

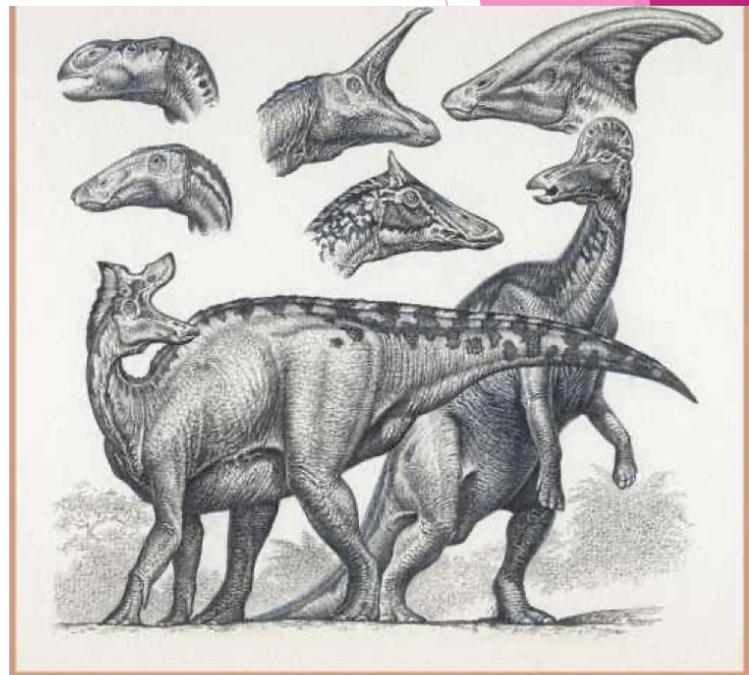
SBL100-Lecture

Introduction to Cancer

Part III

# 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

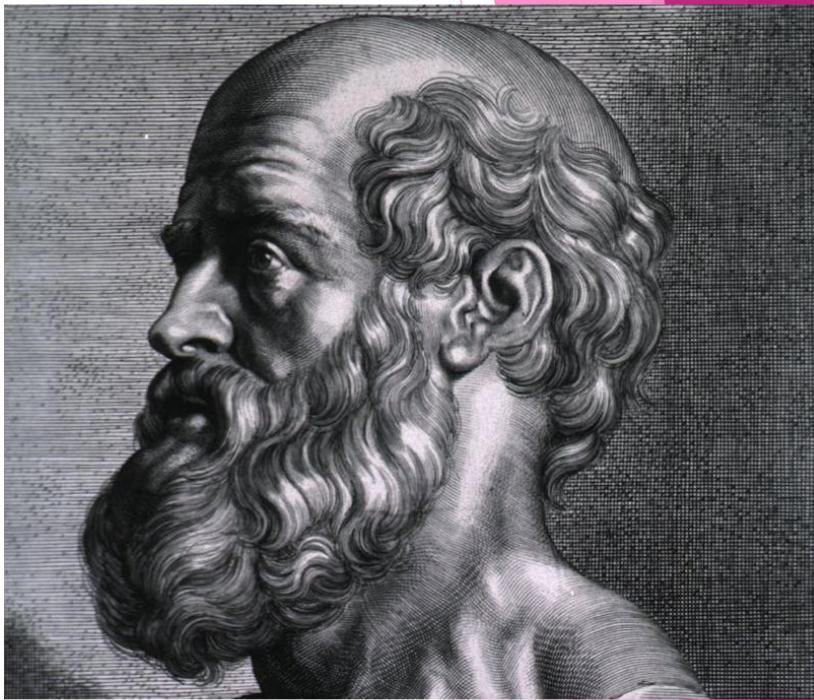
# History of Cancer

- 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

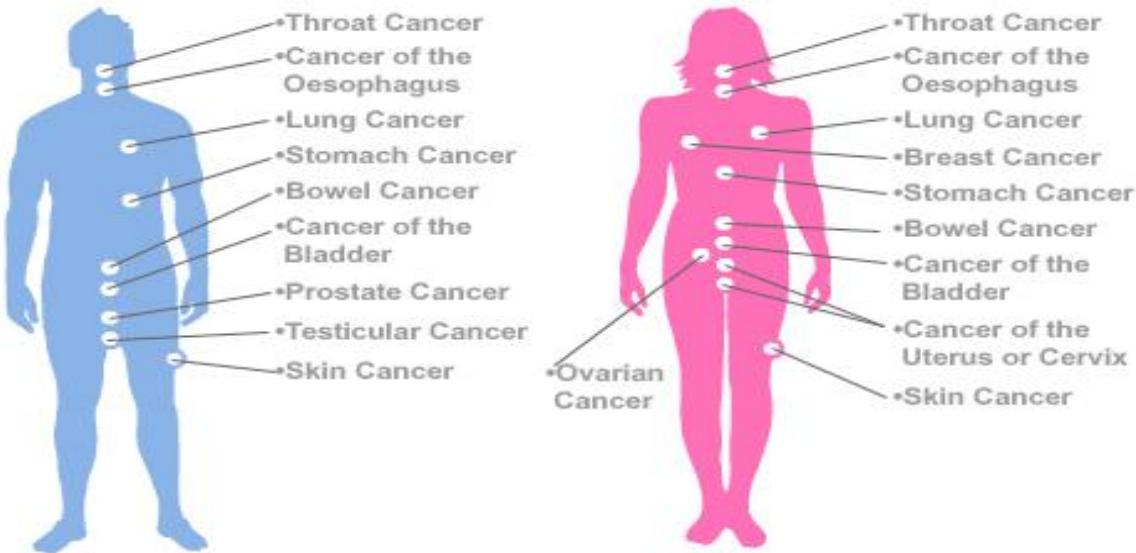
- The 19th century saw the birth of scientific oncology with the use of the modern microscope in studying diseased tissues
- **Rudolf Virchow**, often called the founder of cellular pathology, provided the scientific basis for the modern pathologic study of cancer
- This method not only allowed a better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



# 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?

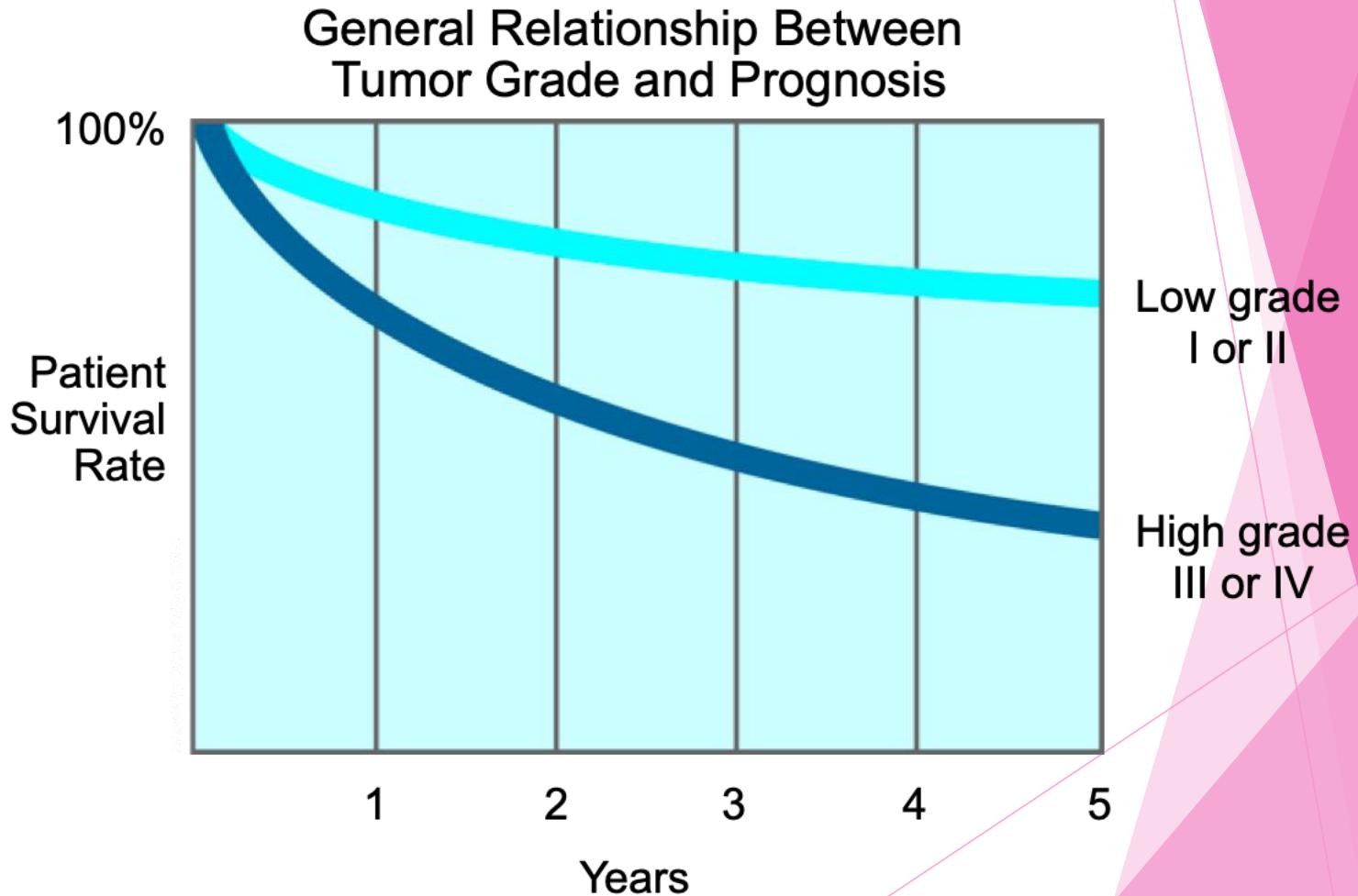


► Almost all the major parts of our body may be affected by **cancer**.

► Size of cancer cells:

- One million cancer cells = head of a pin
- One billion cancer cells = a small grape

# 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

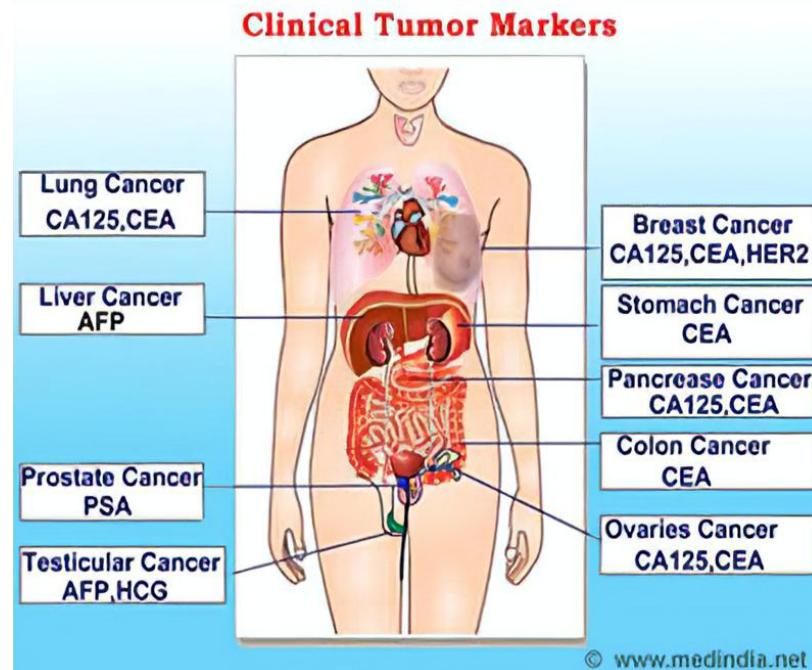
CEA – Carcinoembryonic Antigen

AFP – Alpha-fetoprotein

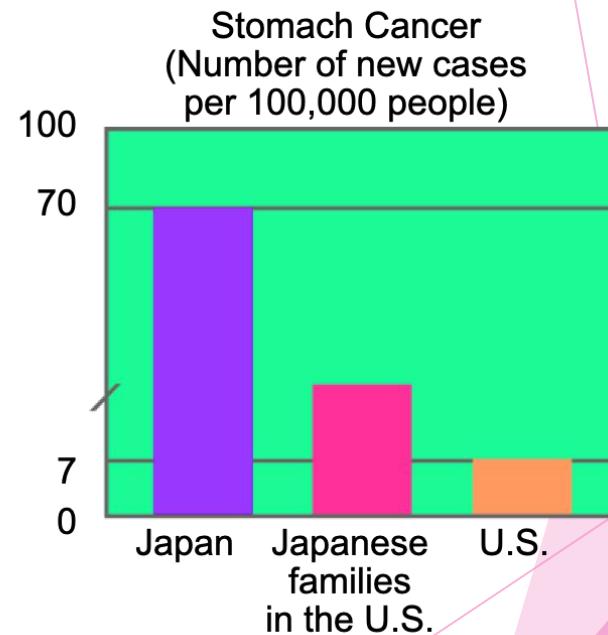
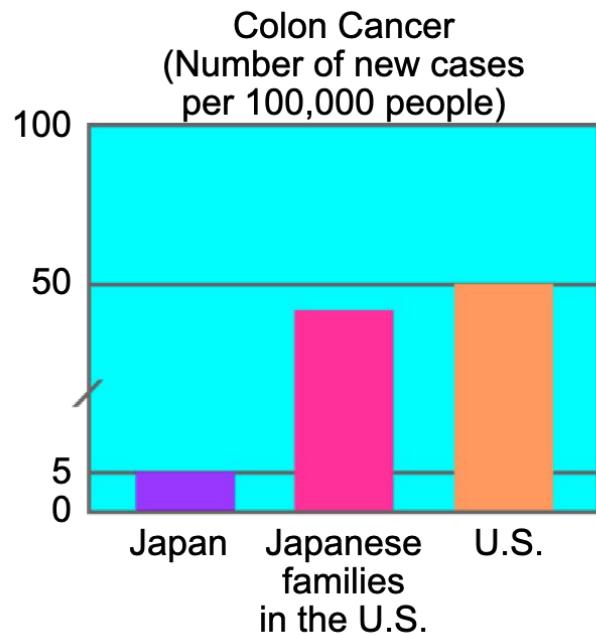
PSA – Prostate Specific Antigen

CA-125 (Mucin-16)

HCG – Human Chorionic Gonadotropin



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



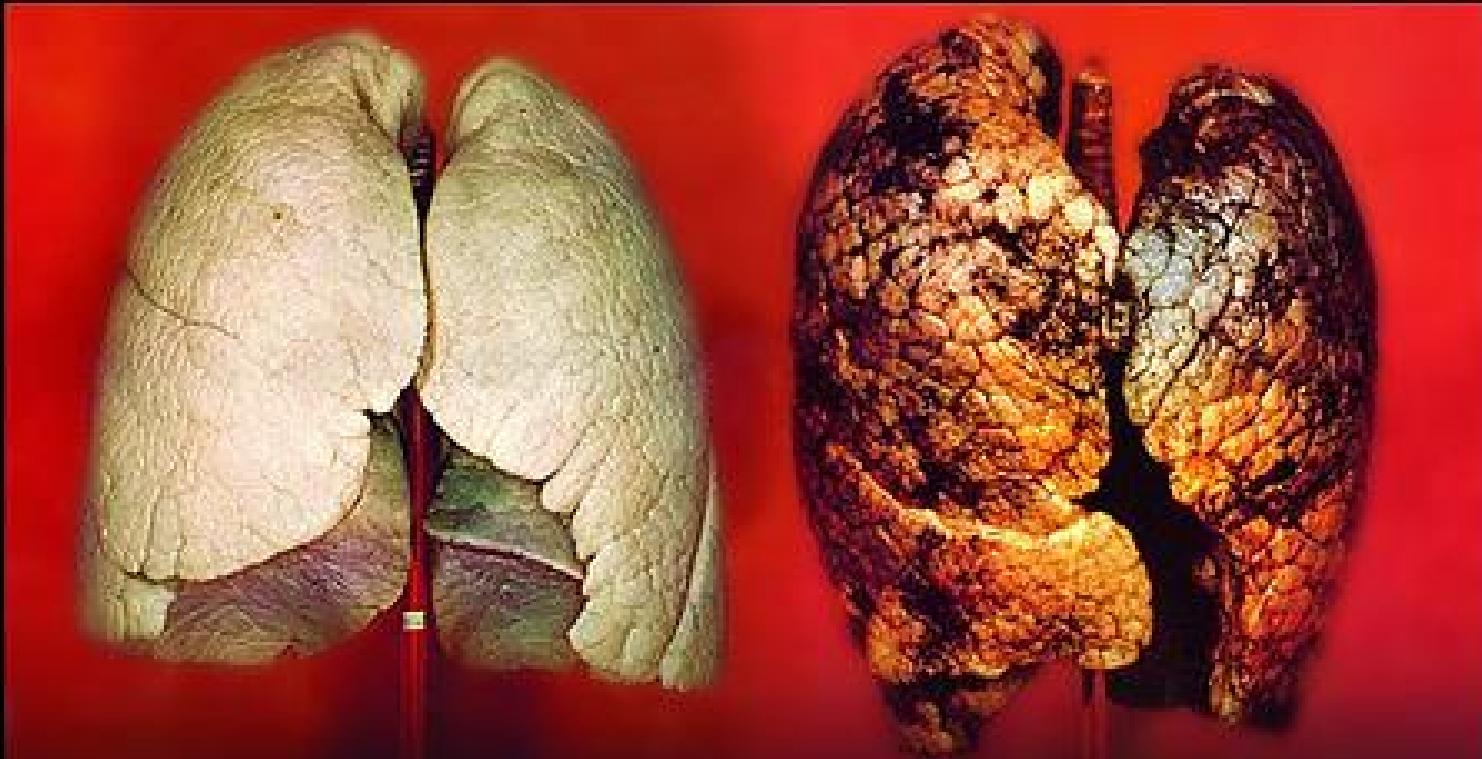
# Environmental Risk Factors

## **Increased**

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

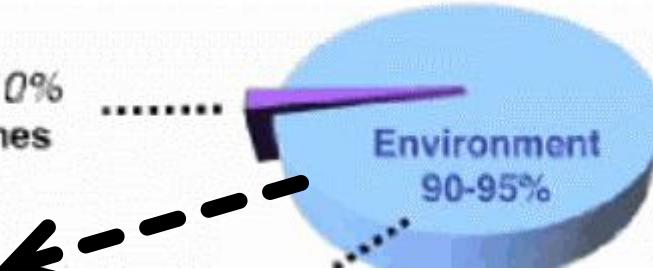
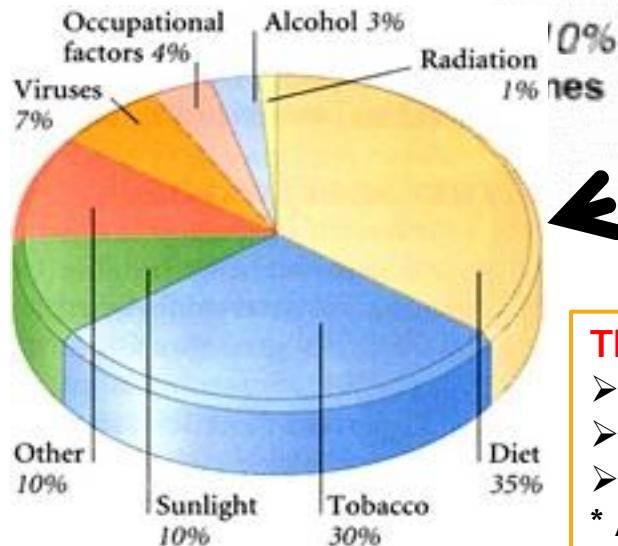
## **Decreased**

- \* Exercise
- \* Proper Diet



**Smoking  
causes fatal lung cancer**

# CAUSES OF CANCER



## The Etiology of Cancer

- Viruses (papilloma, Epstein-Barr, hepatitis B, retrovirus)
- Radiation exposure
- Environmental/ industrial carcinogens
  - \* Asbestos
  - \* Aromatic amines
  - \* Bischloromethyl ethers
  - \* Beta-naphthalene and benzedrine
  - \* Polycyclic hydrocarbons
  - \* Drug-induced cancers (alkylators such as melphalan and cyclophosphamide)
  - \* Nickel
  - \* Vinyl chloride
  - \* Isopropyl alcohol
- Diet and nutrition
- Tobacco and alcohol consumption
- Immunodeficiency syndromes: HIV is associated with Kaposi's sarcoma,
- Genetic susceptibility

Cancer is caused by external factors, such as tobacco, infectious organisms, and an unhealthy diet, and internal factors, such as inherited genetic mutations, hormones, and immune conditions etc..

# Chemicals



- ▶ Alcohol
- ▶ Asbestos
- ▶ Wood dust
- ▶ Rubber, plastics, dyes
- ▶ Tobacco

# Smoking

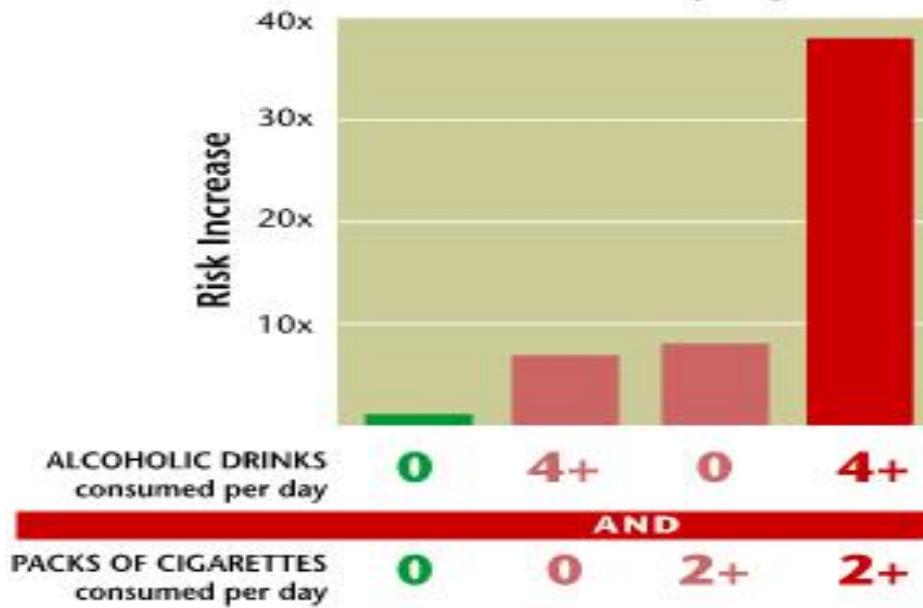
- ▶ Single biggest cause of cancer
- ▶ 25-40% smokers die in middle age
- ▶ 9 in 10 lung cancers
- ▶ Known to cause cancer in 1950



- Tobacco
  - Multipotent carcinogenic mixture
  - Linked to cancers of the lung, lower urinary tract, aerodigestive tract, liver, kidney, pancreas, cervix
  - Linked to myeloid leukemia

# Smoking and alcohol

## Combination of Alcohol and Cigarettes Increases Risk for Cancer of the Esophagus



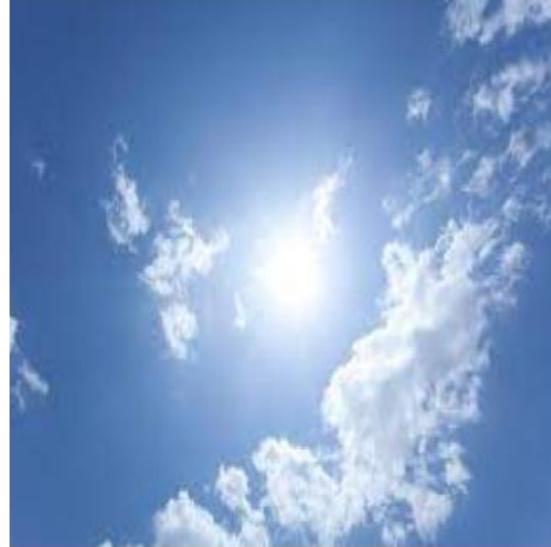
# Life style



Highly caloric diet  
Rich in fat  
Low physical activity  
Smoking /drinking  
Tobacco

# Environmental risk factors

- Ultraviolet radiation
- Causes basal cell carcinoma, squamous cell carcinoma, and melanoma
- Principal source is sunlight
- Ultraviolet A (UVA) (Longer wavelength – skin aging) and ultraviolet B (UVB) – shorter wavelength and skin burning.
- Promotes skin inflammation and release of free radicals



# Carcinogens

Any agent that provoke the development of cancer is called carcinogenic.

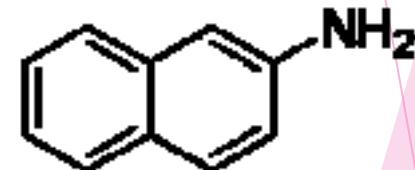
Carcinogenesis is linked to mutagenesis (i.e. cause mutations)

Carcinogens are classified into 2 classes

- 1) Chemical carcinogen: Typically cause simple local changes in nucleotide sequence and
- 2) Radiations such as **X- Rays**: Typically cause chromosomal breakage and Translocation & **UV Rays**: Cause specific DNA base alteration i.e. Point mutation

**Oncogene** : genes whose products play important roles in the regulation of biochemical activities within cells, including those activities related to cell division

2-Naphthylamine is used to make azo dyes ( $R-N=N-R'$ ).



It is found in cigarette smoke and suspected to be contributory to the development of bladder cancer. It is activated in the liver but quickly deactivated by conjugation to glucuronic acid.

In the bladder, glucuronidase re-activates it by deconjugation, which leads to the development of bladder cancer.

[On average, each cigarette smoked shortens lifespan by 11 minutes and smokers who die of tobacco-related disease lose, on average, 14 years of life.]

## Cancers Develop in Slow Stages from Mildly Aberrant Cells

Lung cancer does not begin to rise until after 10 or 20 years of heavy smoking.

Leukemias in Hiroshima and Nagasaki did not show rise until about 5 years after the explosion of atomic bombs;

Industrial workers exposed for a limited period to chemical carcinogens do not usually develop the cancers characteristic until 10, 20, or even more years (Fig 6).

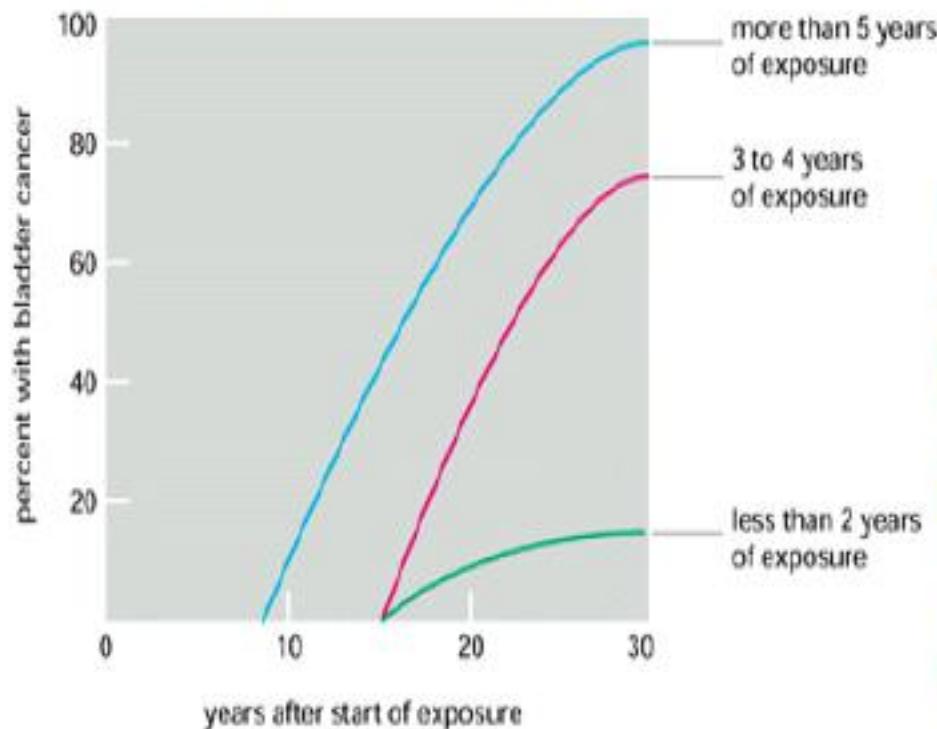


Figure 6. Delayed onset of cancer following exposure to a carcinogen. The graph shows the length of the delay before onset of bladder cancer in a set of 78 men who had been exposed to the carcinogen 2-naph-thylamine, grouped according to the duration of their exposure. (Modified from J. Cairns, Cancer: Science and Society. San Francisco: W.H. Freeman, 1978. After M.H.C. Williams, in Cancer, Vol. III (R.W. Raven, ed.). London: Butterfield, 1958.)

# Clinical symptoms or signs of cancer

## 12 WARNING SIGNS

The symptoms do not necessarily mean cancer, but don't ignore if they persist beyond three weeks



- Persistent headache
- Shortness of breath
- A cough or hoarseness that refuses to go
- Indigestion or difficulty in swallowing
- Loss of appetite
- A sore or bruise that does not heal
- A change in bowel or bladder habits for no reason
- Unexplained changes to fingernails
- Blood in urine, stool or sputum
- A mole that changes shape, size or bleeds
- Unexplained weight loss or tiredness
- New lumps or growths on skin

# Cancer diagnosis and treatment

- The earlier cancer diagnosis, the better the chance of its being cured.
- Some cancer – such as skin, breast, mouth, testicles, prostate, and rectum -- may be detected by routine self-exam or other screening measures.
- Cancer diagnosis begins with a thorough physical exam and a complete medical history.
- Followed by Laboratory studies of blood, urine, and stool can detect abnormalities that may indicate cancer.
- When a tumor is suspected, imaging tests such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and fiber-optic endoscopy examinations help doctors determine the cancer's location and size.
- To confirm the diagnosis of most cancers , a biopsy needs to be performed in which a tissue sample is removed from the suspected tumor and studied under a microscope to check for cancer cells.

# Physical Diagnosis - Melanoma

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A = Asymmetry, one half the mole does not look like the other half.



B = Border, irregular scalloped or poorly circumscribed border.



C = Color, varied from one area to another; shades of tan, brown, black, or sometimes white, red, or blue.



D = Diameter, larger than 6 mm (the diameter of a pencil eraser).

# The Gold Standard of Diagnosis - Biopsy

- ✧ A biopsy is the surgical removal of a small piece of tissue for microscopic examination, which will tell whether a tumor is actually present and if so, whether it is malignant or benign.
- ✧ There are three ways tissue can be removed for biopsy:
  - Endoscopy
  - Needle biopsy
  - Or surgical biopsy

## Endoscopy

By using a thin lighted tube, doctor is able to look at areas inside the body, see what's going on, take pictures, and remove tissue or cells for examination, if necessary.(colonoscopy/bronchoscopy)

## Needle Biopsy

The doctor takes a small tissue sample by inserting a needle into the abnormal area

**Surgical Biopsy:** excisional biopsy when the doctor removes the entire tumor, often with some surrounding normal tissue. While An incisional biopsy when the doctor removes just a portion of the tumor. If cancer is found to be present, the entire tumor may be removed immediately or during operation. (local/regional/general anesthesia)

# **SBL100-Lecture**

## **Introduction to Cancer**

### **Part IV**

# The Gold Standard of Diagnosis - Biopsy

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**Next step is to determine the “aggressiveness” of the cancer or how fast the cancer is growing**

after the diagnosis of cancer the doctor want to learn the stage, or extent, of the disease. This process is referred to as “staging” and tells the doctor how far the cancer has spread in body. Treatment based on the results of staging.

**The four common stage of cancer are:**

**Stage 1: In situ : Early cancer that has not spread to neighboring tissue.**

**Stage 2: Local: Cancer is found only in the organ where it started to grow**

**Stage 3: Regional: Cancer has spread to the surrounding tissues or lymph nodes.**

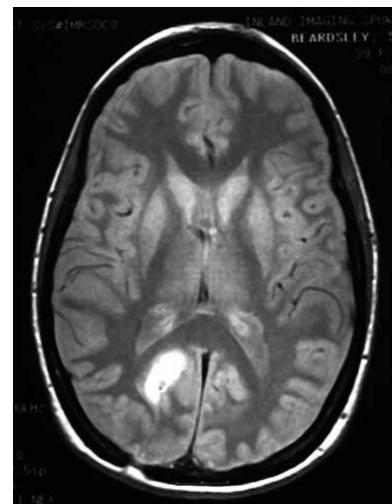
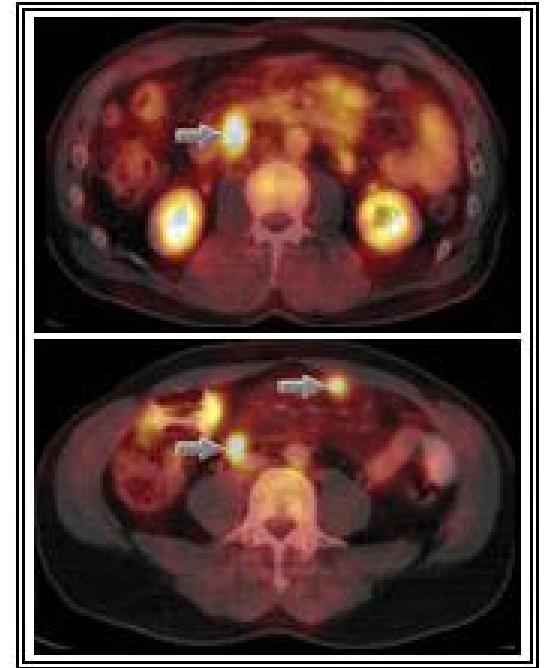
**Stage 4: Distant: Cancer has spread to other organs and systems of the body.**

**Staging determines the extent of the disease.**

**Staging is performed using a number of methods such as Imaging studies (ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT scan), x- rays, various blood tests, bone marrow biopsy, and surgery.**

# Imaging

- ▶ **CT** computed tomography scan
- ▶ **PET** positron emission tomography
- ▶ **SPECT** (single photon emission computed tomography)
- ▶ Patients are injected with a small amount of radioactive material and then have to lie in a machine that captures the gamma ray emissions from the material. The images that are created represent thin 'slices' through the body. Computer software is then used to combine the slices to make a virtual three dimensional model that can be viewed from any angle
- ▶ **MRI** magnetic resonance imaging



Modern diagnostic imaging technologies provide the ability to discriminate tissues down to a millimetre, using magnetic resonance imaging (MRI) and X-ray computed tomography (CT), while the range of positron emission tomography (PET) and single photon emission tomography (SPECT) are a few millimetres.

## 1. BIOPSY

A **biopsy** involves removing a piece of tissue to be examined in a laboratory.

The collection and analysis of cells, enables cancer cells to be identified and be differentiated from non-cancerous cells and a more definitive diagnosis to be made.



### There are many different types of biopsies:

Needle biopsy, CT-guided biopsy, ultrasound-guided biopsy, bone biopsy, bone marrow biopsy, liver biopsy, kidney biopsy, aspiration biopsy, prostate biopsy, skin biopsy and surgical biopsy.

## 2. BLOOD TEST

Blood tests can be extremely useful as they evaluate levels of essential molecules such as sugars, fats, proteins and DNA and enable doctors to associate abnormal levels with specific cancers.

Complete Blood Counts (CBC) are commonly used as all-encompassing measurements of the body's health; they measure size, number, and maturity of blood cells in a specific volume of blood.



## 3. COMPUTED TOMOGRAPHY (CT)

Computed Tomography (CT) scans are an important diagnostic tool to determine the presence of a cancer and its particular stage of development. CT scans involve picturing the inside of the body with an x-ray to create a 3-dimensional (3D) picture of the inside of the body.



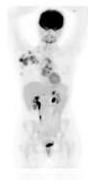
These three-dimensional pictures will be configured to form a cross-sectional view that can display any abnormalities and tumors. These can then be analyzed to determine the existence and/or stage of the cancer.



## 5. POSITRON EMISSION TOMOGRAPHY (PET)

Positron Emission Tomography (PET) involves injecting radioactive tracer into the vein of a patient. The tracer commonly used is a radioactive form of glucose. This is effective since cancer, maintaining the continuous division of cells, **increases the metabolism of glucose**.

PET imaging allows physicians to examine the way glucose is being metabolized in the body, and thus may be an indicator of cancer.



## 7. X-RAY

An X-ray involves electromagnetic radiation to image the inner processes of the body.

In an X-ray denser materials, which have a lower absorption rate, show up as a lighter color, while less dense materials such as fat and muscle show up as darker grays and blacks.

X-rays can be used to find, image, and analyze the progress of a tumor in low-doses of radiation.

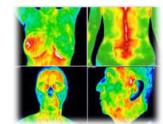


High doses of radiation actually have a therapeutic ability to destroy cancerous cells.

## 8. THERMOGRAPHY

A thermography involves digital infrared imaging capable of differentiating metabolic activity and circulation within the veins of cancerous and non-cancerous cells.

Cancer cells, with higher metabolic activity associated with heightened levels of cell production and growth, tend to display increased circulation by both utilizing existing blood vessels to a greater capacity and forming new ones.



## 6. ULTRASOUND

Ultrasound testing involves using sound waves to form images of inner organs and body parts. It is extremely successful at visualizing blood flow and finding abnormalities in blood vessels.

There are multiple types of ultrasound procedures, depending on the type of cancer, consisting mainly of Guided Biopsy/Fine Needle Aspirate (FNA) and Contrast Enhanced Ultrasound.

The **Guided Biopsy/FNA** is a procedure, which combines biopsies with ultrasounds depending on abnormalities seen in the ultrasound.



## 4. MAGNETIC RESONANCE IMAGING (MRI)

Magnetic Resonance Imaging (MRI), involves using magnetic fields and radio waves, registering signals from water molecules and forming intricate images of specific areas of the body.

This form of imaging may **not** be recommended if a patient has a heart pacemaker, metal heart valve replacements, aneurysm clips in his/her brain, or has had metal fragments in his/her eyes.

Like the CT scan, it involves minimal preparation before the scan, which lasts no more than an hour, and allows an immediate return to daily activity.



Surgery may be done to further examine a tumor or abnormal area. If less invasive procedures to remove tissues, such as biopsies, do not produce enough information, an open surgical exploration might be performed.

Surgeons typically make an incision and look at the abnormal area to further determine the location and stage of the tumor. In addition, doctors may completely remove a tumor in question to analyze it and further determine its stage and growth (cancerous or noncancerous).



## 9. SURGERY



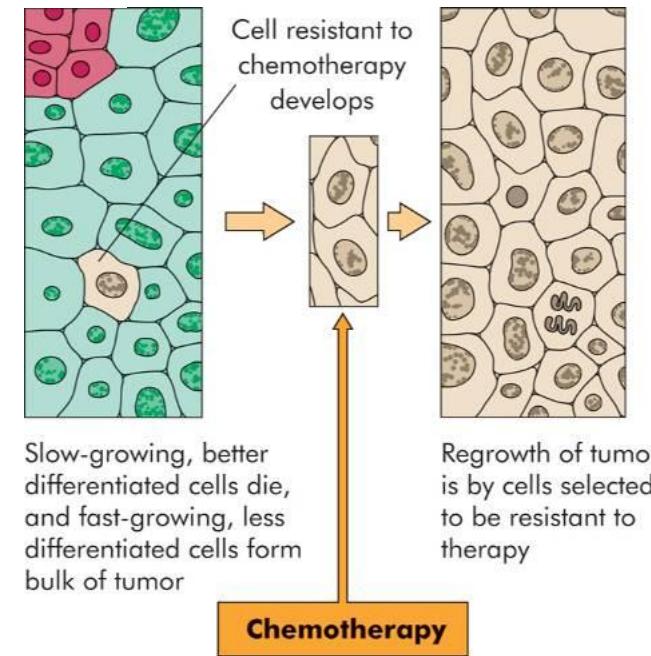
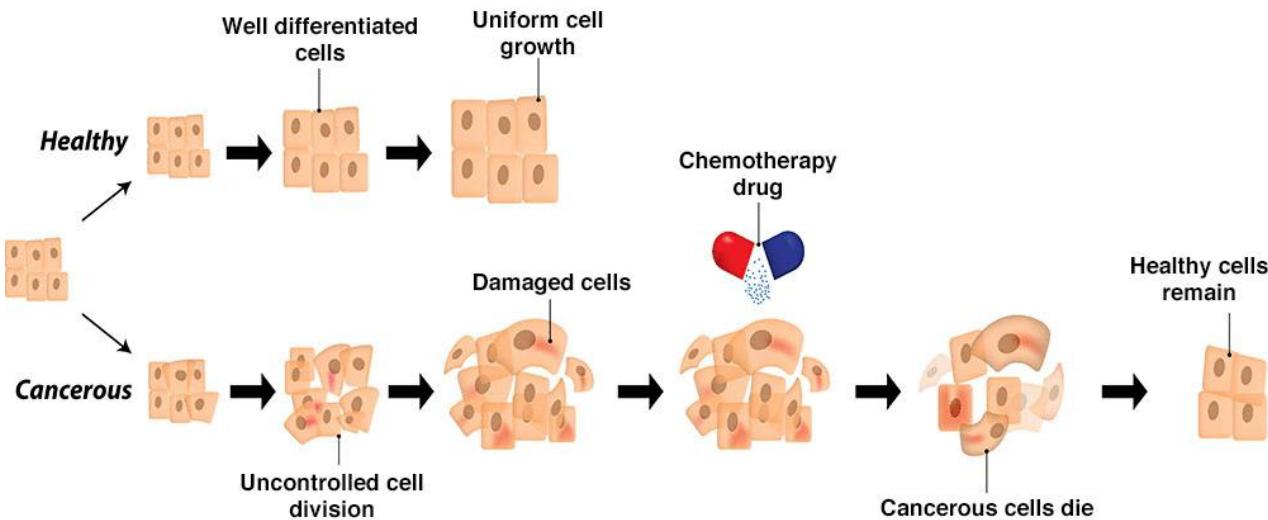
# Clinical Manifestations of Cancer

- Anemia
  - A decrease of hemoglobin in the blood
  - Mechanisms
    - Chronic bleeding resulting in iron deficiency, severe malnutrition, medical therapies, or malignancy in blood-forming organs
- Leukopenia and thrombocytopenia
  - Direct tumor invasion to the bone marrow causes leukopenia and thrombocytopenia
- Infection
  - Risk increases when the absolute neutrophil and lymphocyte counts fall

# Cancer Therapy

- **Surgery:** Depending on the [type of cancer](#), carcinoma may be treated with the surgical removal of cancerous tissue, as well as some surrounding tissue. Minimally invasive surgical treatment methods may help to reduce healing time and reduce the risk of infection after surgery.
- **Radiation therapy:** Radiation therapy may be used in combination with surgery and/or chemotherapy. Advanced radiation therapies use image guidance before and during treatment on target tumors, and are designed to help spare healthy tissues and surrounding organs.
- **Chemotherapy:** Chemotherapy treats carcinoma with drugs designed to destroy cancer cells, either throughout the whole body, or in a specific area. In some cases, chemotherapy may be used in combination with other treatments, such as radiation therapy or surgery.

# Chemotherapy



After chemotherapy, bulk of tumor dies; only resistant cells survive

From Stevens A, Lowe J. Pathology. Illustrated review in color, ed 2. Edinburgh, 2000. Mosby

# Cancer Therapy: Systemic treatment

## ➤ Chemotherapy

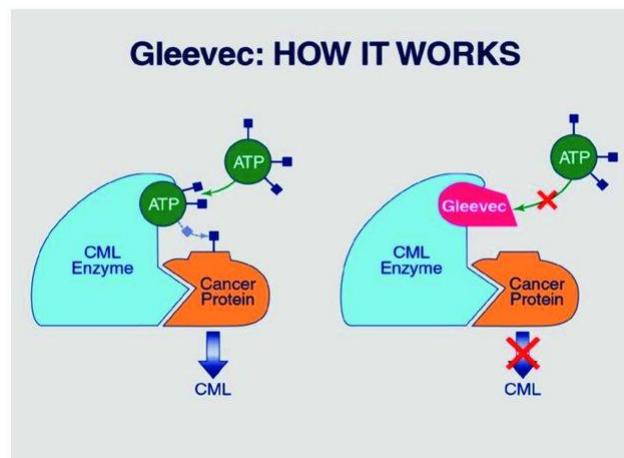
- Cytotoxic drugs + body defenses
- Single agent
- Combination chemotherapy
- E.g. Cisplatin, Paclitaxel, Etoposide

➤ Typical chemotherapy or radiation therapy has severe drawbacks.

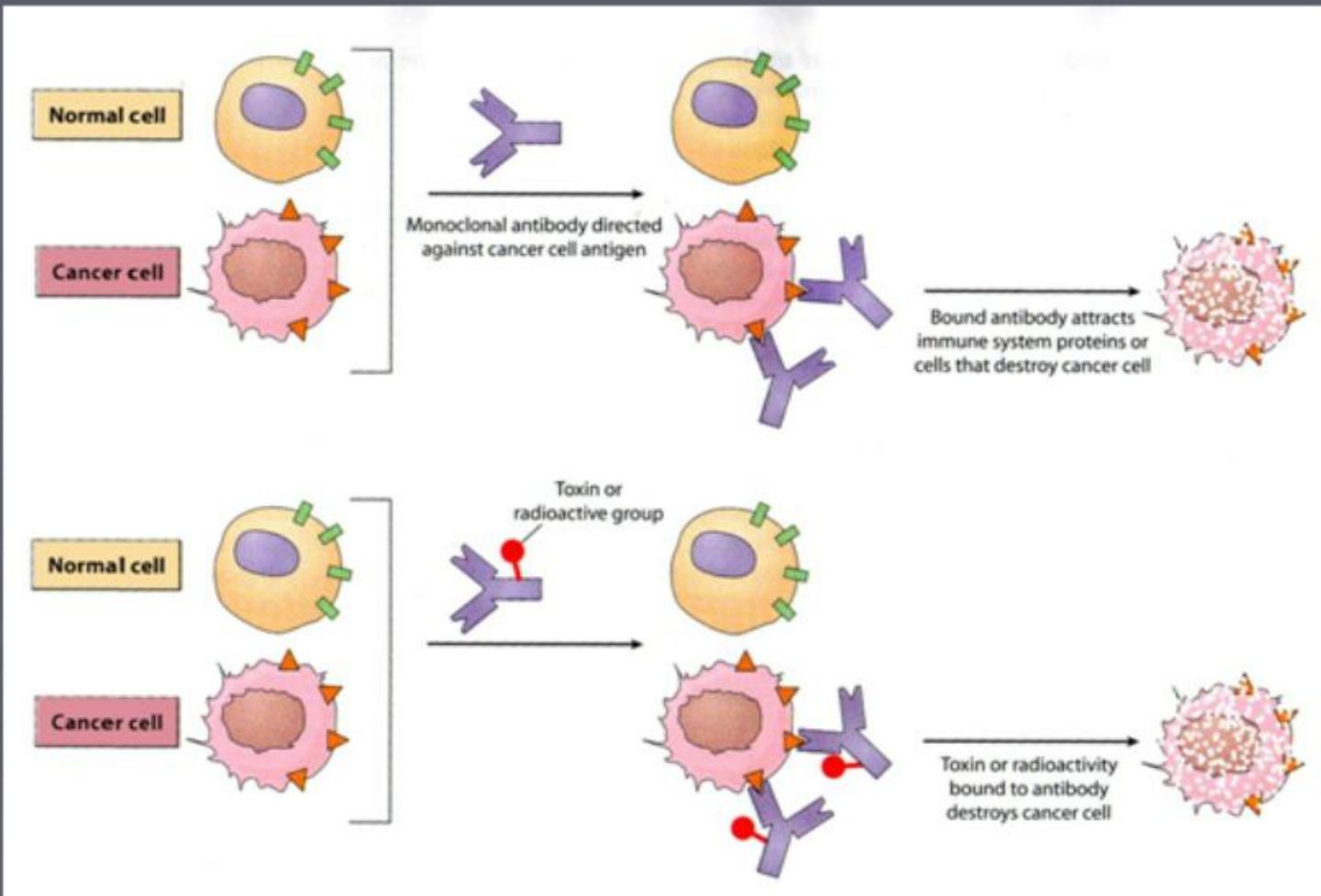
- **Gleevec:** Inhibits the receptor protein kinase activity of *Abl*, one of the receptor oncogenes (cancer gene) in Chronic myelogenous Leukemia.
- Revolutionized treatment of this disease.

## ➤ Immunotherapy

**passive :** Antibodies against a protein that is unique or overexpressed on cancer cells, can kill the cells. Example: Herceptin.



## Emerging Treatments : Immunotherapy and Molecular Targeting



**Figure 11-14 Two Ways of Using Monoclonal Antibodies for Cancer Treatment.** Monoclonal antibodies can selectively target cancer cells by binding to tumor-specific antigens located on the outer cell surface. (Top) After monoclonal antibodies become selectively bound to cancer cells, the antibody's presence triggers an attack by other cells or proteins of the immune system. (Bottom) Antibodies can also be used as delivery vehicles for radioactive groups or other toxic substances. Linking them to monoclonal antibodies allows such substances to be concentrated at tumor sites without accumulating to toxic levels elsewhere in the body.

# Cancer Therapy: New Approaches

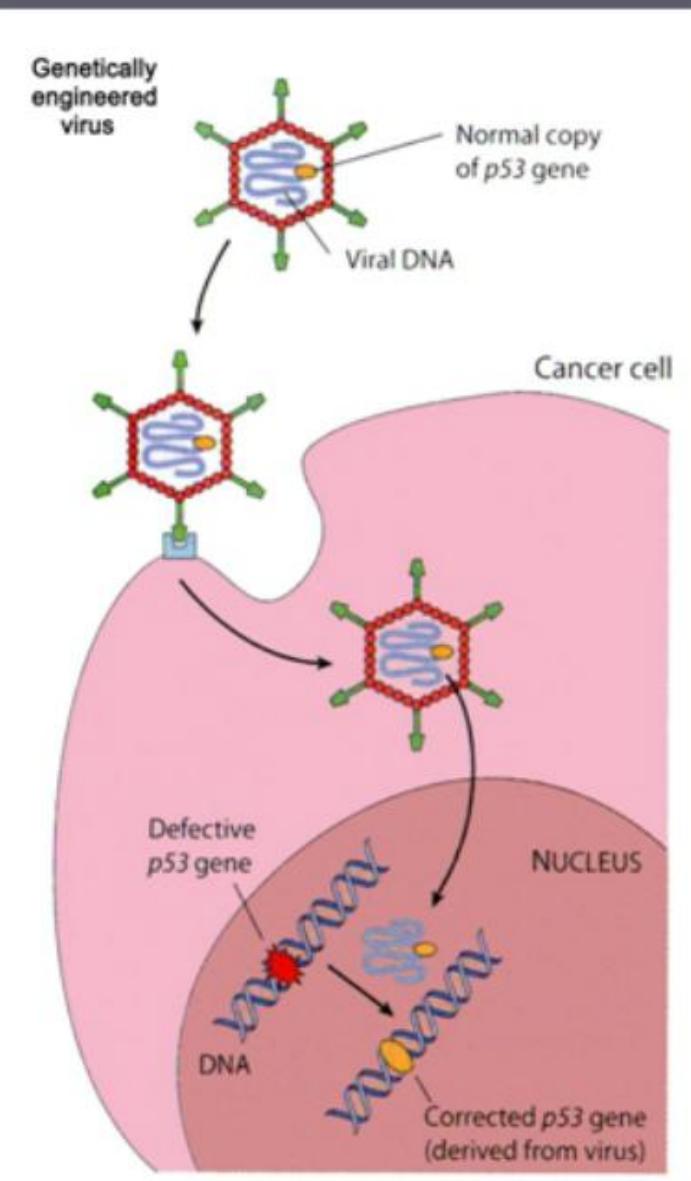
## Cancer Vaccines

- Majority used for treatment not prevention.
- May offer method that can enhance the immune response against cancer
- At this time, cancer vaccines are only available in clinical trials.
- Dendritic cell (DC) vaccines: DC are immune cells; recognize, process and present to T-cells. DC is less in number; DC is prepared from isolated monocytes from patients blood and introduced back to patient for massive response from T cells.
- Tumor cell vaccine: tumor isolated from patients; antibodies generated and introduced to patient.
- DNA vaccine: genetically engineered DNA inserted in patients cell and injected in the body so that the cell prepares the protein inside the patient.

## Gene therapy

- Replaces a faulty gene or adds a new gene in an attempt to cure disease or improve body's ability to fight disease (cancer)
- modified version of the herpes simplex 1 virus which kills melanoma cells

## Emerging Treatments : Immunotherapy and Molecular Targeting



**Figure 11-17 Strategy for Using Gene Therapy to Repair a Defective Cancer Cell Gene.** Many human cancers exhibit defects in the *p53* gene. If these defects could be corrected, restoration of the *p53* pathway might cause cancer cells to self-destruct by apoptosis. Viruses engineered to contain a normal copy of the *p53* gene have therefore been used in gene therapy experiments to infect tumors and insert the normal *p53* gene into the DNA of cancer cells.

**Table 11-3 Examples of Possible Targets for Anticancer Drugs**

Target Protein	Pathway or Function	Drugs Approved*
ErbB2 receptor	Growth factor receptor	Herceptin
EGF receptor	Growth factor receptor	Iressa, Erbitux, Tarceva
FGF receptor	Growth factor receptor	
PDGF receptor	Growth factor receptor	
VEGF	Angiogenesis signaling	Avastin
Bcr-Abl kinase	Apoptosis signaling	Gleevec
Src kinase	Ras-MAPK pathway	
Raf kinase	Ras-MAPK pathway	
Ras	Ras-MAPK pathway	
Cyclin-dependent kinases	Cell cycle progression	
PI 3-kinase	PI3K-Akt pathway	
Hsp90	Stabilizes growth signaling proteins	
Mdm2	Apoptosis inhibitor	
Bcl2	Apoptosis inhibitor	
Matrix metalloproteinases	Invasion/metastasis/angiogenesis	
Proteasome	Targeted protein degradation	Velcade
Telomerase	Limitless replicative potential	

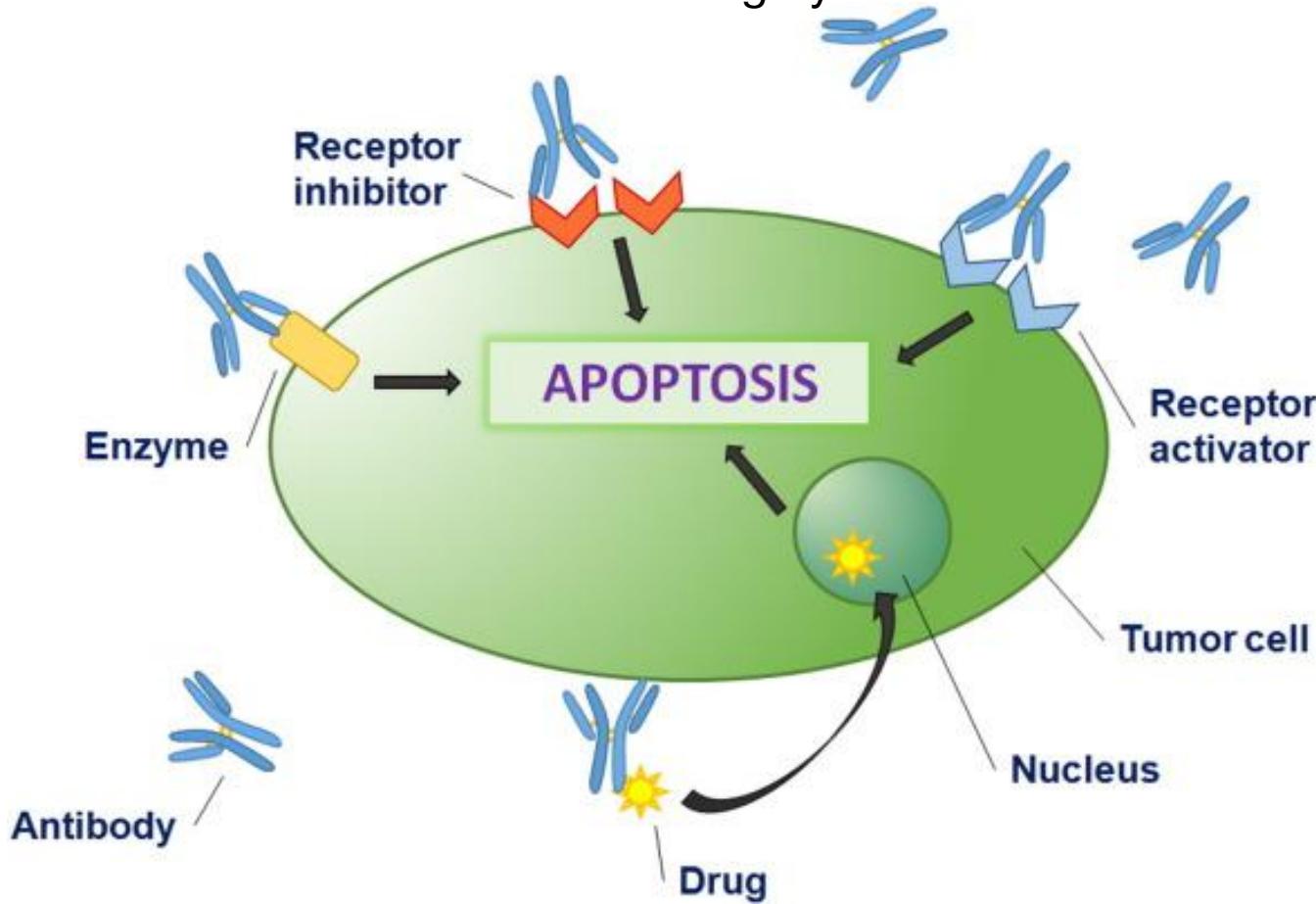
\*Drugs listed in this column have already been approved for treating cancer patients.

# Antibodies

- ▶ Target specific antigen
- ▶ Specificity is relative
- ▶ Various mechanisms of action
  - ▶ Complement activation
  - ▶ antibody-dependent cell-mediated cytotoxicity ADCC
  - ▶ Calcium entry
- ▶ May synergize with chemotherapy
- ▶ Expected or unexpected toxicities



## Direct tumor cell killing by antibodies



This event may be triggered by antibodies binding to a tumor cell surface receptor, leading to its activation and, consequently, apoptosis. Finally, an antibody may bind to an enzyme, leading to signaling abrogation, neutralization and cell death. Conjugated antibody therapies are based around delivering a payload – for example, a drug, toxin, small interfering RNA or radioisotope – to a tumor cell.

# Small molecules

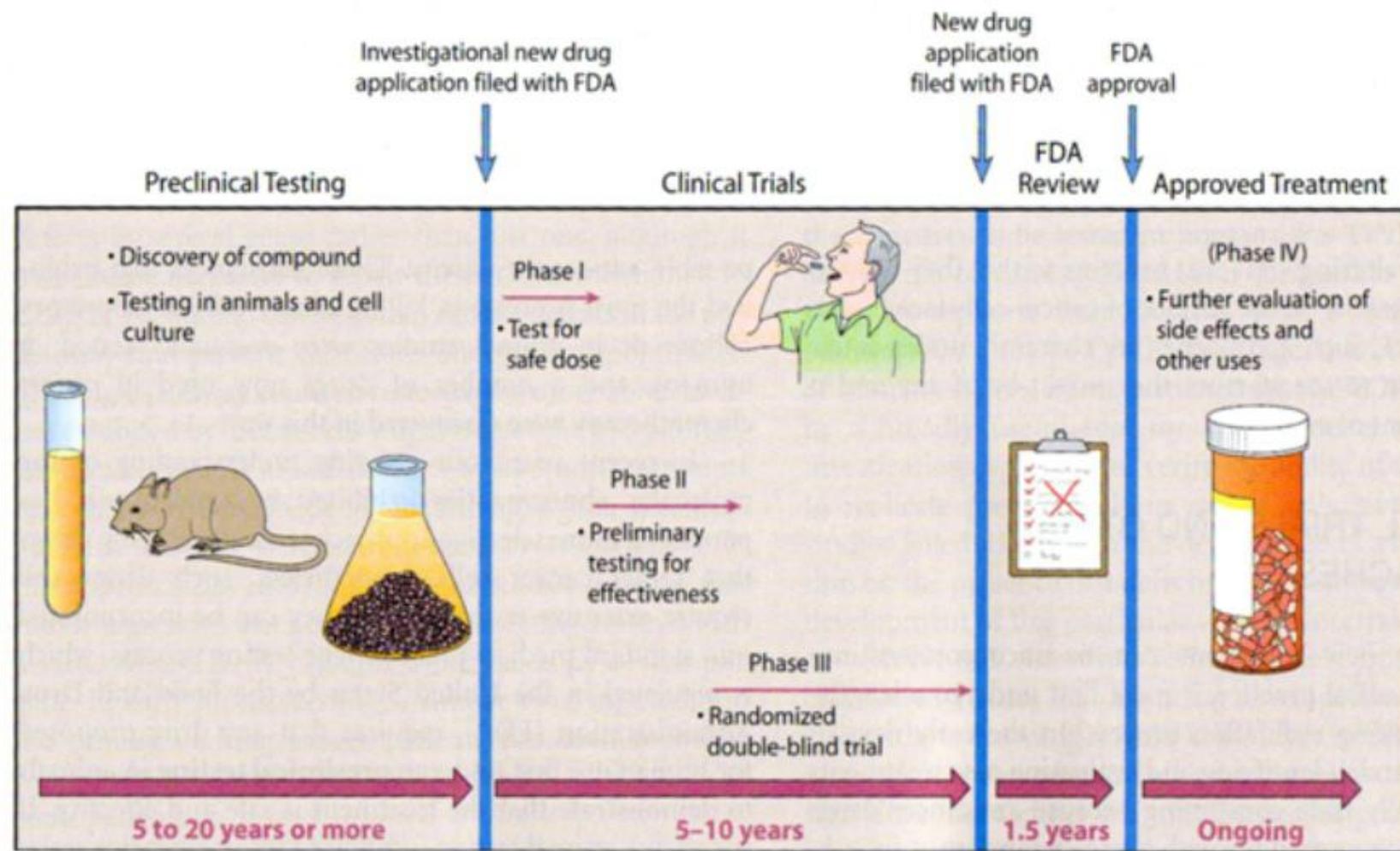
- ▶ Target oncogene product
- ▶ Inhibit signaling at key steps
- ▶ Safer than chemotherapy
- ▶ Specific side effects
- ▶ Specificity is often relative



# Side Effects of Cancer Treatment

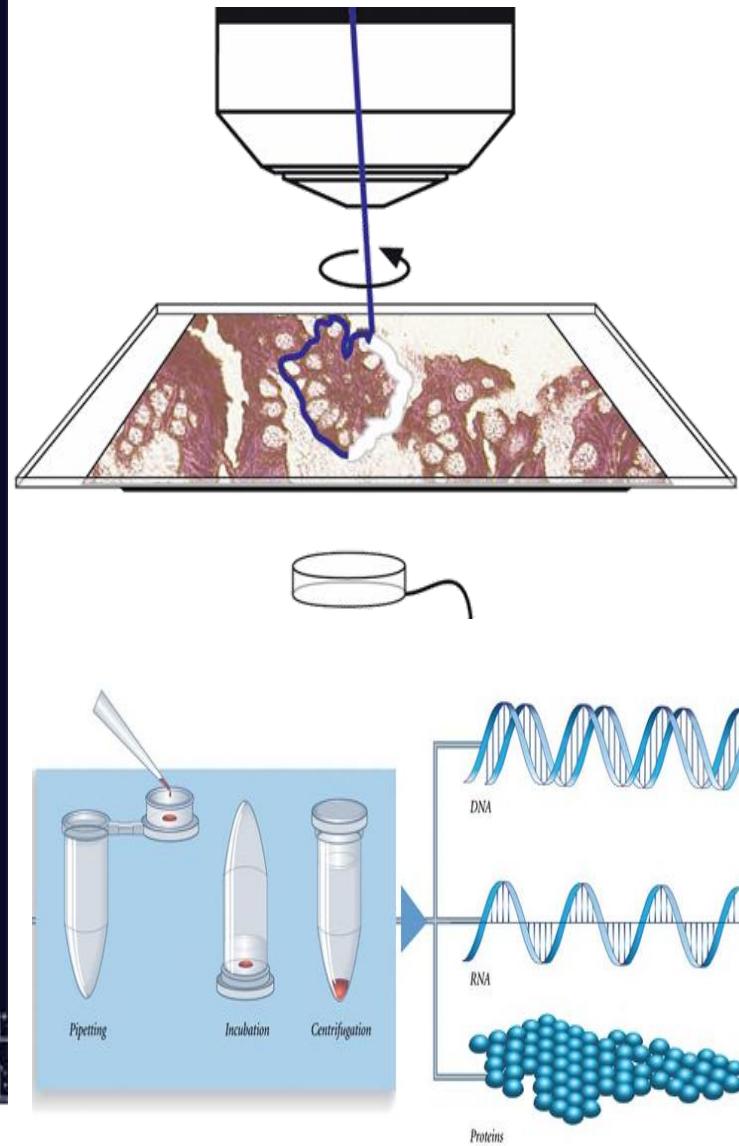
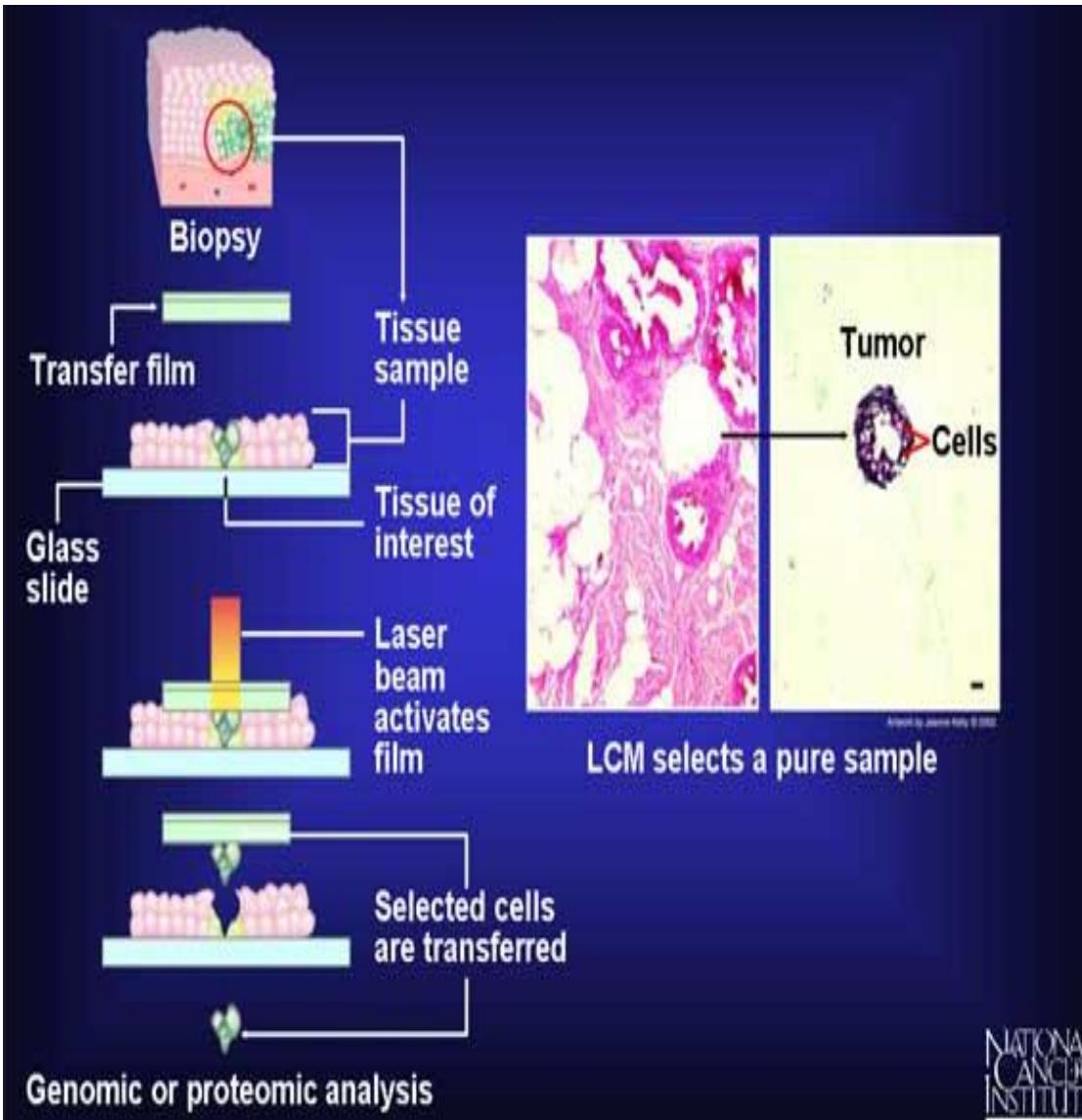
- Gastrointestinal tract
- Bone marrow
- Hair and skin
- Reproductive tract

## Clinical Trials and Other Approaches



**Figure 11-19 Typical Timeline for Developing a New Cancer Drug.** Developing a new cancer treatment takes many years and requires numerous steps, including preclinical laboratory and animal testing, clinical trials in cancer patients, and FDA approval. [Adapted from J. A. Zivin, *Sci. Amer.* 282 (April 2000): 70.]

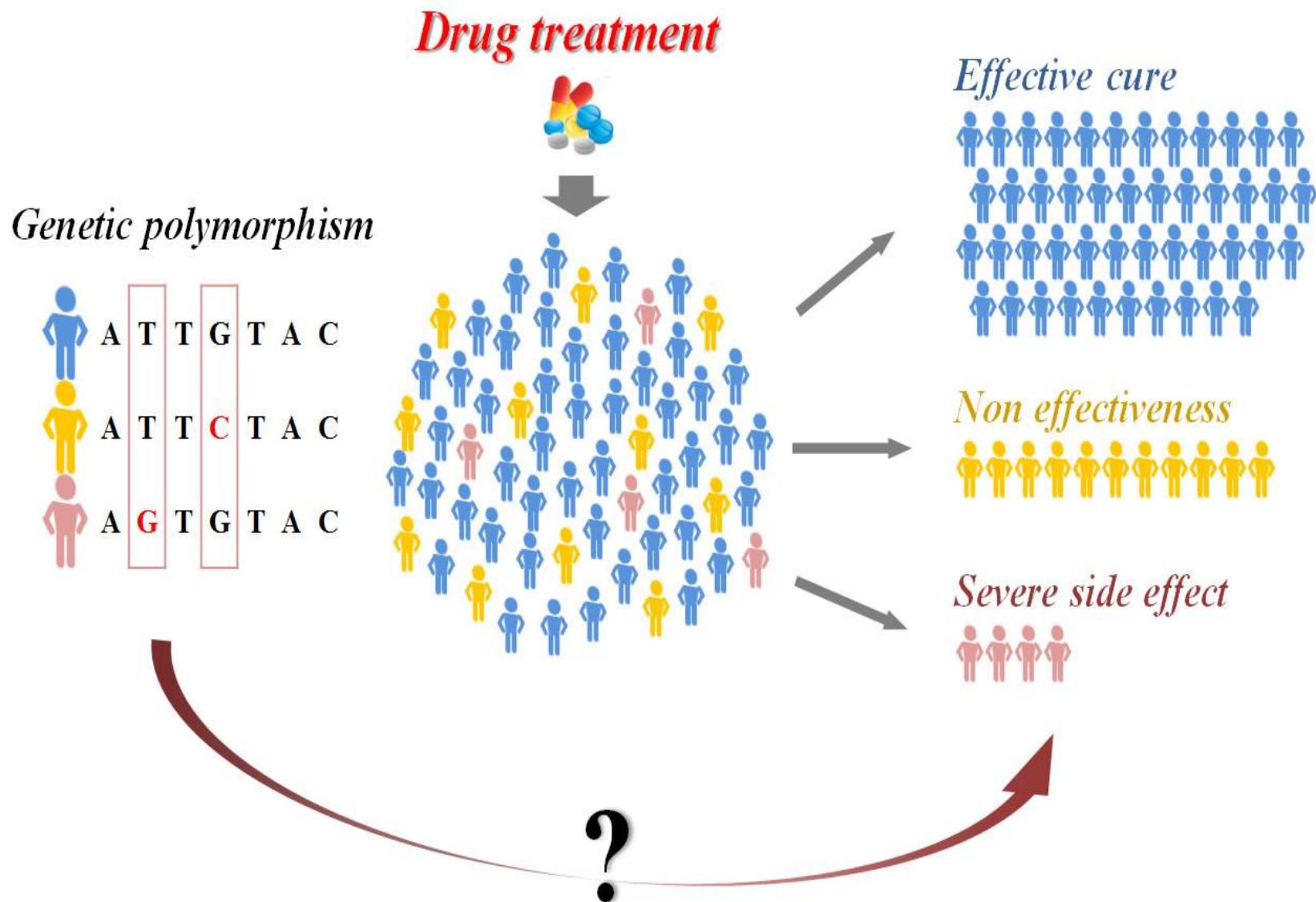
# Laser capture microdissection



# Pharmacogenomics: drug therapies tailored to individuals

- Design therapies based on the individual's genome
- Subtle, but important, differences in genomes
  - Linked to differences in how one responds to drugs
- Identify those who will suffer harmful side effects from particular drugs and who will respond best
- Customized therapy or personalized medicine

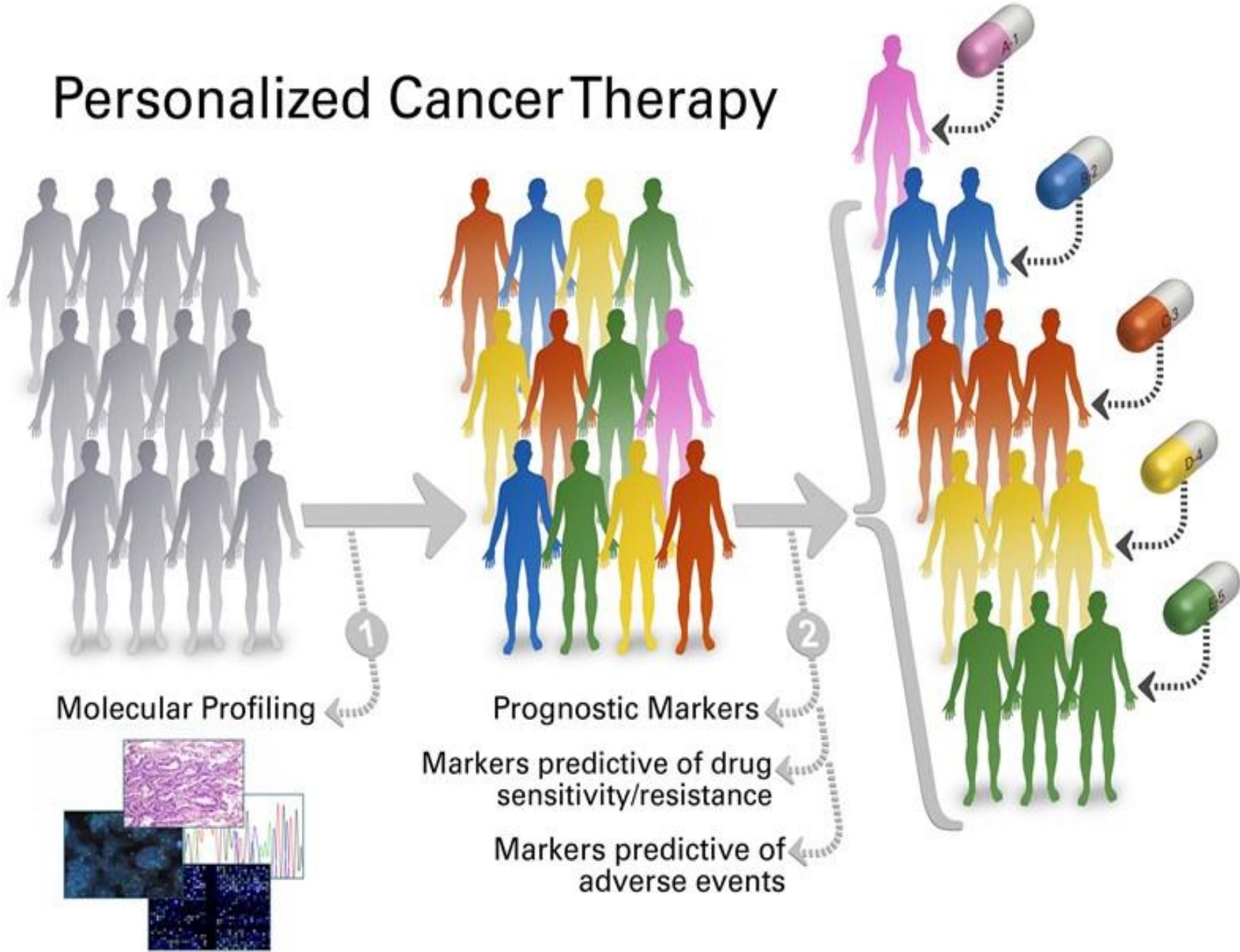
# Pharmacogenomics



# Pharmacogenomics

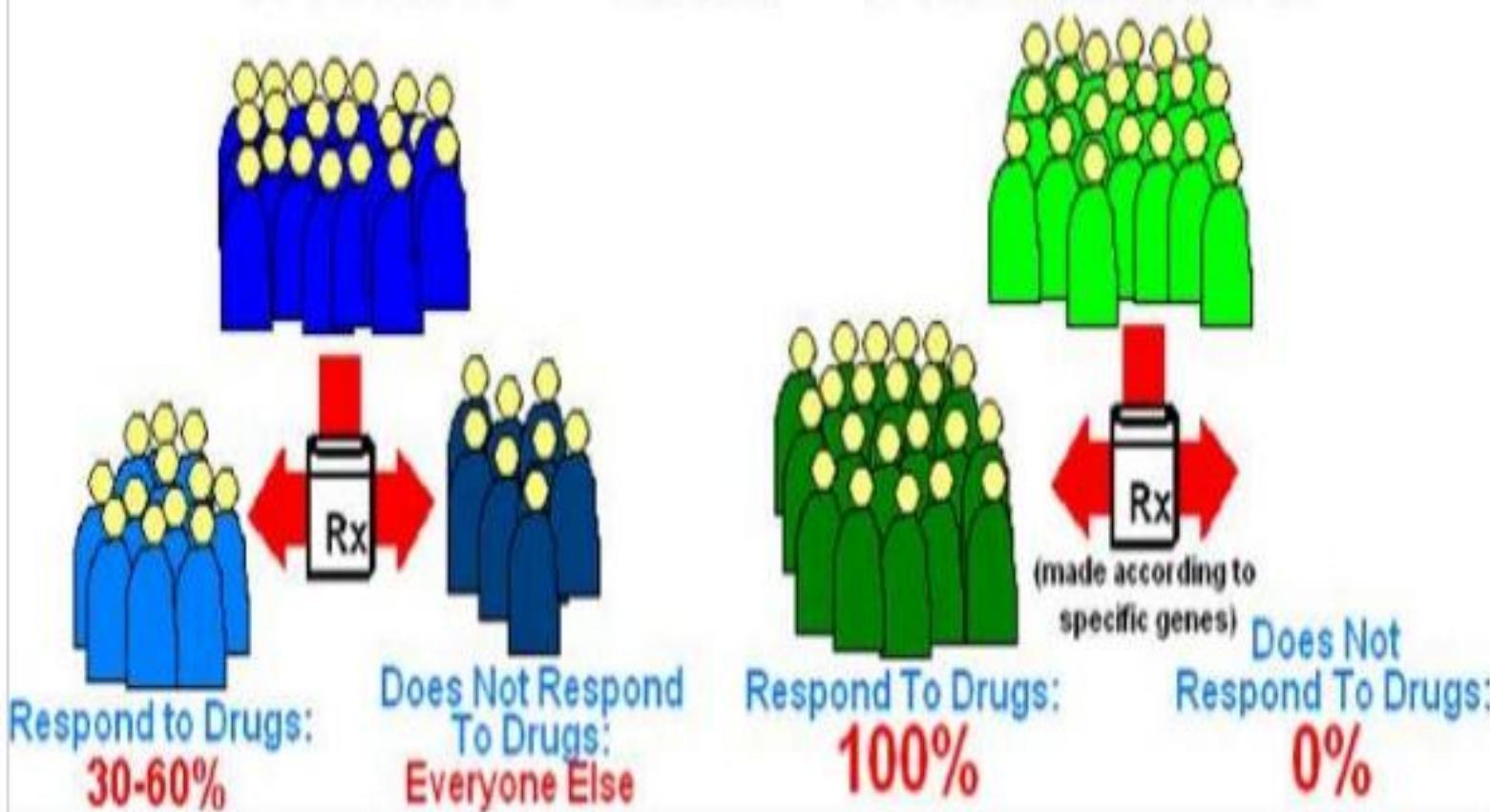


# Personalized Cancer Therapy



# Pharmacogenomics

TODAY versus TOMORROW



## Summary

- Cancer cells proliferate defying normal controls; invades and colonize surrounding tissues (malignant); gives rise to secondary tumors, or metastases; harder to eradicate surgically.
- mutations have important role in cancer.
- phenomenon of tumor progression, takes many years
- It is mainly disturbance of balance between cell division (mitosis) and cell death (apoptosis)
- Thus many factors contribute to the development of cancer, and since some factors are avoidable features of environment, a large proportion of cancers are in principle preventable.
- To cure the disease requires an understanding of the special properties of cancer cells that enable them to evolve, multiply, and spread.
- Drugs for differentiation/ program cell death are good approaches.
- To become malignant, tumor cells must cross basal laminae; antibodies can be designed that interfere with this ability. Drugs can be designed to maintain function of suppressor genes.

## **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.

**Today: We learnt basic introduction about Cancer and some therapy**

**Assignment: what are the measures can be taken to prevent cancer**

**Next class: Stem cells**