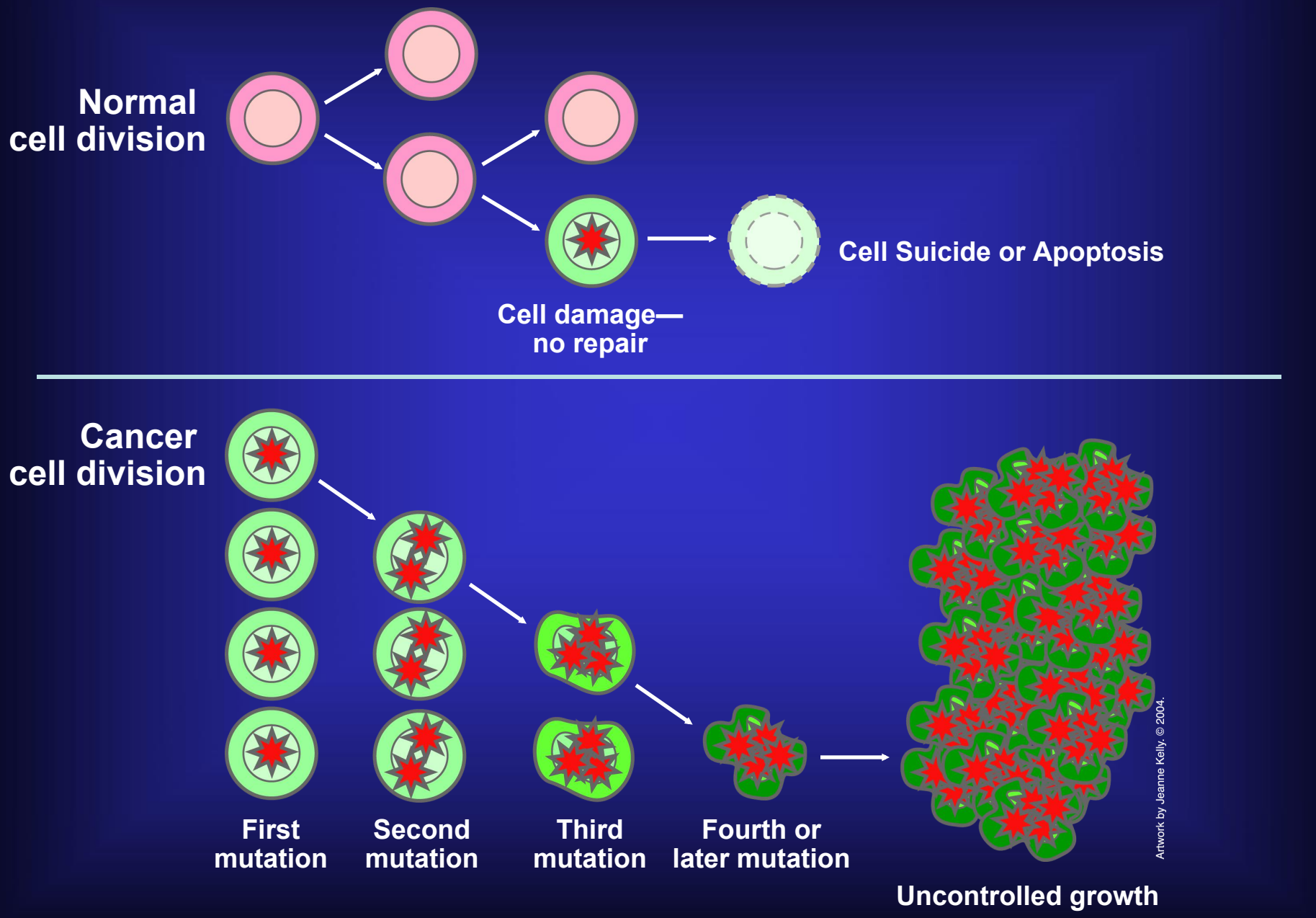
Background / Rationale



- Cancer is uncontrolled cell growth.
- Cancer progression is a multistep process that begins with abnormal cells with malignant potential or neoplastic characteristics and proceeds with tumor growth, stromal invasion, and metastasis.
- However, despite of numerous efforts, effective therapeutic inventions against many cancer types have not been achieved.



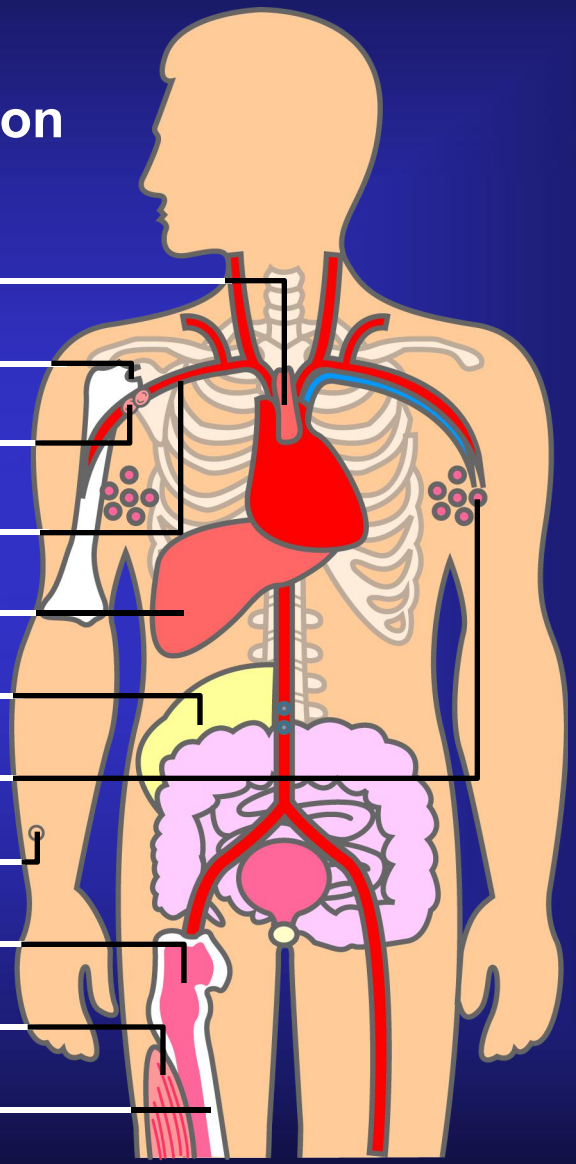
Loss of Normal Growth Control



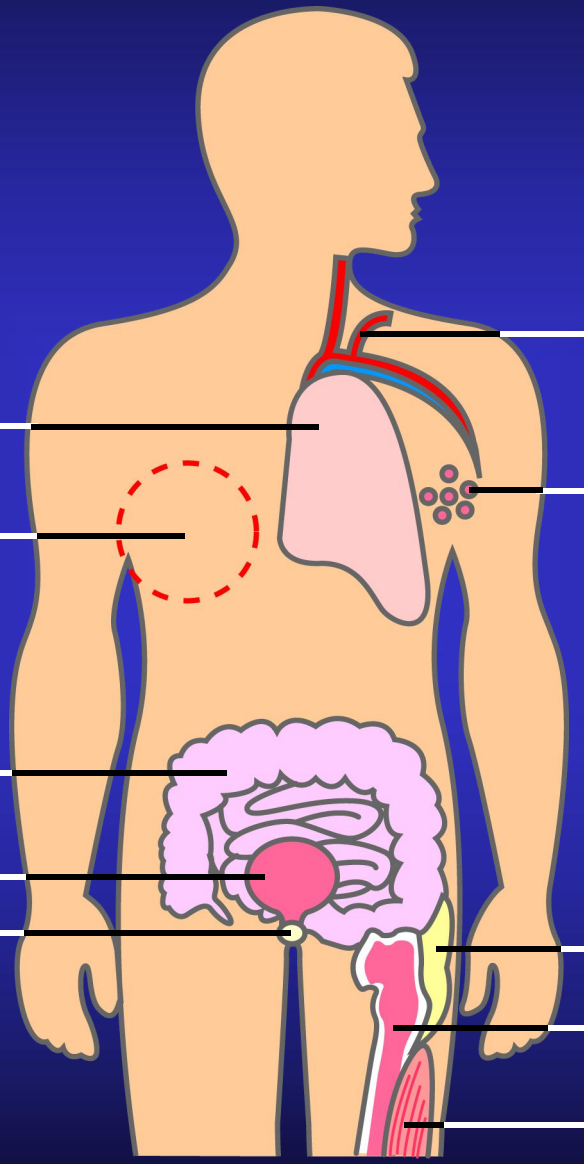
Naming Cancers

Cancer Prefixes Point to Location

Prefix	*Meaning*
adeno-	gland
chondro-	cartilage
erythro-	red blood cell
hemangio-	blood vessels
hepato-	liver
lipo-	fat
lympho-	lymphocyte
melano-	pigment cell
myelo-	bone marrow
myo-	muscle
osteo-	bone



Different Kinds of Cancer



Some common carcinomas:

Lung

Breast (women)

Colon

Bladder

Prostate (men)

Leukemias:

Bloodstream

Lymphomas:

Lymph nodes

Some common sarcomas:

Fat

Bone

Muscle

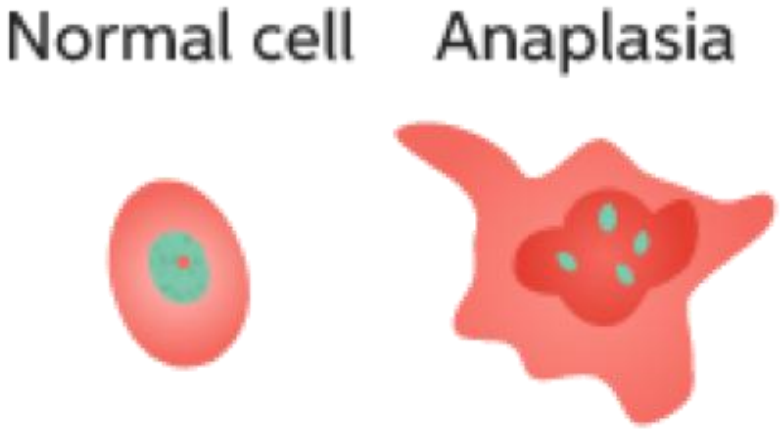
Cancer types: classified by tissue of origin

- **Carcinoma** – cancer of skin or in tissues that line or cover internal organs.
- **Sarcoma** – cancer of bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- **Leukemia** – cancer of blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells.
- **Lymphoma and myeloma** – cancers of the cells of the immune system.
- **Central nervous system cancers** – cancers of the tissues of the brain and spinal cord.

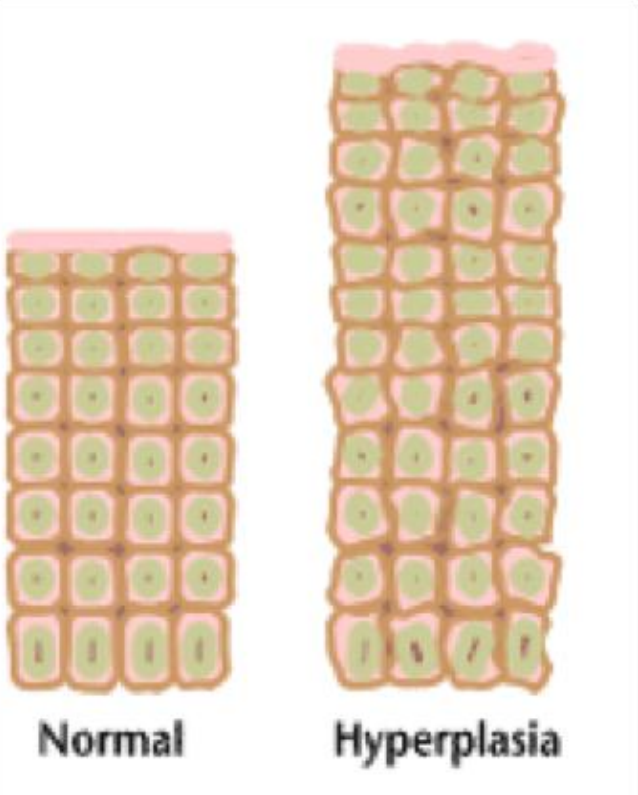
More than 80% of human cancers are carcinomas, because Most cell proliferation in the body occurs in epithelia. Epithelial tissues are most frequently exposed to the various forms of physical and chemical damage that favor the development of cancer.

Common Terminologies in Cancer Biology

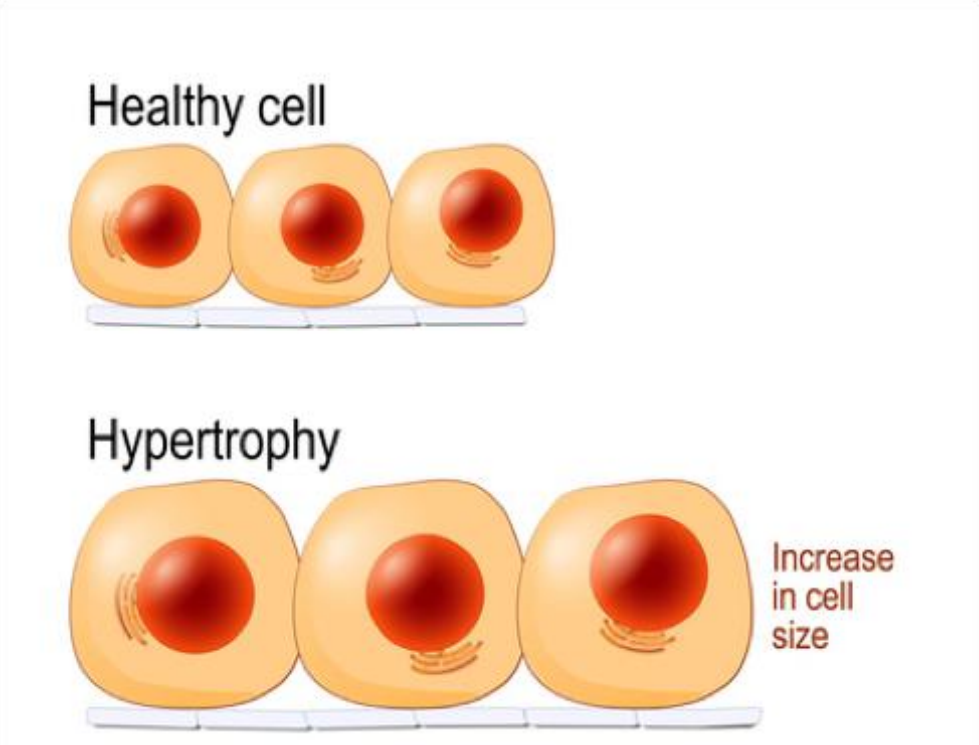
- Anaplasia: Loss of differentiation of cells and/or tissues (Greek: Ana – backward; plasia – formation)
  - Loss of polarity: Normally the nuclei of epithelial cells are oriented along the basement membrane
  - Pleomorphism: variation in size and shape of the tumor cell
  - Nuclei to cytoplasmic ratio – nuclei are enlarged, increased from normal 1:5 to 1:1
  - Anisonucleosis – variation in size and shape of nuclei.



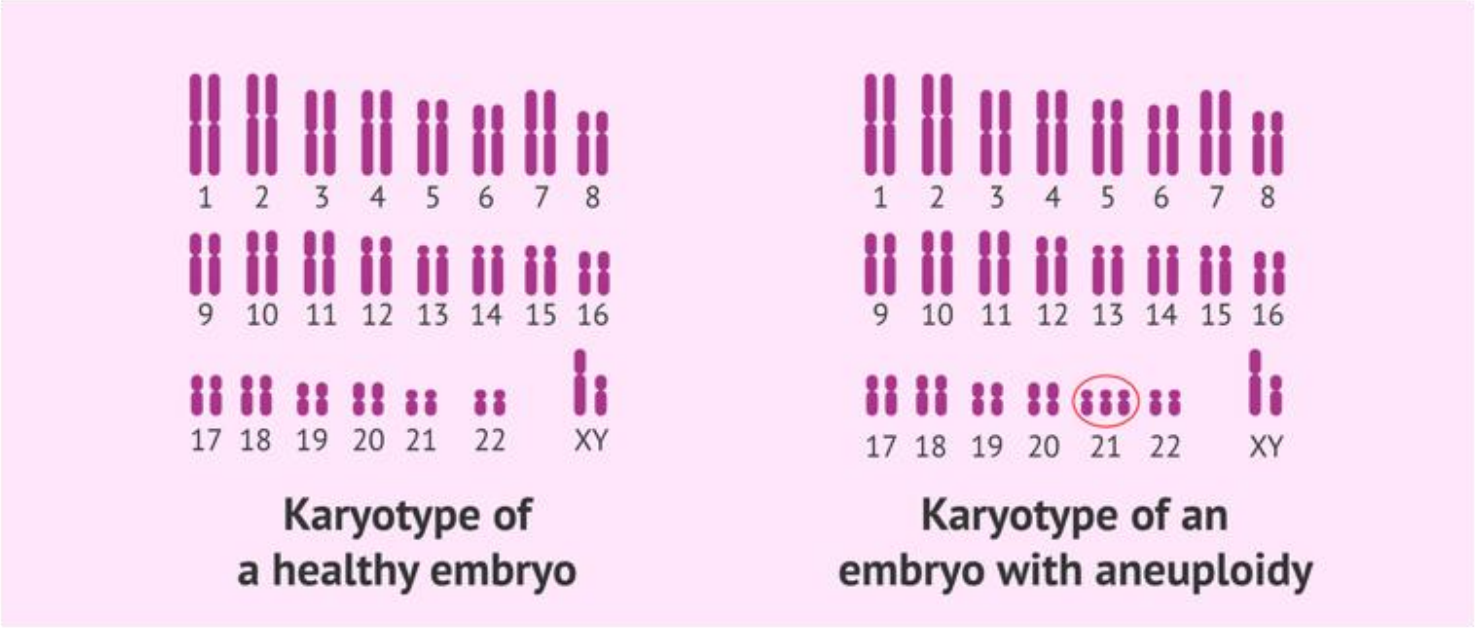
Hyperplasia: Increased number of cells in a tissue
Hyper – over, plasia – formation.



Hypertrophy: Increase in the size of a tissue
hyper – over; trophy -

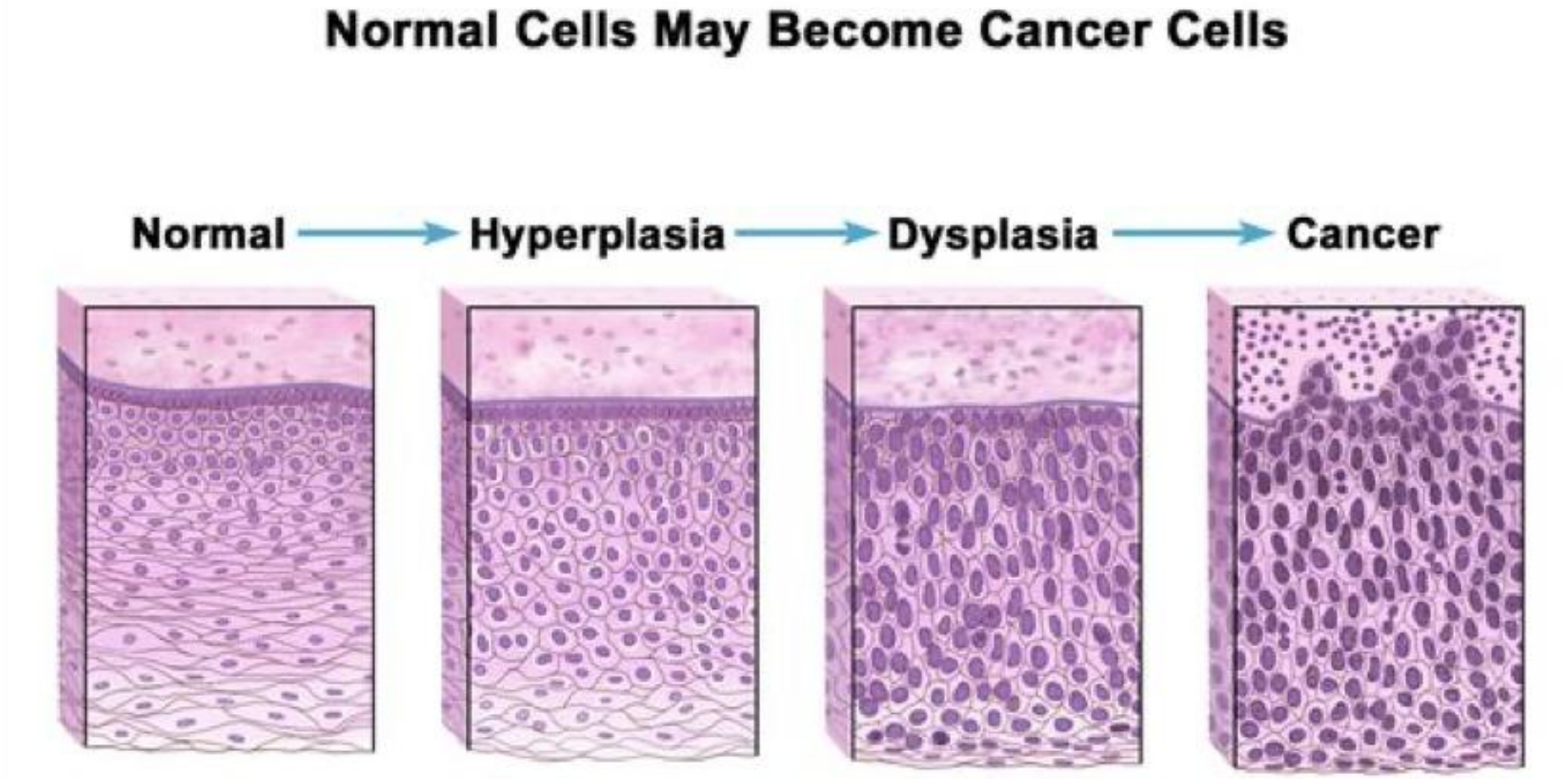


Aneuploidy: Possessing an abnormal number of chromosomes



Around 90 % of the tumors have cancer cells with extra or missing chromosomes

Dysplasia: Abnormal tissue development



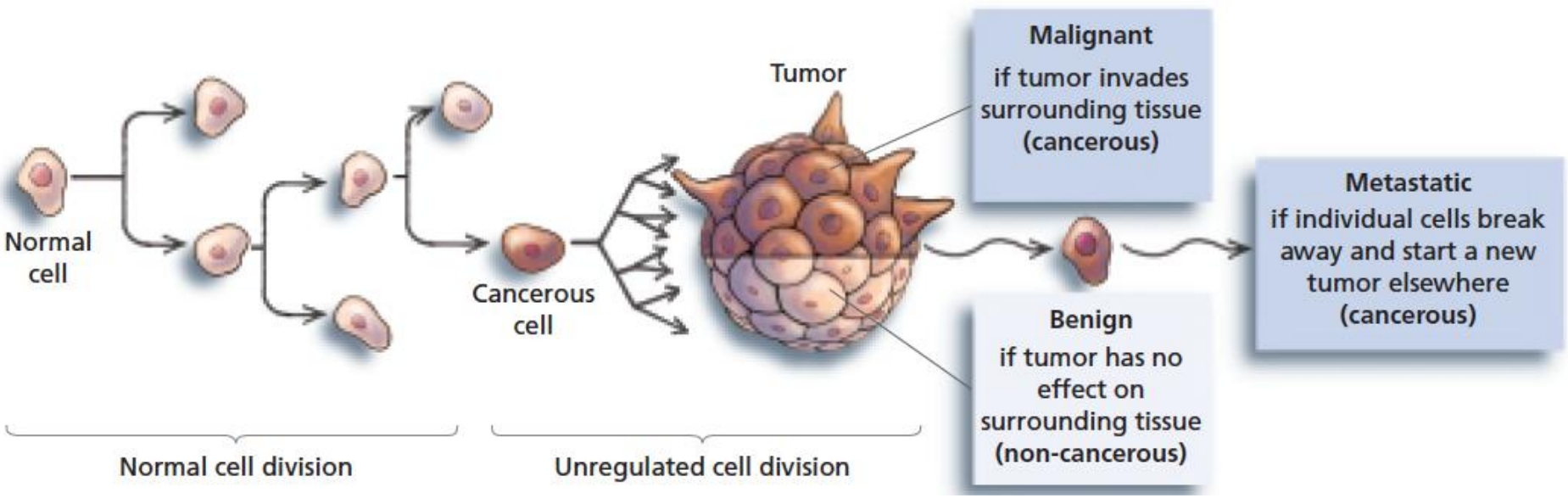
Cancer and metastasis

Tumor: Unregulated cell division that leads to a pile of cells that form a lump.

A tumor is a mass of tissue that has no apparent function in the body.

Tumors that stay in one place and do not affect surrounding tissues are said to be benign

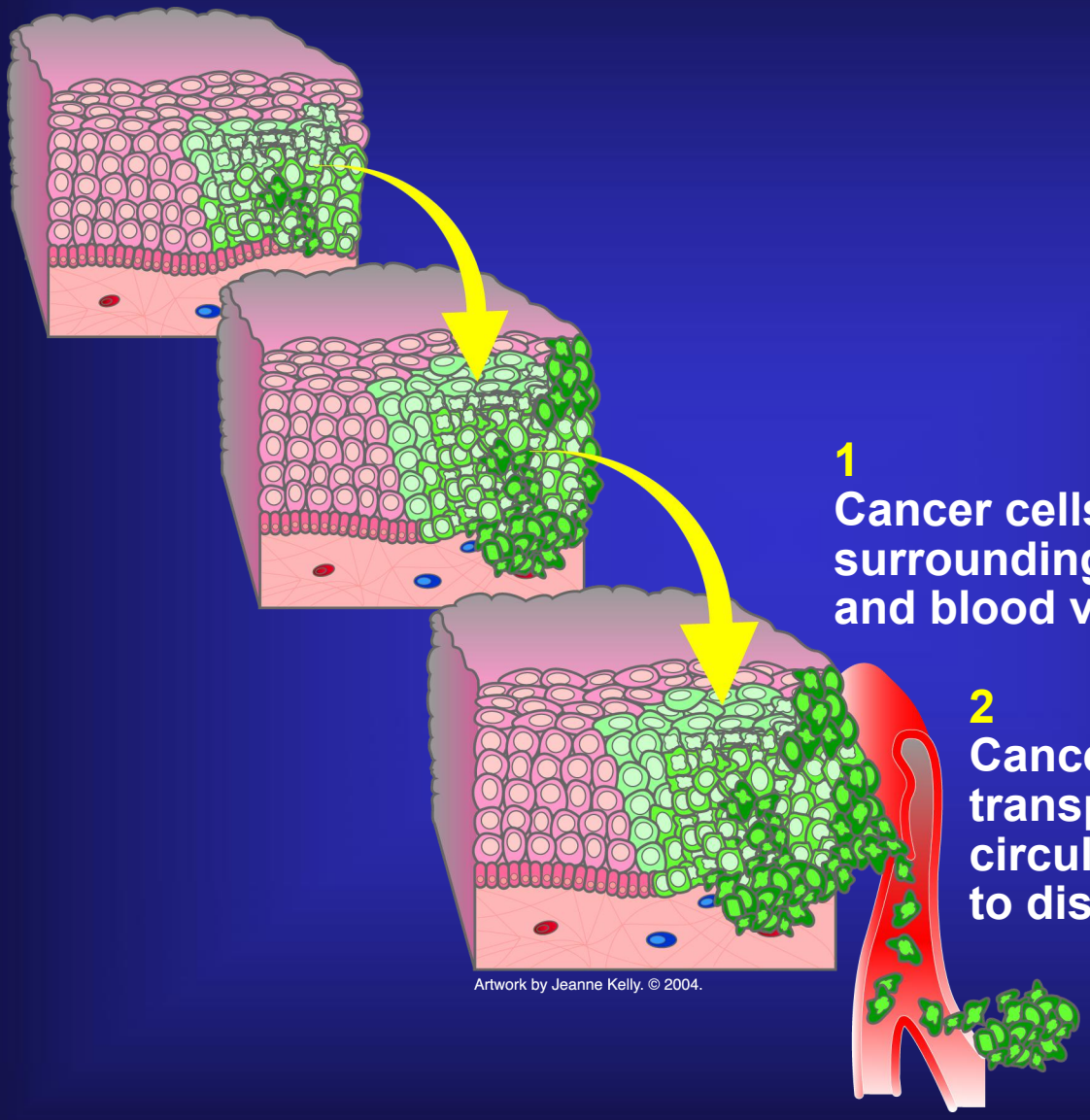
Cells from the original tumor can break away and start new cancers at distant locations, this process is called metastasis



Malignancy

- A term for diseases in which abnormal cells divide without control and can invade nearby tissues.
- Malignant cells can also spread to other parts of the body through the blood and lymph systems.
- There are several types of malignancy
  - Carcinoma
  - Sarcoma
  - Leukemia
  - Lymphoma

Invasion and Metastasis



1
Cancer cells invade surrounding tissues and blood vessels

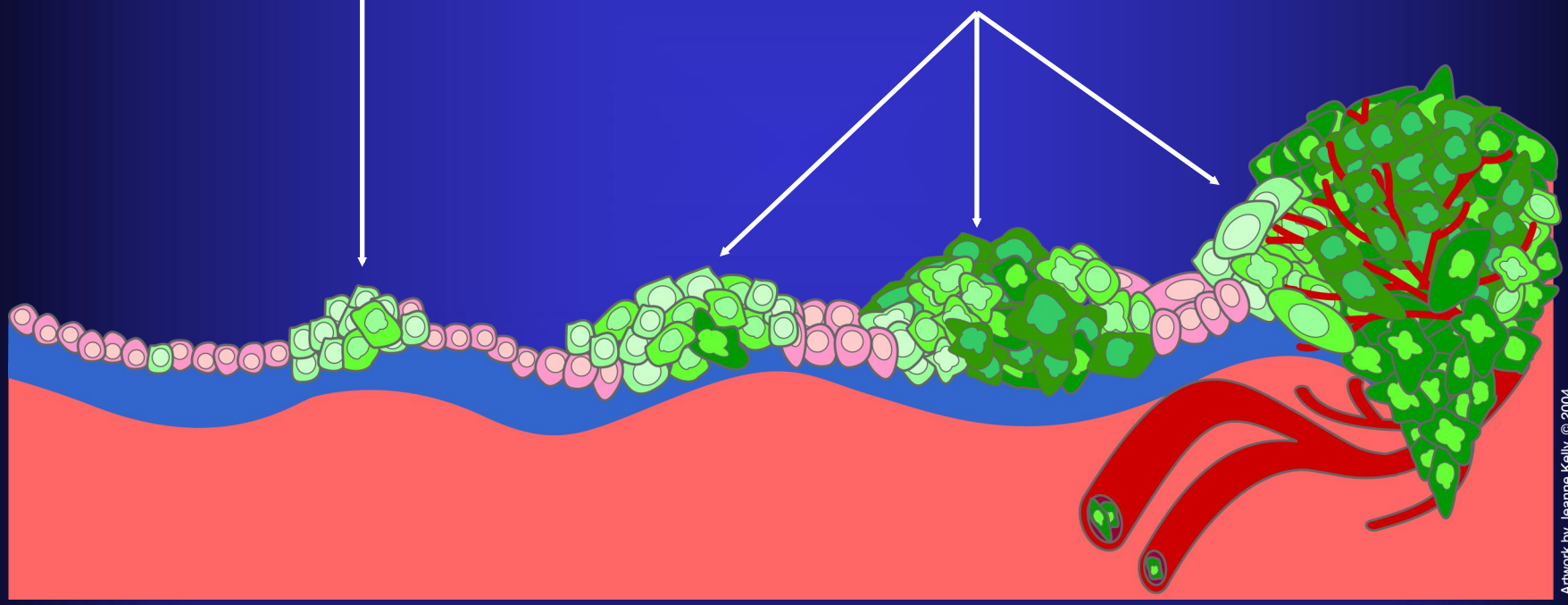
2
Cancer cells are transported by the circulatory system to distant sites

3
Cancer cells reinvade and grow at new location

Malignant versus Benign Tumors

Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time

Cancer cells differ from normal cells in three ways:

(1) they divide when they should not;
(2) they invade surrounding tissues; and
(3) they move to other locations in the body.

➢The purpose of cell division is to heal wounds, replace damaged cells, and help tissues and organs grow.

➢ Normal cells are programmed to divide a certain number of times— usually 60– 70— and then they die.

➢Cancer cells do not obey these life-span limits, instead they are immortal.

➢This is because cancer cells can activate a gene that is usually turned off after early development.

➢This gene produces an enzyme called telomerase . This enzyme, only active early in development and in cancer cells, allows cells to divide without limit. Cells with active telomerase enzyme are immortal.

SBL100-Lecture

Introduction to Cancer

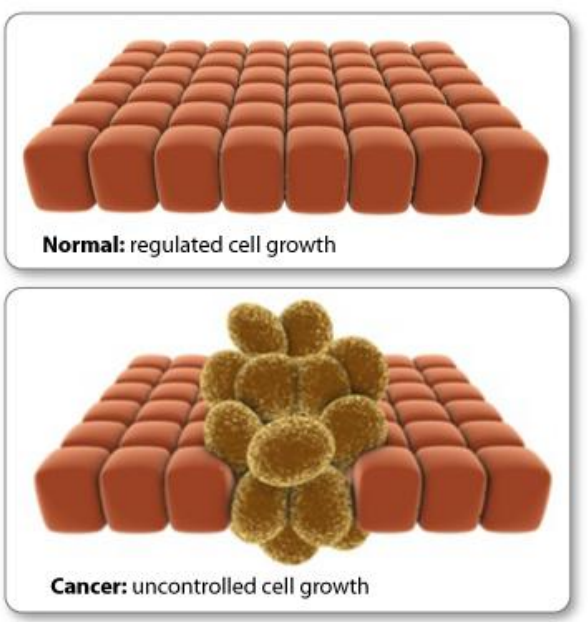
Part II

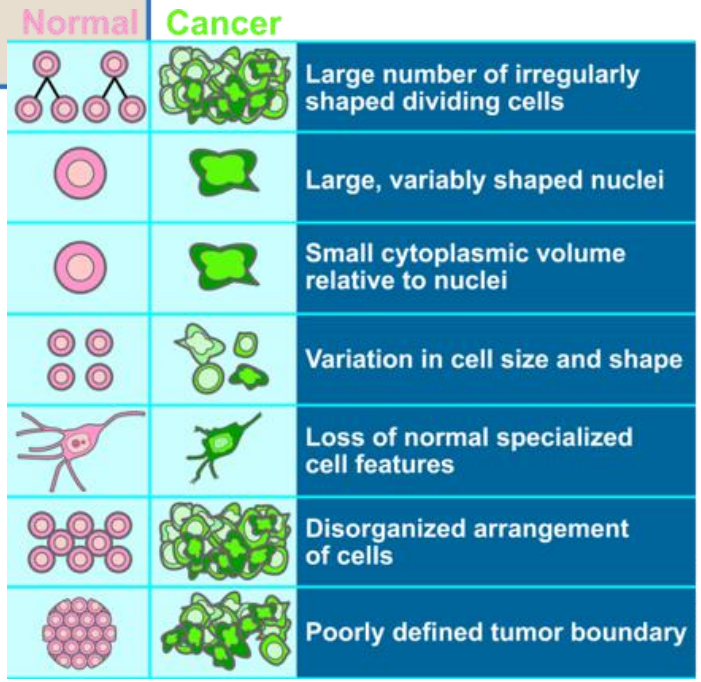
Cancer Cells Versus Normal Cells

TABLE 9.2

Cancer Cells Versus Normal Cells

Cancer Cells	*Normal Cells*
Nondifferentiated cells	Differentiated cells
Abnormal nuclei	Normal nuclei
Do not undergo apoptosis	Undergo apoptosis
No contact inhibition	Contact inhibition
Disorganized, multilayered	One organized layer
Undergo metastasis and angiogenesis	

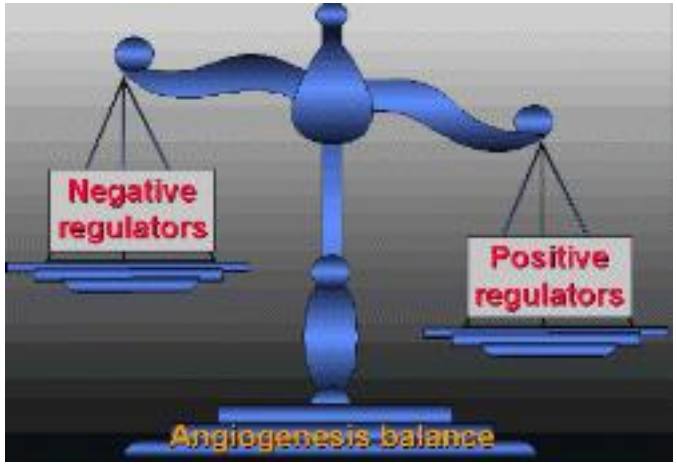




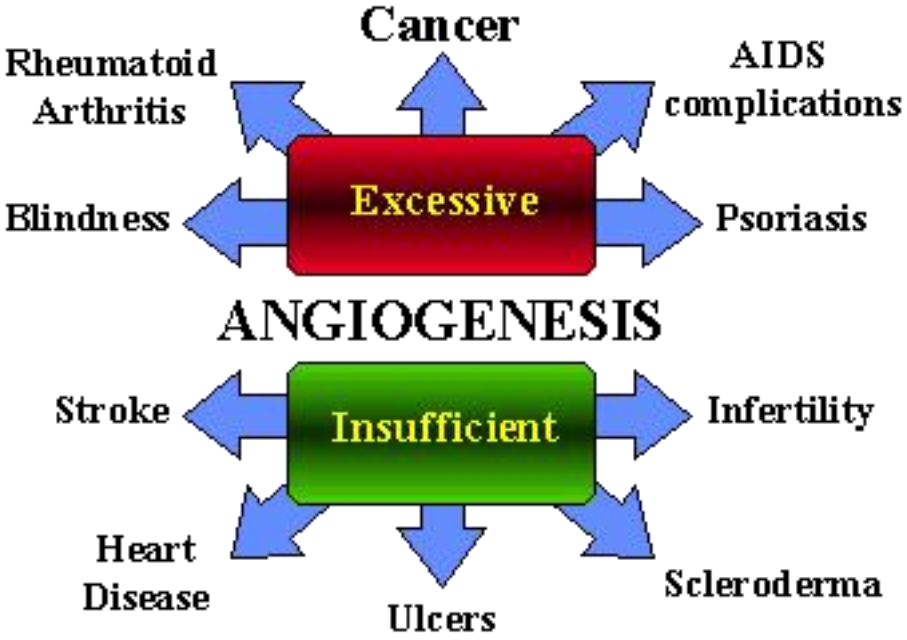
What is Angiogenesis?

It is growth of new capillary blood vessels in the body. It is an important natural process used for healing and reproduction. The body controls angiogenesis by producing a precise balance of growth and inhibitory factors in healthy tissues.

Abnormal blood vessel growth leads to cancer.

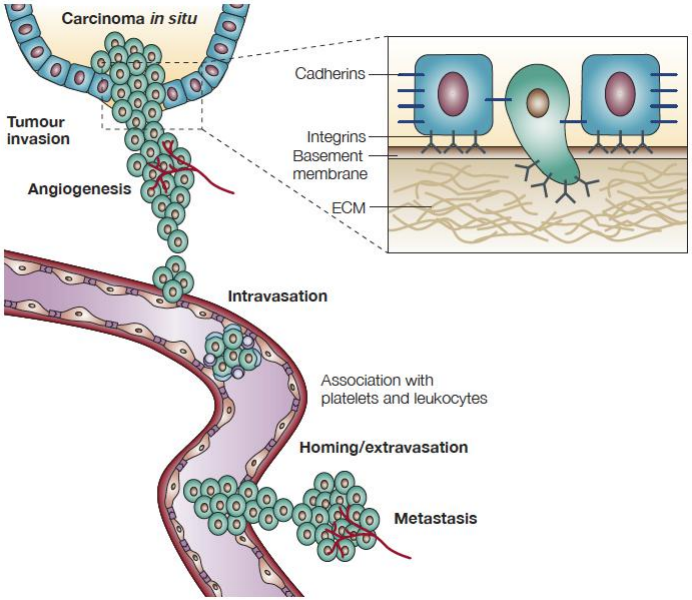


http://bcove.me/erpvo6ia

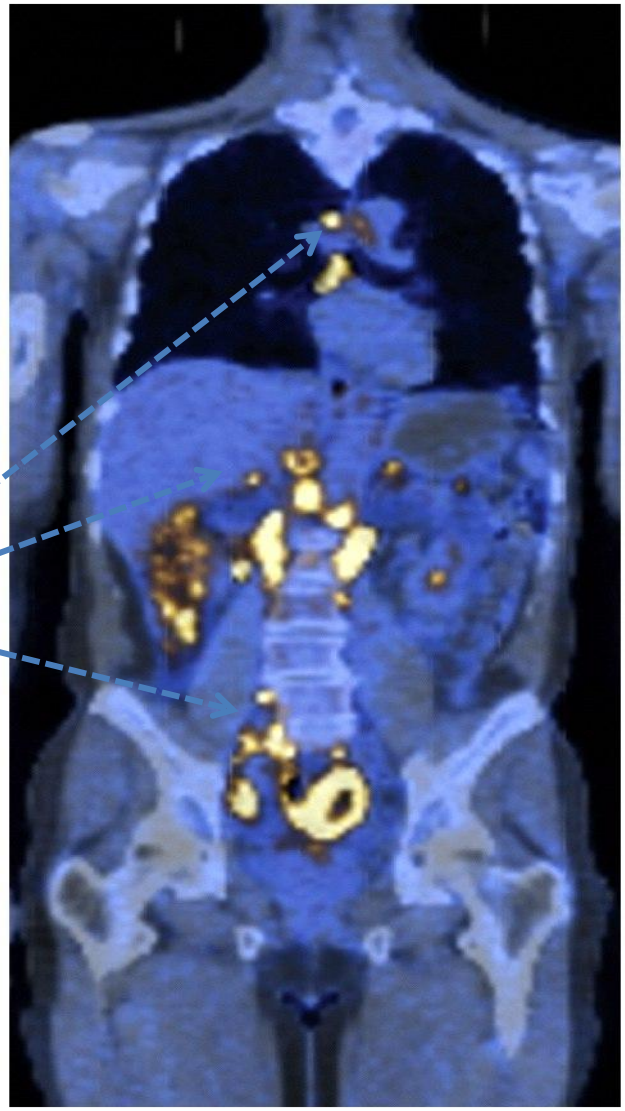


http://www.med.unibs.it/~airc/angiogen.html

What is Metastasis? It is process by which a tumor cell leaves the primary tumor, travels to a distant site via the circulatory system, and establishes a secondary tumor.



Metastatic tumors



Malignant tumors typically give rise to metastases, making the cancer hard to eradicate.

(From Union Internationale Contre le Cancer, TNM Atlas: Illustrated Guide to the Classification of Malignant Tumors, 2nd ed. Berlin: Springer- Verlag, 1986.)

Acquired capabilities that contributes to the deadly behaviour of metastatic cells:

- ability to move through, and thereby invade, other tissues.

- metastatic cells have to induce angiogenesis to escape the limits that passive diffusion of nutrients and oxygen impose on tumour growth.
angiogenesis provides a gateway for tumour cells to enter the circulation, which facilitate the migration and invasion of tumour cells.

- metastatic cells have to survive in various foreign microenvironments before they colonize their target organ, and they have to survive

Cancerous growth often depends on defective control of cell death, cell differentiation, or both

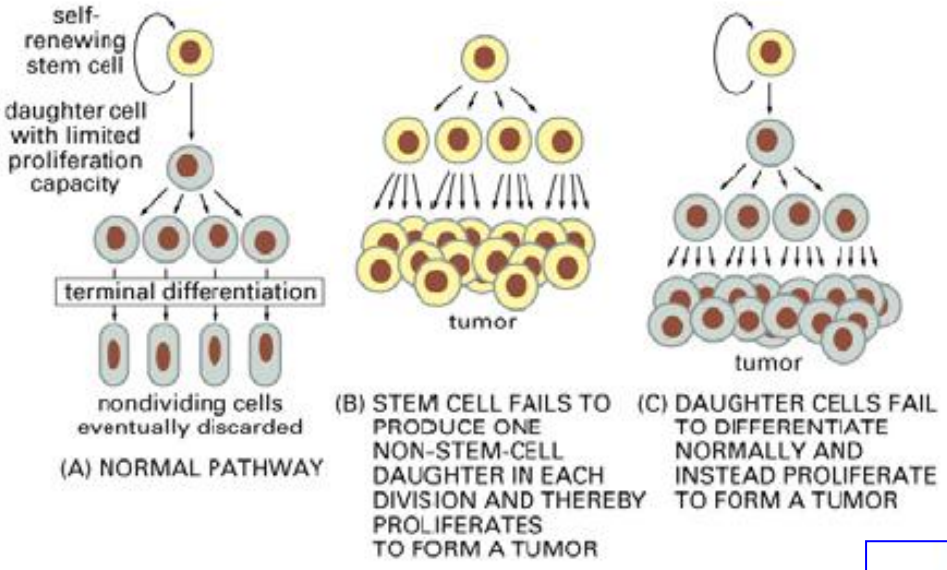
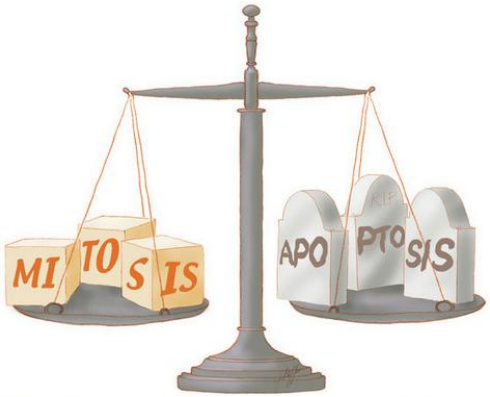


Figure 23–14. Molecular Biology of the Cell, 4th Edition.

Apoptosis is needed to destroy cells

Examples: Cells infected with viruses
Cells of the immune system
Cells with DNA damage
Cancer cells



- Apoptosis is called programmed cell death, which means coordinated collapse of cell, protein degradation, DNA fragmentation followed by rapid engulfment of corpses by neighbouring cells.
- **Apoptosis is needed for proper development.**

Examples:

- The resorption of the tadpole tail.
- The formation of the fingers and toes of the fetus.
- The formation of the proper connections between neurons in the brain.

Increased cell division & deceased apoptosis

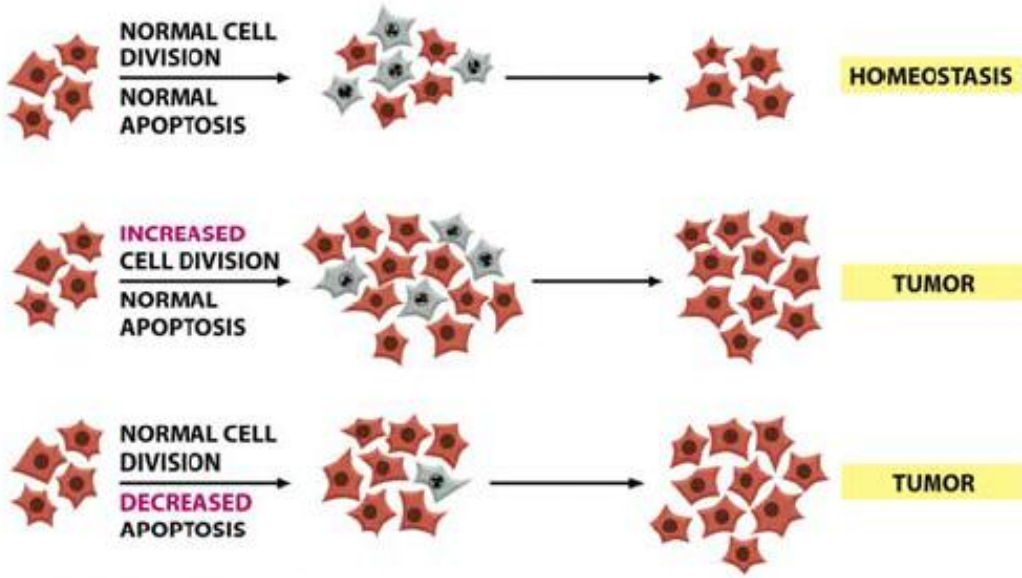
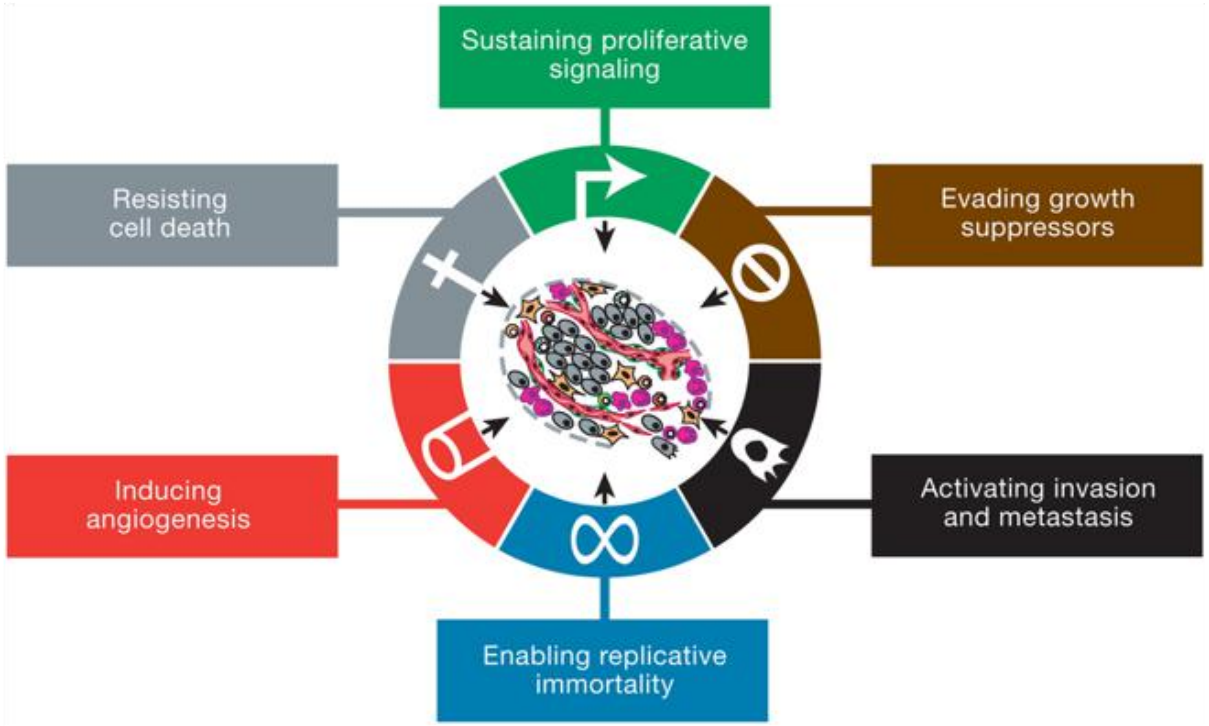


Figure 20-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Hallmarks of Cancer



Hanahan D and Weinberg R, Cell, 2000

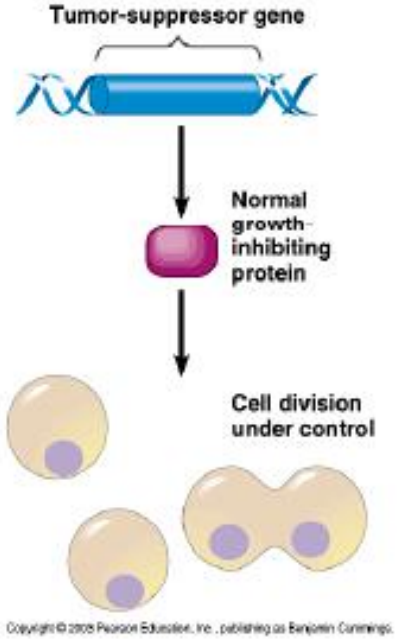
Hallmarks of Cancer

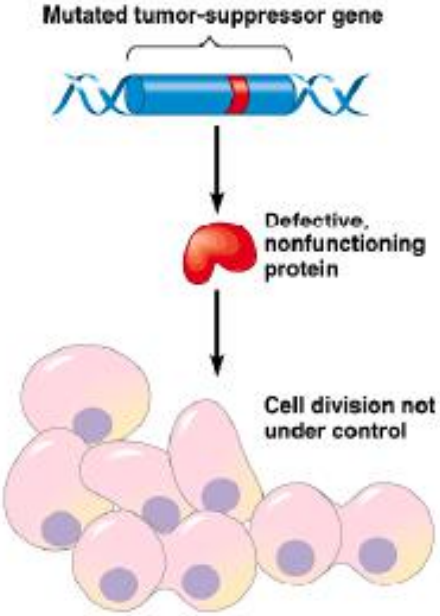
- We foresee cancer research developing into a logical science, where the complexities of the disease, described in the laboratory and clinic, will become understandable in terms of a small number of underlying principles.
- Rules that govern the transformation of normal human cells into malignant cancers
- A small number of molecular, biochemical and cellular traits – acquired capabilities – shared by most and perhaps all types of human cancers.
- Our faith in such simplification derives directly from the teachings of cell biology that virtually all mammalian cells carry a similar molecular machinery regulating their proliferation, differentiation and death.

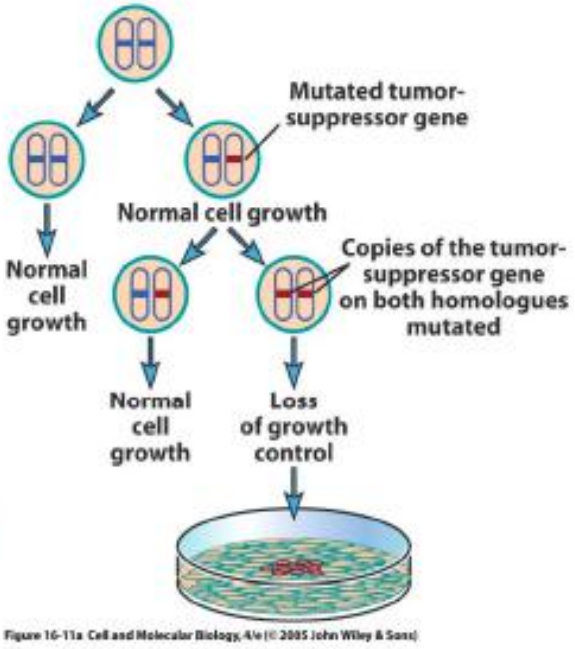
Hanahan D and Weinberg R, Cell, 2000

Tumor suppressor

- Genes in the body that can suppress or block the development of cancer
- Need TWO bad copies before problems occur- **recessive**
- Homozygous loss of p53 is found in 65% of colon cancers, 30–50% of breast cancers, and 50% of lung cancers.







Oncogenes & Proto-oncogenes

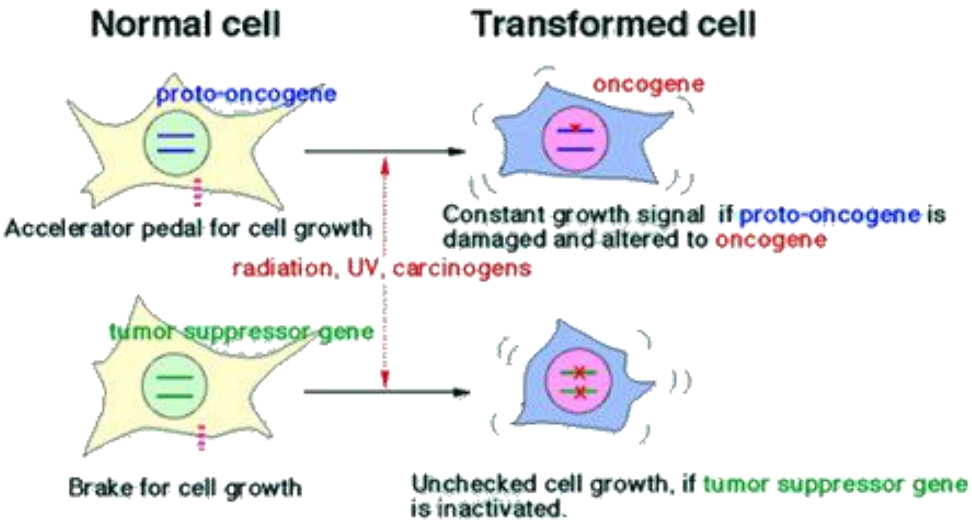
- Oncogene - Genes that promote cell growth and/or motility, which when upregulated or deregulated, empower cells with the cancerous properties of unregulated growth and motility.
- Can transform healthy cells.
- Proto-oncogenes - Proto-oncogenes are a group of genes that cause normal cells to become cancerous when they are mutated.
- Mutations in proto-oncogenes are typically dominant in nature.
- Often, proto-oncogenes encode proteins that stimulate cell division.
- First oncogene was discovered in chicken (Rous Sarcoma Virus)

TUMOR SUPPRESSOR GENES

VERSUS

PROTO ONCOGENES

TUMOR SUPPRESSOR GENES	PROTO ONCOGENES
Protective genes that help to control the cell growth	Normal genes which, when altered by mutation, become oncogenes that can contribute to cancer
Mutations alter the gene products that inhibit the progression of the cell cycle, causing the development of tumors	Mutations alter the gene products in such a way to increase their expression, which cause cancers by increasing cell division
Suppress cell division	Activate cell division
Inactivation (loss of function) causes cancers	Activation (gain of function) causes cancers
Cancer development is recessive since both copies of alleles have to be mutated to develop cancer	Cancer development is dominant since a mutation of a single copy can cause cancers



1. Three Nobel Prizes for a chicken virus

Rous (1879–1970)
1966 Nobel Prize
"Rous sarcoma virus"

- In 1910 Peyton Rous extracted material from a cancer tumor in a hen and injected it into a healthy chicken.
- The chicken developed cancer, and he concluded that cells from the hen's tumor contained an infectious substance, a virus, that transmits cancer.
- However, the study could not be replicated in mammals and was long overlooked.
- When research showed that viruses can operate by affecting the genetic material of normal germ cells, interest in Rous' discovery was reignited.

2. Three Nobel Prizes for a chicken virus

Howard Temin

- At the beginning of the 1960s, Howard Temin, a young virologist at the University of Wisconsin in Madison, came up with the "provirus hypothesis"
- A discovery that was more intuitive than based on solid experiments.
- According to the provirus hypothesis, a DNA provirus is synthesized after an RNA virus has entered a host cell.
- Temin's provirus hypothesis was heavily attacked, because it was in conflict with the central dogma
- The enzyme, which became known as reverse transcriptase, was not localized in the cells but in the viruses: the RNA tumor viruses were called retroviruses.

3. Three Nobel Prizes for a chicken virus

Bishop (1936–)
1989 Nobel Prize
"Src oncogene"

Varmus (1939–)
1989 Nobel Prize
"Src oncogene"

- Varmus and Bishop showed that nearly-identical versions of cancer-causing genes (so-called oncogenes) carried by retroviruses, viruses that integrate themselves into the DNA of infected cells, are present in the genome of normal, uninfected cells in a wide range of species
- Normal cells carried within them the seeds of cancer in the form of genes they called proto-oncogenes.

3. Three Nobel Prizes for a chicken virus

Bishop (1936–)
1989 Nobel Prize
"Src oncogene"

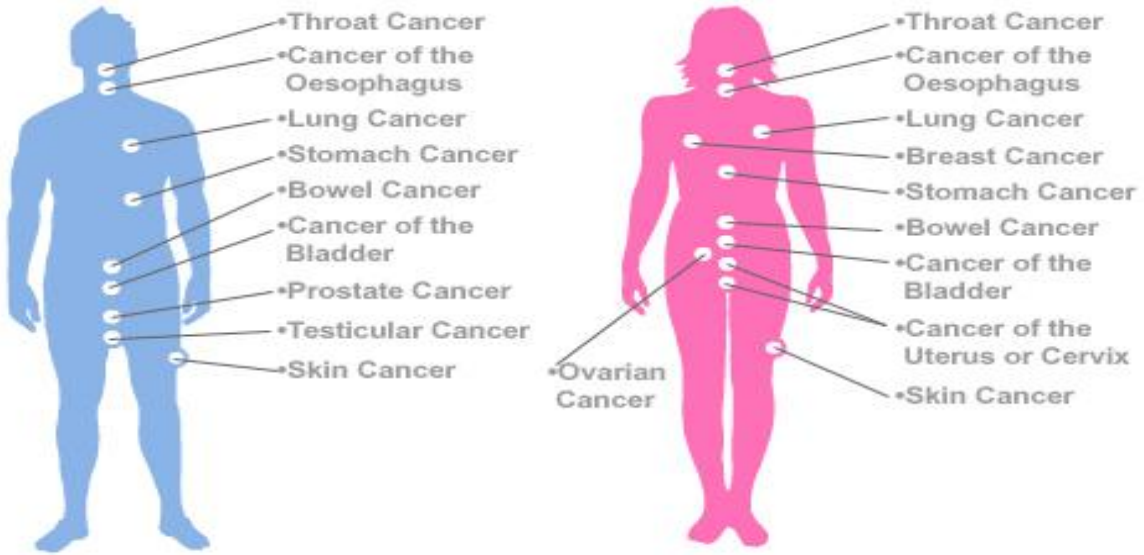
Varmus (1939–)
1989 Nobel Prize
"Src oncogene"

- Proto-oncogenes are conserved and are present across species, from yeast to fish to humans.
- Only when a proto-oncogene is altered through the rearrangement of the cell's chromosomes or through cumulative mutations--mutations at several different sites in the gene are required--does it trigger uncontrolled cell growth and division.
- "Unified theory of cancer"

Stages of Cancer Spread

- Stage 1: Confined to organ of origin
- Stage 2: Locally invasive
- Stage 3: Spread to lymph nodes
- Stage 4: Spread to distant sites

WHICH PARTS OF THE BODY ARE AFFECTED BY CANCER?

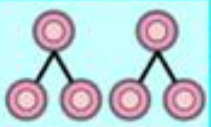


- Almost all the major parts of our body may be affected by **cancer.**
- Size of cancer cells:
  - One million cancer cells = head of a pin
  - One billion cancer cells = a small grape

Cancer Staging

- The extent to which cancer has spread is called its stage.
- It’s important for doctors to determine the cancer stage in order to design the best course of treatment (prognosis).
- Cancer stage is determined during diagnosis and depends on the size, type and location of the cancer.
- Tumor grade is a term used to refer to the appearance and behavior of cancer cells (how likely they are to grow and spread).

What does a pathologist look for examining biopsy tissue?

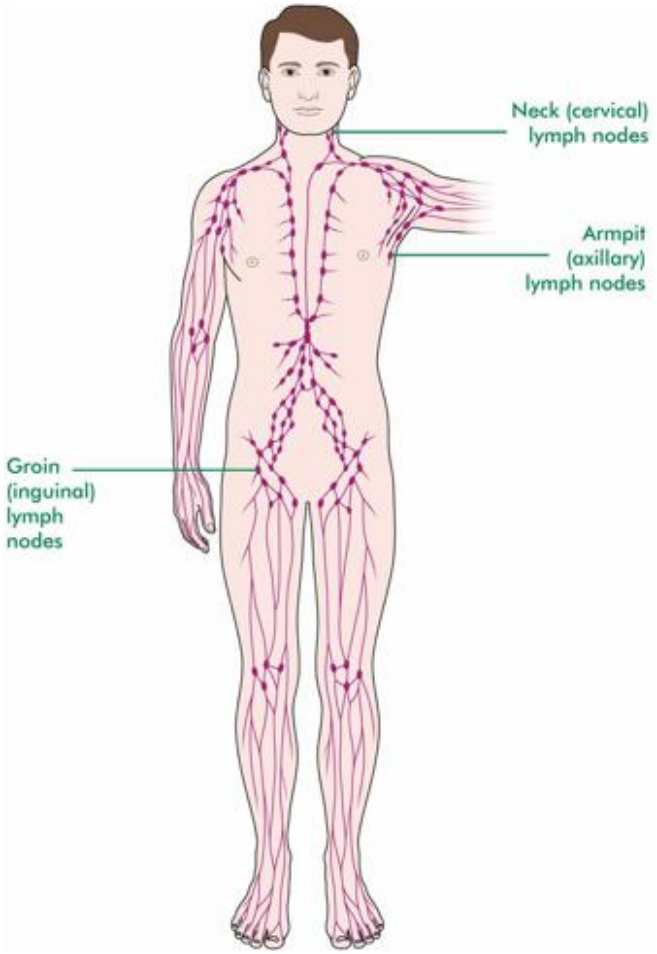
Normal	Cancer	
		Large number of irregularly shaped dividing cells
		Large, variably shaped nuclei
		Small cytoplasmic volume relative to nuclei
		Variation in cell size and shape
		Loss of normal specialized cell features
		Disorganized arrangement of cells
		Poorly defined tumor boundary

Cancer Staging

- **TNM** is the most common tumor staging system used to describe cancer.
- **T—Tumor** represents the size and magnitude of the primary tumor and has the following subsets:
  - **TX**. TX means there's no information about the primary tumor, or it can't be measured..
  - The proper use of X is to denote the absence or uncertainty of assigning a given category (T, N, or M) when all reasonable clinical or pathologic maneuvers have been used in staging
  - **T0**. Primary tumor cannot be found.
  - **Tis** means that the cancer cells are only growing in the layer of cells where they started, without growing into deeper layers. This may also be called in situ cancer or pre-cancer.
  - **T1, T2, T3, T4**: These denote the size and progression of the primary tumor, increasing in progression with each number, and may be further broken down into subsets.

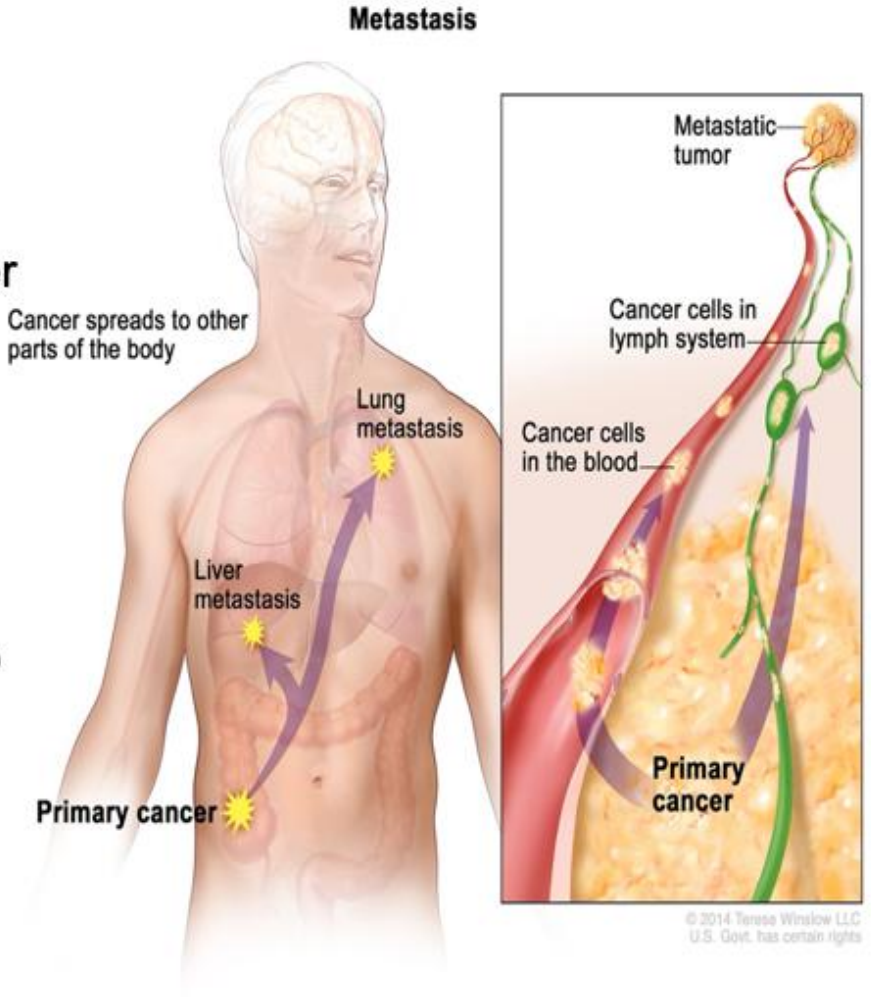
Cancer Staging

- **N—Node** represents the specific number of lymph nodes that also have cancer. and it has the following subsets:
  - **NX**. Presence of cancer in nearby lymph nodes is unmeasurable.
  - **N0**. There is no cancer in the lymph nodes.
  - **N1, N2, N3**. These denote the number and location where cancer-containing lymph nodes have been detected, increasing in progression with each number.



Cancer Staging

- **M—Metastasis** represents distant metastasis, or whether or not the cancer has spread to other areas, and it includes the following subsets:
  - **MX**. Rate of metastasis is unmeasurable.
  - **M0**. Cancer has not metastasized to other areas.
  - **M1**. Cancer has metastasized to other areas.



Cancer Staging

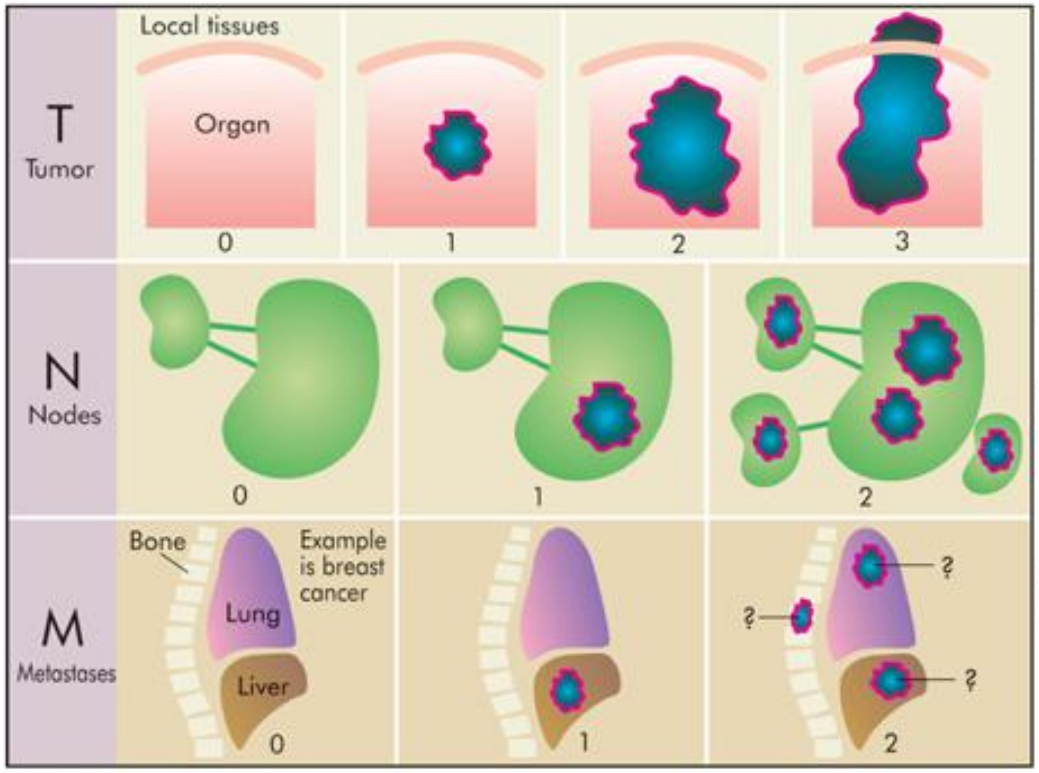


Fig. 9-3. Tumor Staging by the TNM System
Example of staging for breast cancer.

TUMOR

T = Primary tumor; the number equals size of tumor and its local extent. The number can vary according to site.
T0 = Breast free of tumor
T1 = Lesion <2 cm in size
T2 = Lesion 2-5 cm
T3 = Skin and/or chest wall involved by invasion

NODES

N = Lymph node involvement; a higher number means more nodes are involved.
N0 = No axillary nodes involved
N1 = Mobile nodes involved
N2 = Fixed nodes involved

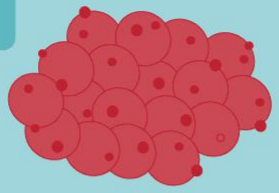
METASTASIS

M = Extent of distant metastases.
M0 = No metastases
M1 = Demonstrable metastases
M2 = Suspected metastases

Mobile lymph nodes are **those that can be easily moved**, while fixed lymph nodes are stuck to an internal structure. Mobile nodes are generally benign (non-cancerous), while fixed nodes are commonly seen with cancer.

TNM System for Staging Breast Cancer

T



Tumor size

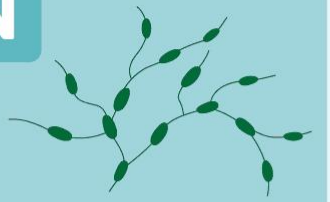
T-1: 0-2 centimeters

T-2: 2-5 centimeters

T-3: >5 centimeters

T-4: Tumor has broken through skin or attached to chest wall

N



Lymph Node Status

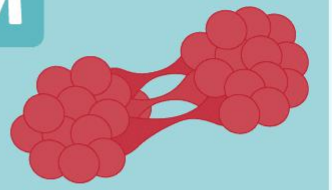
N-0: Surgeon can't feel any nodes

N-1: Surgeon can feel swollen nodes

N-2: Nodes feel swollen and lumpy

N-3: Swollen nodes located near collarbone

M



Metastasis

M-0: Tested nodes are cancer-free

M-1: Tested nodes show cancer cells or micrometastasis

Cancer Staging

- **Stage 0** refers to cancer in situ, or cancer that's limited to the place it started.
- **Stage 1** cancer hasn't spread far into nearby tissues or other parts of the body.
- **Stage 2** is used to designate larger tumors and those that have spread deeply into nearby tissues and lymph nodes.
- **Stage 3** is similar to stage 2, but with increased severity.
- **Stage 4** is an advanced stage of metastatic cancer in which the primary cancer has spread to distant organs and areas of the body.

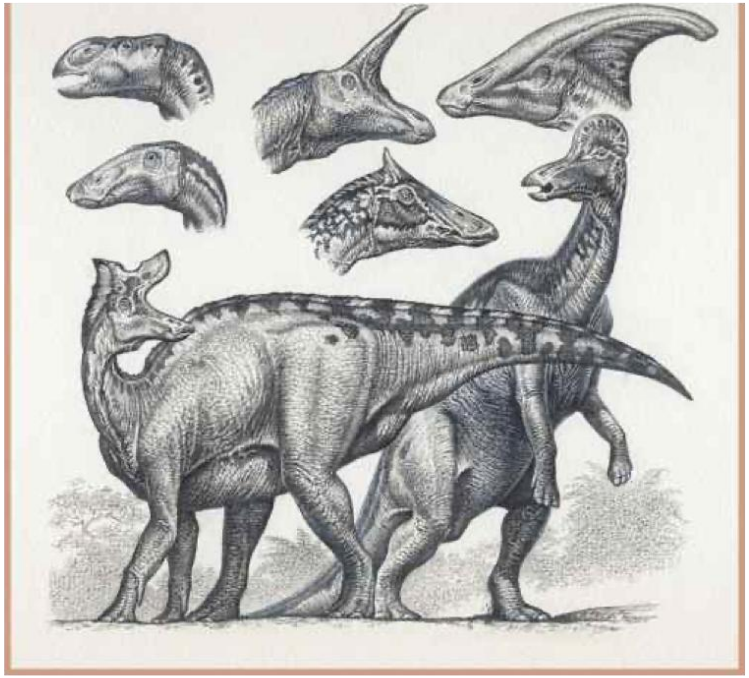
Stage of the tumor	TNM
STAGE 0	Tumor in situ
STAGE I	T1-2 N0 M0
STAGE II	T1-2 N1 M0 T3 N0 M0
STAGE III	T1-2 N2-3 M0 T3 N1-3 M0 T4 N0-3 M0
STAGE IV	T1-4 N0-3 M1 (or every cancer with distant metastasis)

Textbook & Readings:

- Alberts B. et al., **The Molecular Biology of the Cell** Garland Science Press, ISBN 0-8153-3218-1 is recommended.
- Robert A. Weinberg, **The Biology of Cancer** Garland Science Press, ISBN 0-8153-4078-8.
- Lauren Pecorino, **Molecular Biology of Cancer**, Oxford University Press. ISBN 978-0-19-921148-7.
- M. Molls, P. Vaupel, C. Nieder, M.S. Anscher. **The impact of tumor biology on cancer treatment and multidisciplinary strategies**, Springer. ISBN 978-3-540-74385-9.
- Yi Lu, R. I.Mahato, **Pharmaceutical perspectives of cancer therapeutics**, Springer. ISBN 978-1-4419-0130-9.

History of Cancer

- The oldest credible evidence of cancer in mammals consists of tumor masses found in fossilized dinosaurs and human bones from prehistoric times
- a recent large-scale study that screened by fluoroscopy over 10,000 specimens of dinosaur vertebrae for evidence of tumors and further assessed abnormalities by computerized tomography
- Out of several species of dinosaurs surveyed, only Cretaceous hadrosaurs (duck-billed dinosaurs), that lived 70 million years ago, harbored benign tumors (hemangiomas and osteoblastoma but 0.2% of specimens exhibited malignant metastatic disease



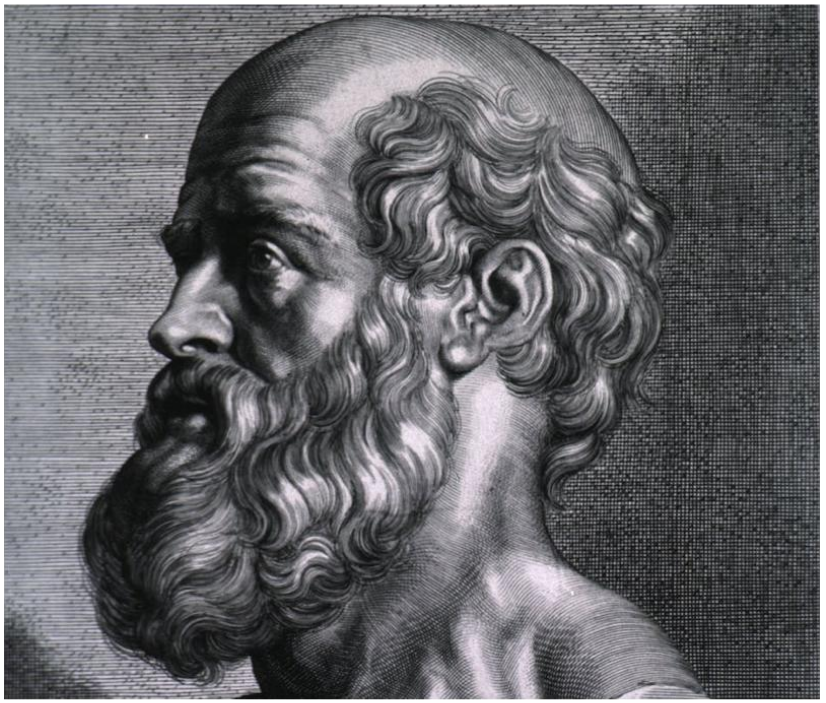
Guy B Faguet, Int J Cancer 2015

History of Cancer

- 2,000 year old mummy
- Bone cancer ‘osteosarcoma’
- Nasopharyngeal Cancer
- Oldest description of cancer – 3000 BC – ancient Egyptian textbook on trauma surgery – 8 cases of tumors
- “There is no treatment”

Origin of the word Cancer

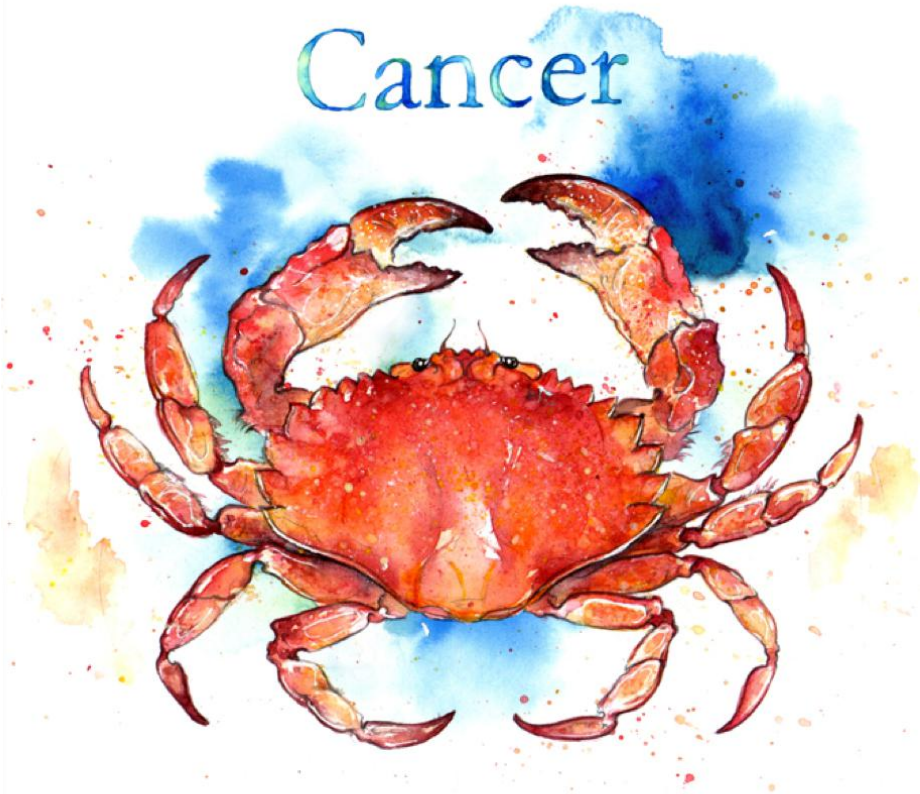
- Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors



Hippocrates – The father of medicine

Origin of the word Cancer

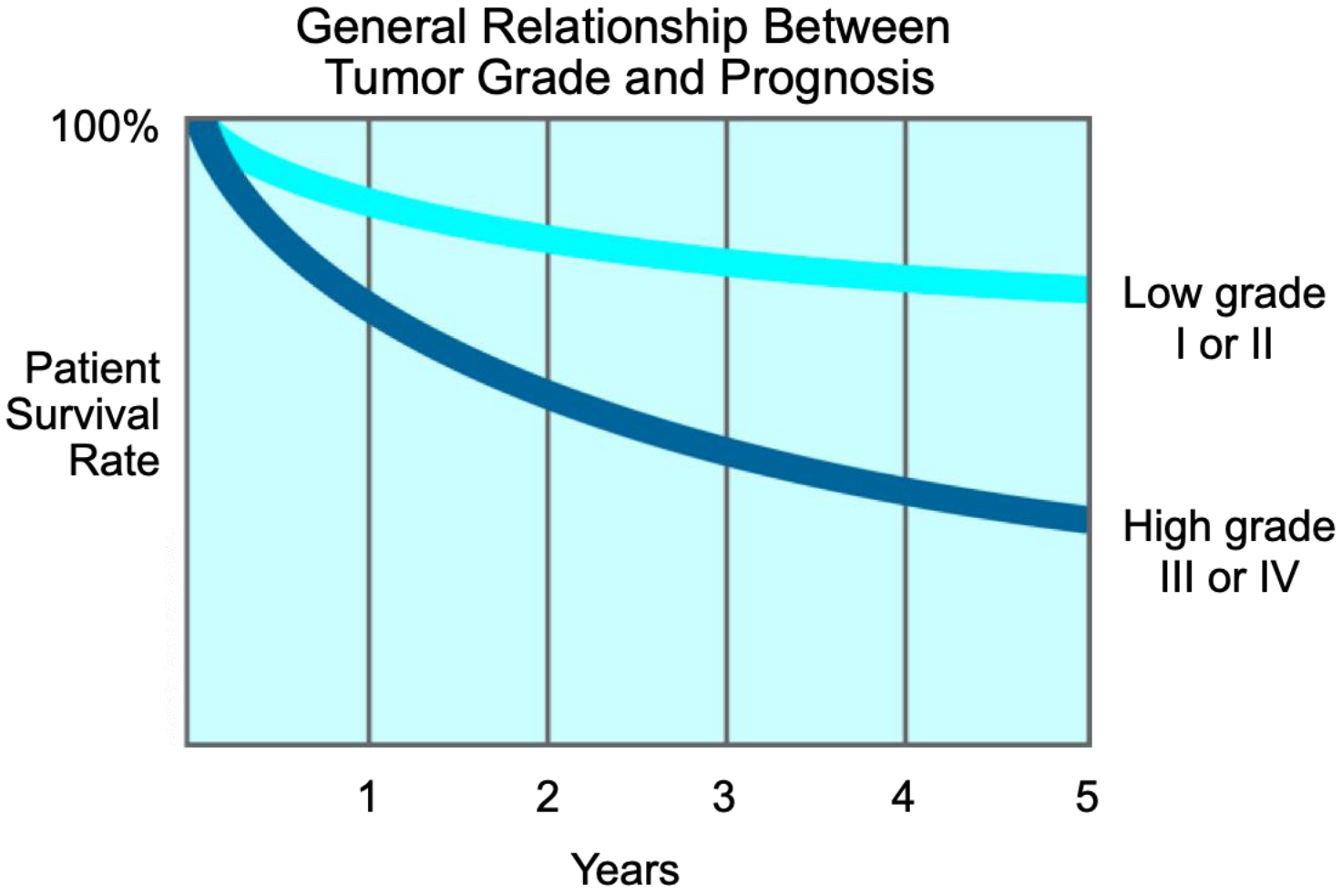
- In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab
- The Roman physician, Celsus (28-50 BC), later translated the Greek term into ***cancer***, the Latin word for crab
- Galen (130-200 AD), another Greek physician, used the word **oncos** (Greek for swelling) to describe tumors.



History of Cancer

- The 19th century saw the birth of scientific oncology with the use of the modern microscope in studying diseased tissues
- Rudolf Virchow, often called the founder of cellular pathology, provided the scientific basis for the modern pathologic study of cancer
- This method not only allowed a better understanding of the damage cancer had done but also aided the development of cancer surgery.

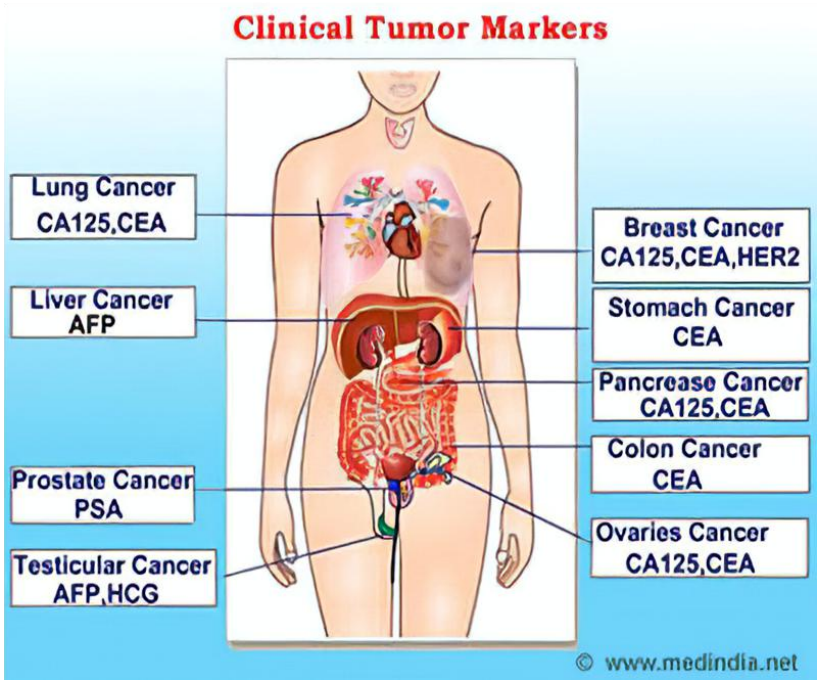
What is the relationship between tumor grade and patient survival?



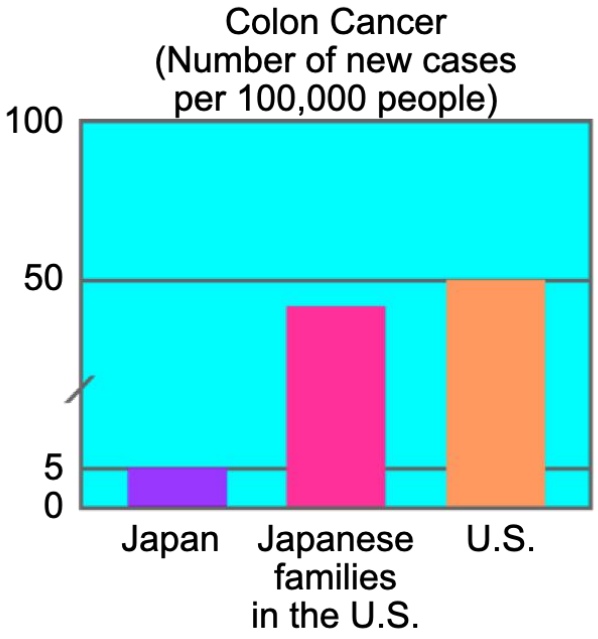
Tumor Markers

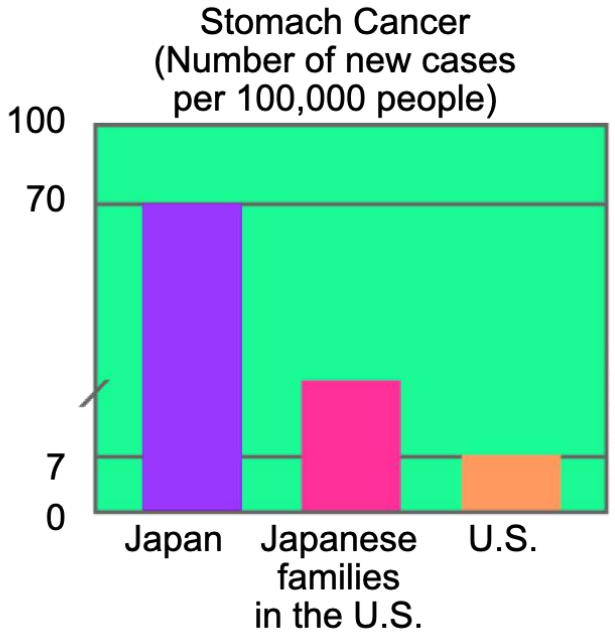
- Tumor cell markers (biologic markers) are substances produced by cancer cells or that are found in plasma, cell membranes, in the blood, CSF, or urine
  - Hormones
  - Enzymes
  - Genes
  - Antigens
  - Antibodies

CEA – Carcinoembryonic Antigen
AFP – Alpha-fetoprotein
PSA – Prostate Specific Antigen
CA-125 (Mucin-16)
HCG – Human Chorionic Gonadotropin



Is the incidence of these cancers due to gene behavior or environmental risk?





Environmental Risk Factors

Increased

- Tobacco
- Radiation
  - Ionizing
  - UV
- Alcohol
- Diet
- Obesity
- Occupational Hazards

Decreased

* Exercise
* Proper Diet

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