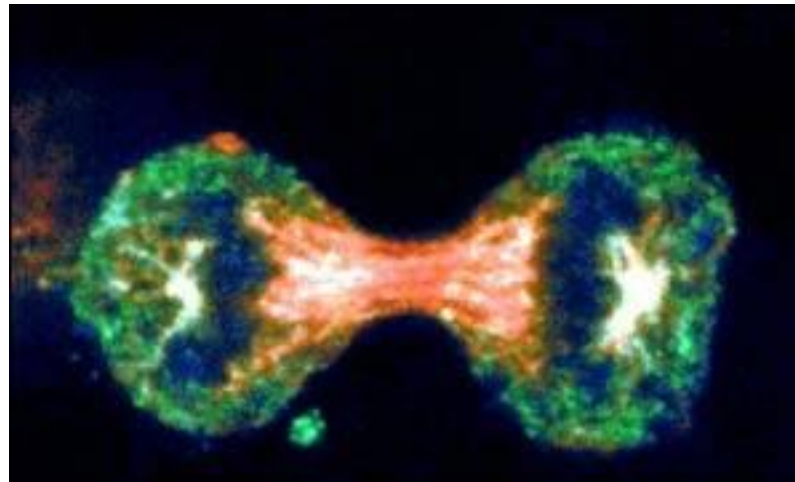
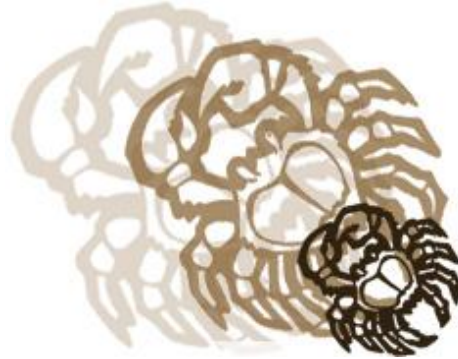


The Biology of Cancer

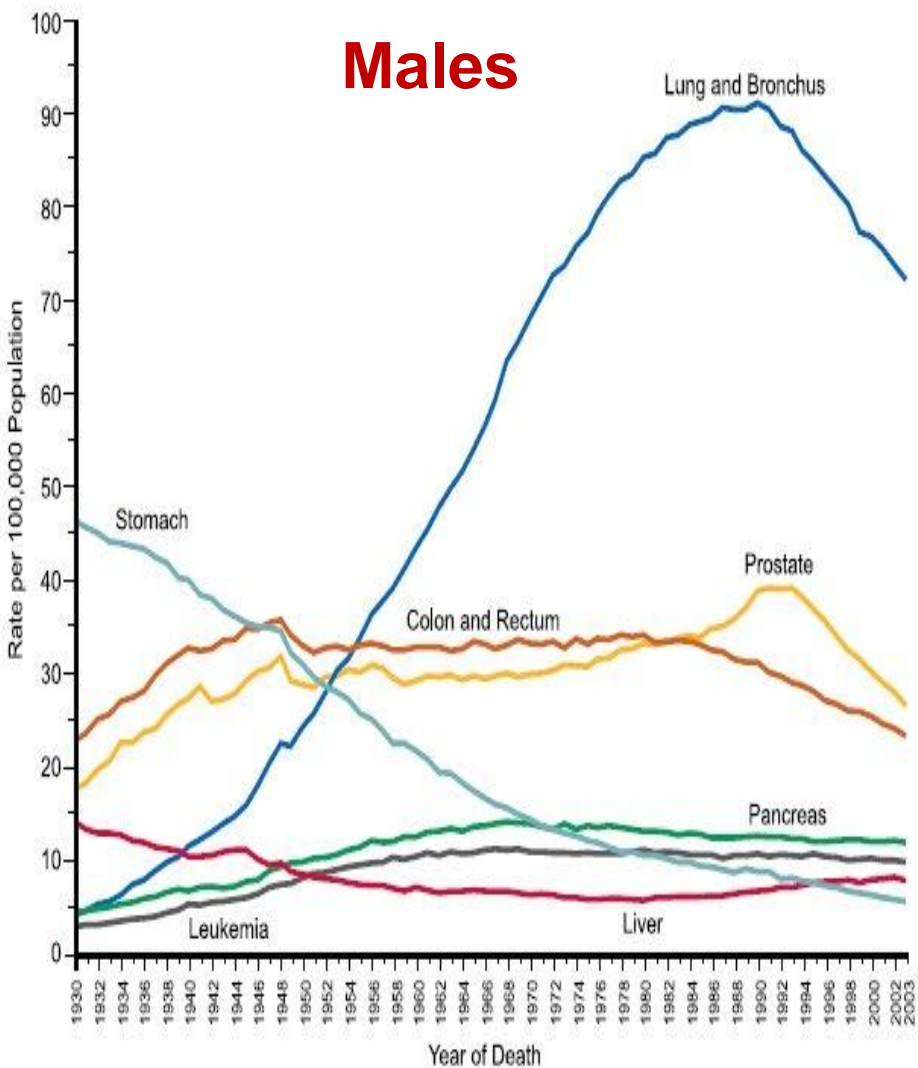


“Death in old age is inevitable, but death before old age is not.”

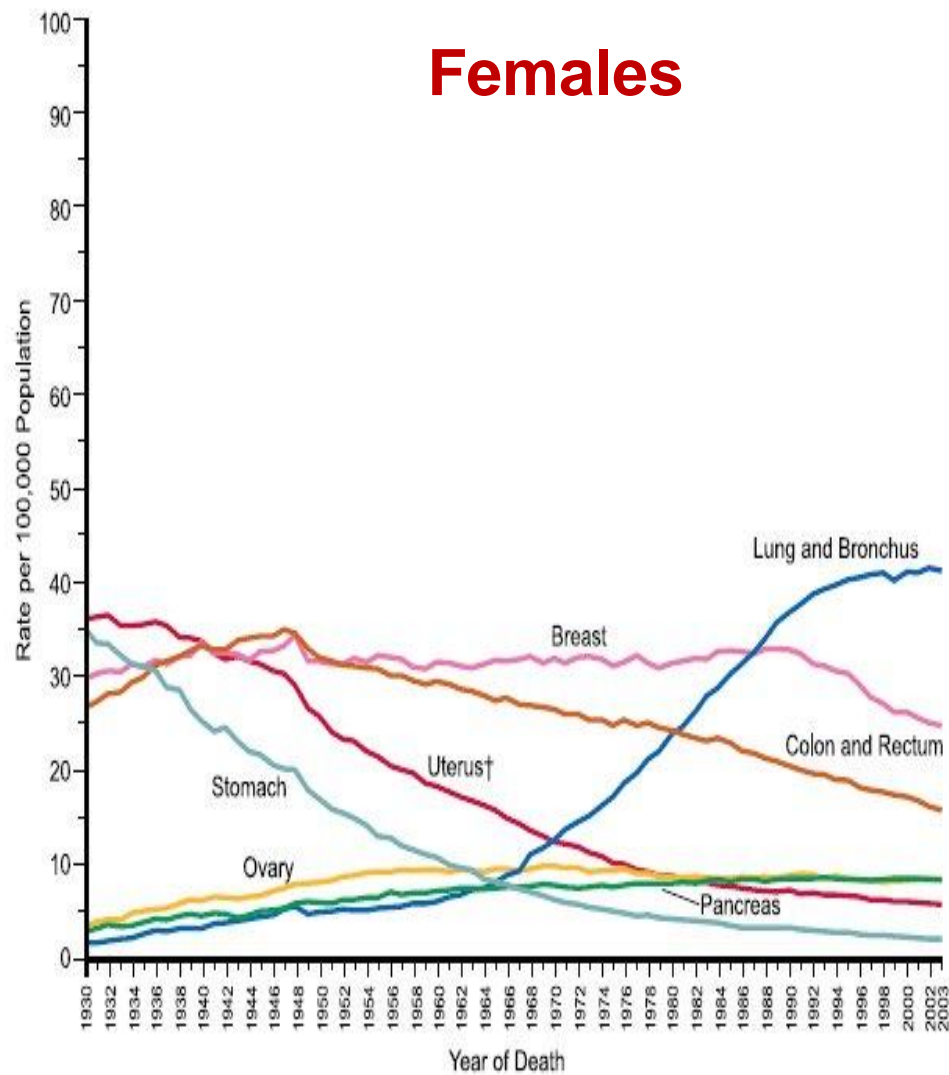
Sir Richard Doll

Cancer Rates

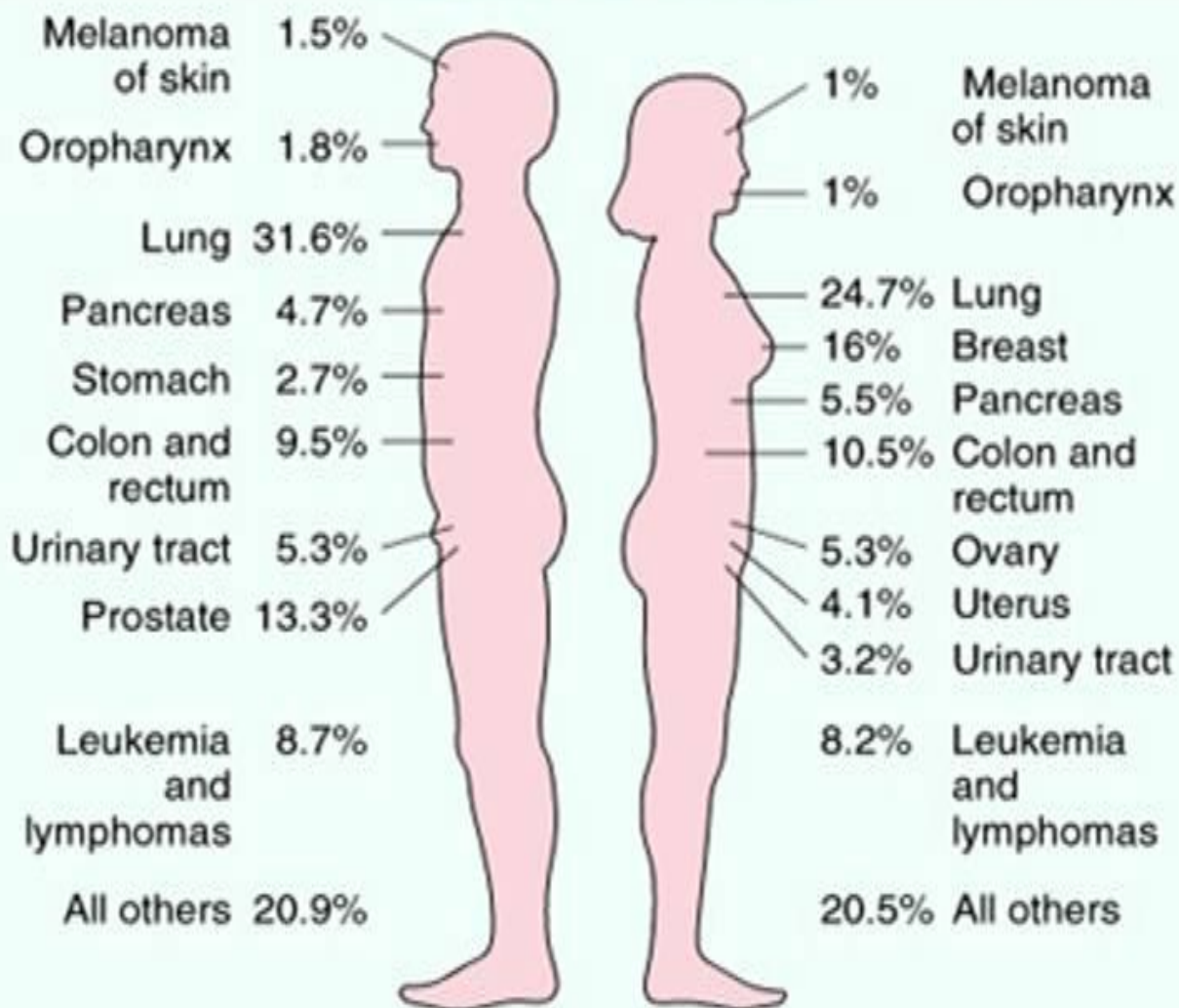
Males



Females



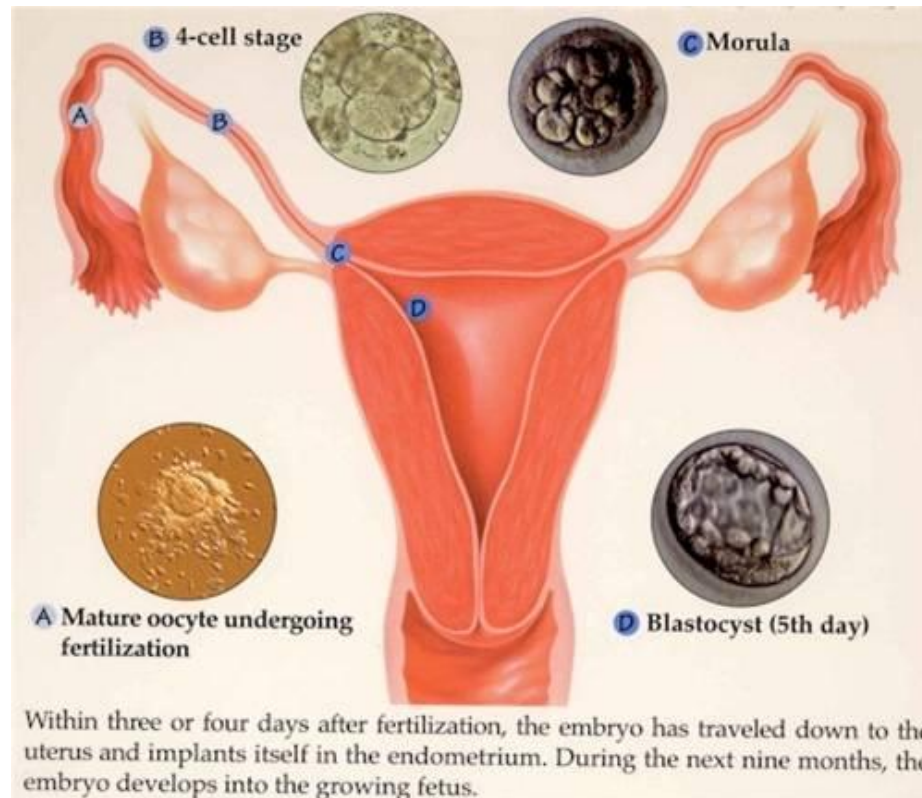
B. 1998 ESTIMATED CANCER DEATHS BY SITE AND SEX*
(Total number 564,800)



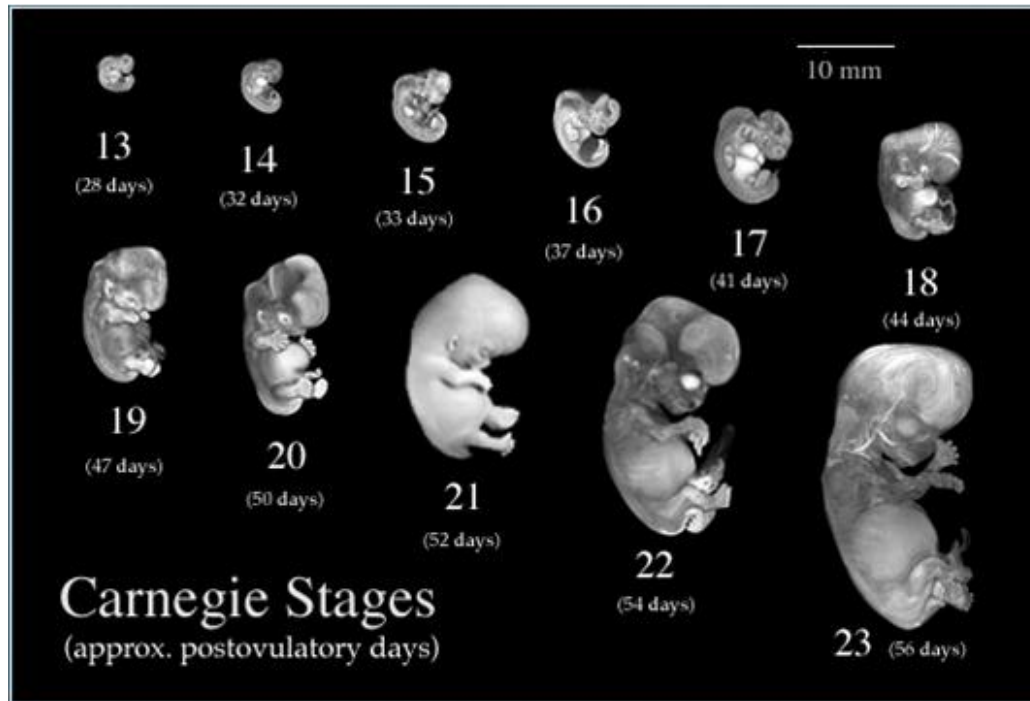
* Excluding nonmelanoma skin cancer and carcinoma in situ, except urinary bladder

Cell Differentiation

All cells of an embryo are descended from the same fertilized egg and have the same genes. As the embryo develops, cells develop different morphologies and functions as a result of selective activation of certain groups of genes.

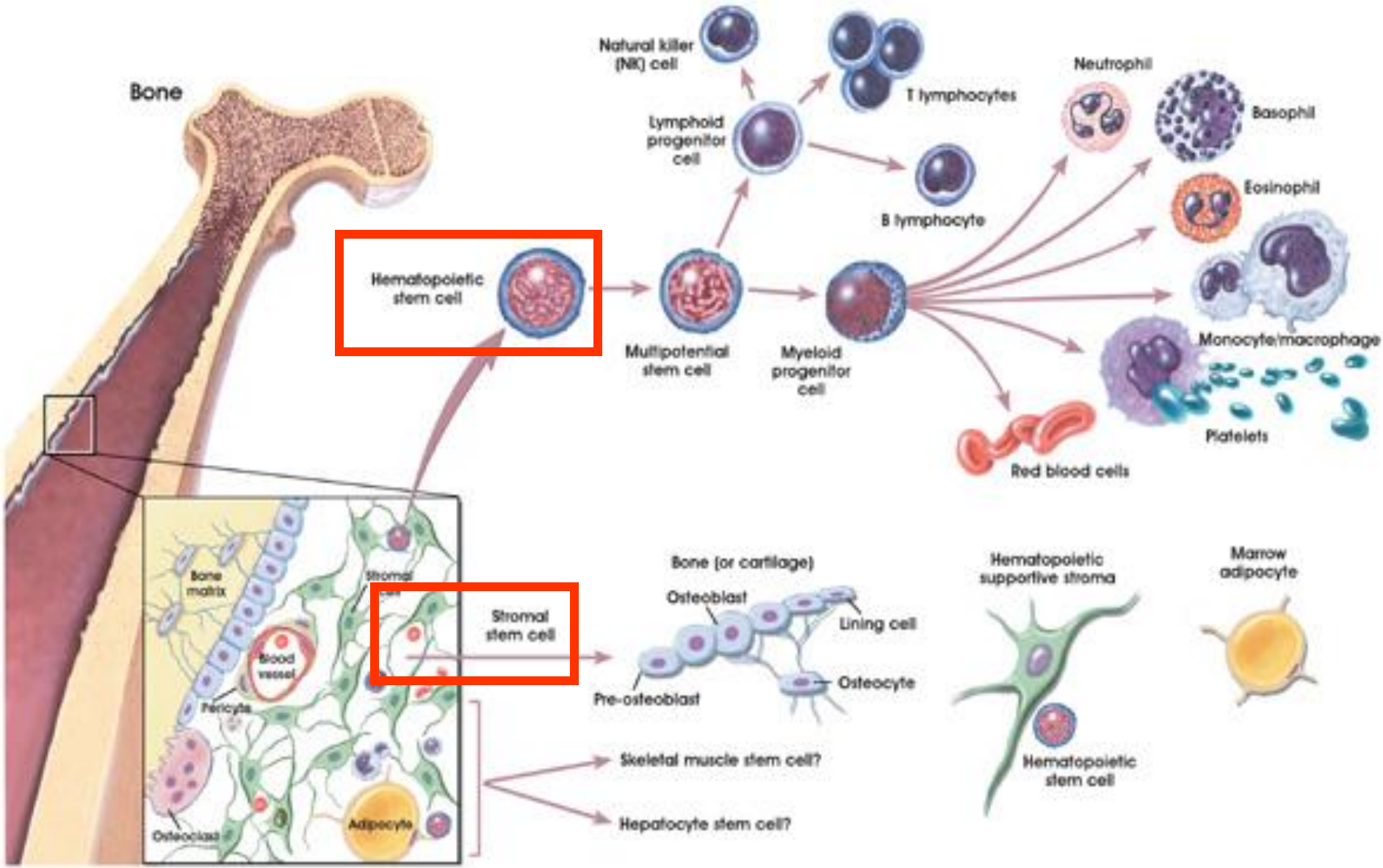


Cell Differentiation



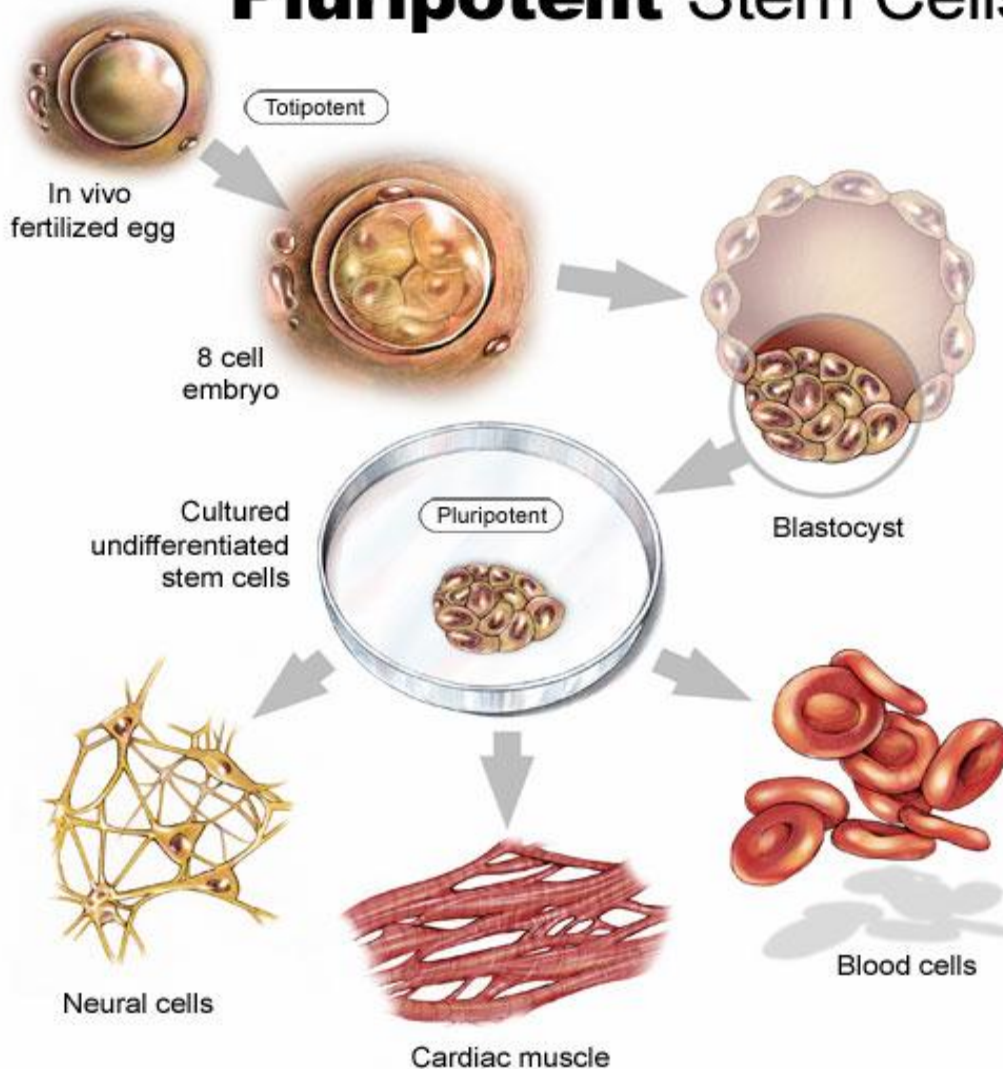
Cell differentiation: selective activation of genes that synthesize proteins not found in other cell types. Cells become specialized in structure and function. Embryonic development involves an orderly program of cellular changes that contribute to the embryo's size and shape the form and function of cells, tissues, and organs. **Example:** only lymphocytes make antibodies.

Adult Bone Marrow



Embryonic Stem Cells

Pluripotent Stem Cells



Embryonic stem cells are **pluripotent**, meaning that can differentiate into any cell type.

Cell Proliferation & Death

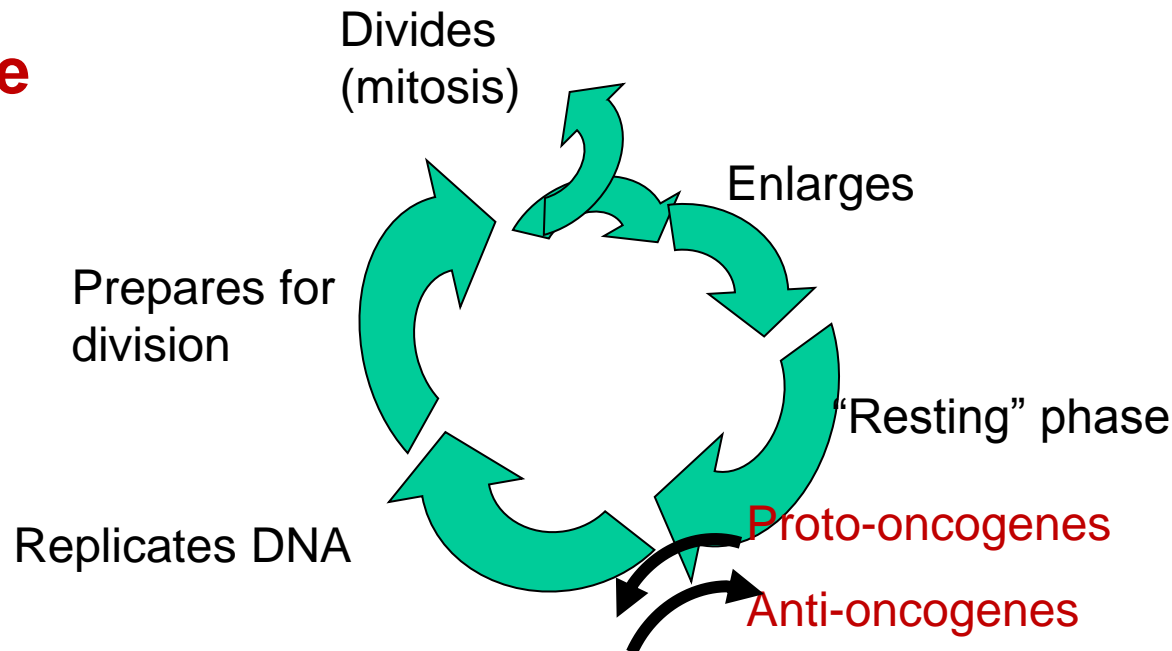
Cell proliferation & **cell death** (apoptosis) occur throughout life.

- In a growing organism there is more proliferation than death.
- In an adult, cell proliferation and death should be in balance.

Normal Cell Growth & Division

In a normal cell, division is controlled; it divides only when appropriate for its type and circumstances, and it does not lose its specialized differentiated identity. The generation of new cells replaces old or damaged cells.

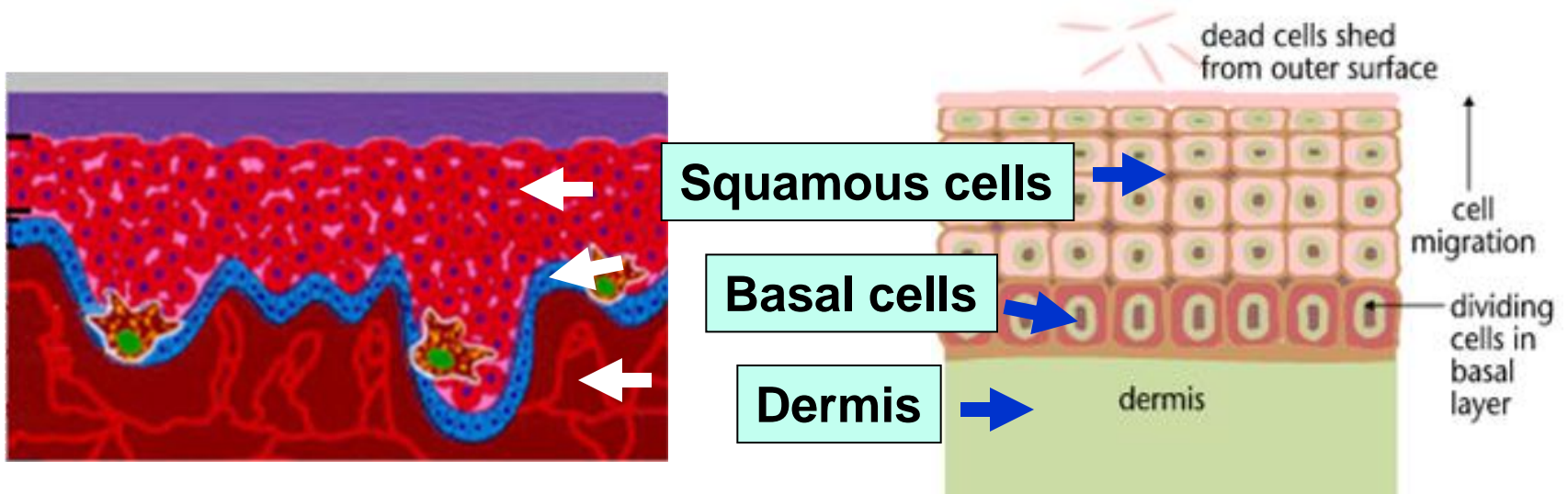
Cell Cycle



Cell Proliferation Signaling Pathway

<http://youtu.be/qpLfA3Am5Nk>

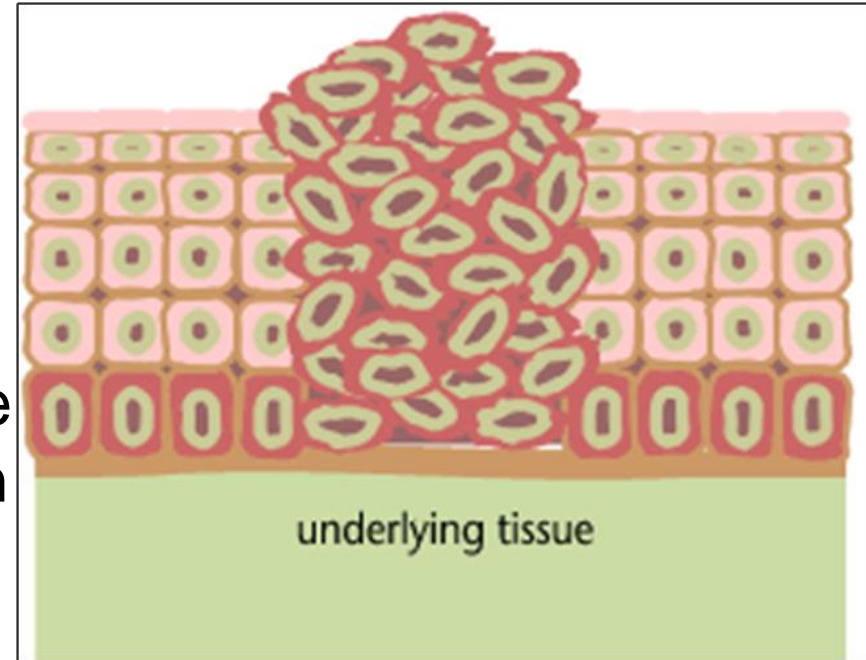
Normal Cell Growth & Division



Example: The outer layer of skin (epidermis) is about 12 cells thick. Cells in the basal layer (bottom row) divide just fast enough to replenish cells that are shed. When a basal cell divides, it produces two cells. One remains in the basal layer and retains the capacity to divide. The other migrates out of the basal layer and loses the capacity to divide. The number of dividing cells in the basal layer, therefore, stays the same.

The Transition to Tumor Formation

Skin cancer occurs when the normal balance between cell division/cell loss is disrupted. Basal cells divide **faster than needed** to replenish the cells being shed, and with each division both of the two newly formed cells will often retain the capacity to divide, leading to an increased number of dividing cells.

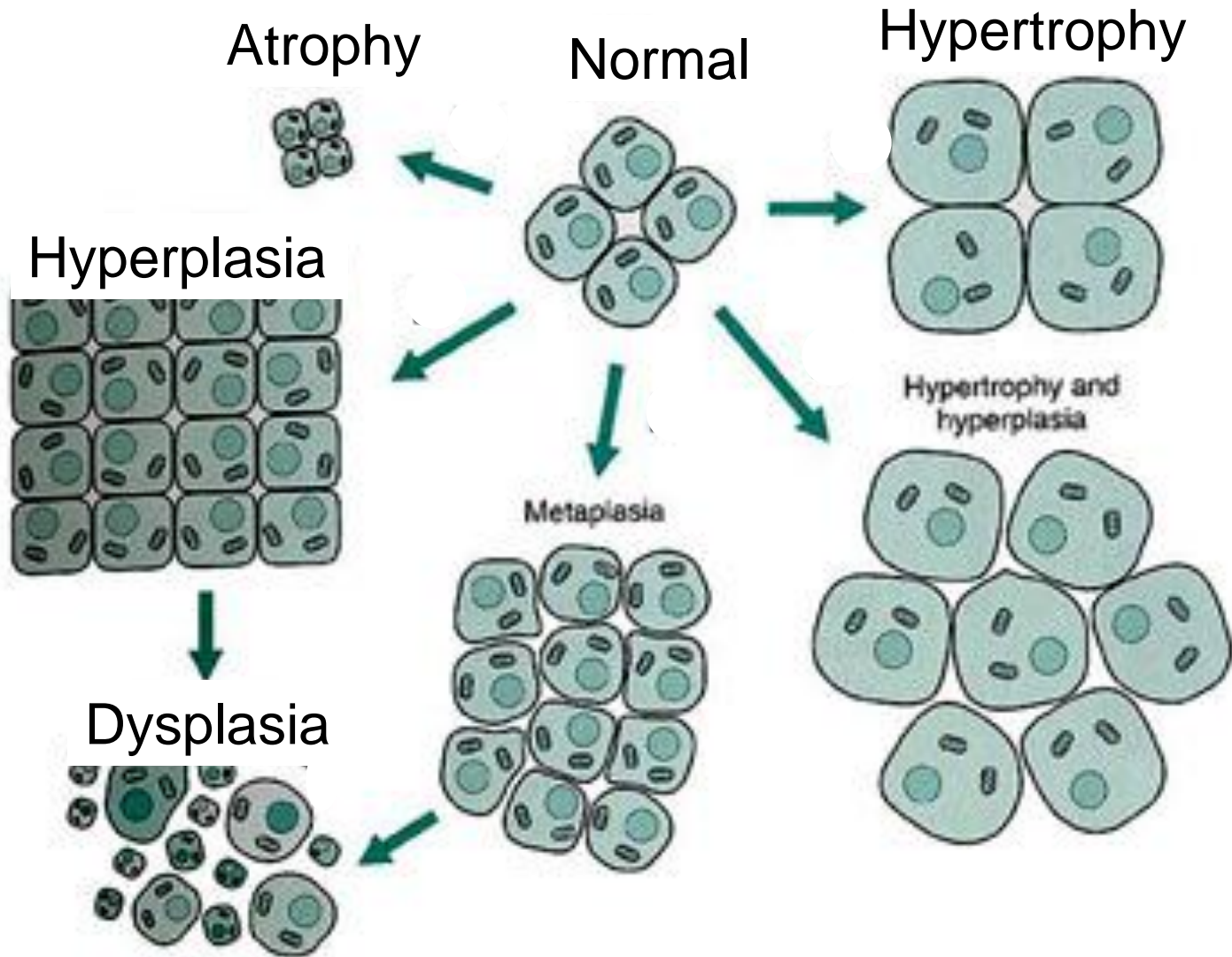


This creates a growing mass of tissue called a "**tumor**" or "**neoplasm**." As more and more dividing cells accumulate, the normal organization of the tissue gradually becomes disrupted.

Evolution of Squamous Cell Tumors of the Head and Neck

<http://youtu.be/oFWPKS5OBI0>

Changes in Cell Morphology



Tumors

Tumors (neoplasms) are masses of cells that are no longer under normal control of growth and division because of mutations in the genes that govern these processes.

Benign tumors (e.g. skin moles, lipomas): abnormal growths that are no longer under normal regulation, but they grow slowly, resemble normal cells, and still have surface recognition proteins that bind them together and keep them from invading or metastasizing.

Warts



Warts are benign tumors of the epidermis caused by any one of 60 types of human papillomavirus (some of which cause cervical cancer). Warts do not have "roots"; but when they grow down, they displace the dermis.

They are most common in children and young adults. They spread by direct contact, and frequently resolve over several months, but some may take years.

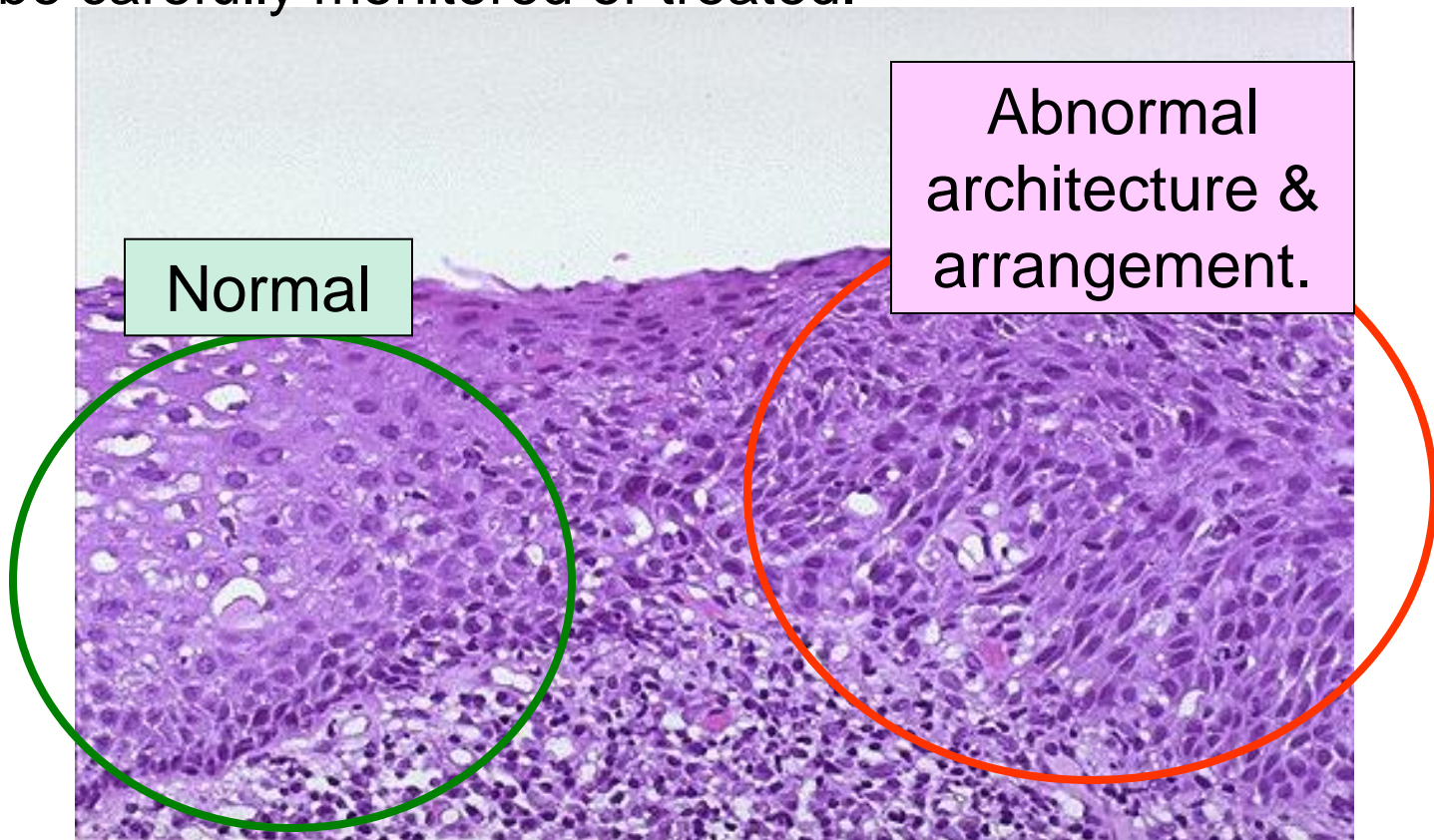


Rx: salicylic acid: First pare the wart with a blade, pumice stone, or emory board. Soak it in warm water to increase uptake of salicylic acid, apply the acid, & let it dry, and cover. Normal skin may be protected with petroleum jelly. Repeat daily.

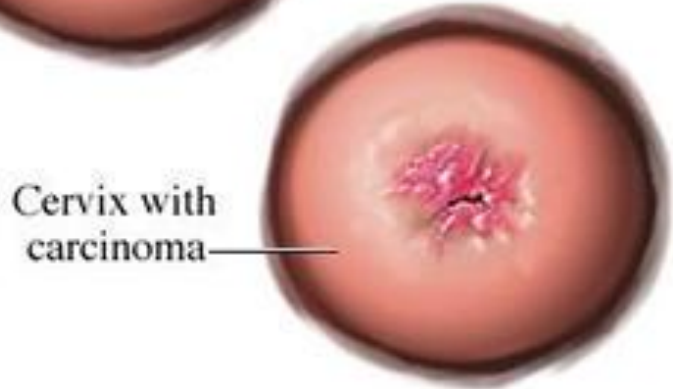
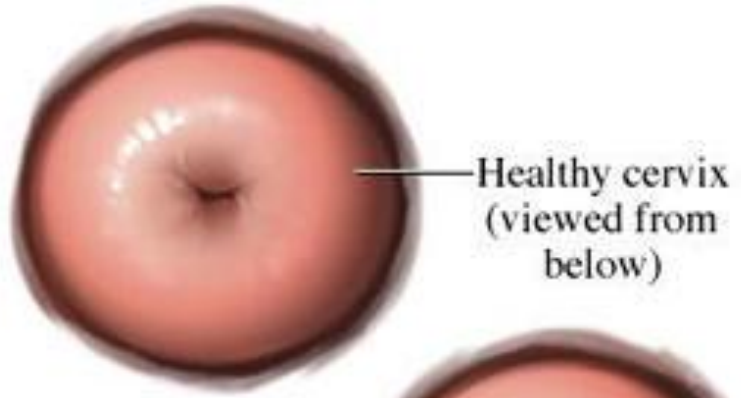
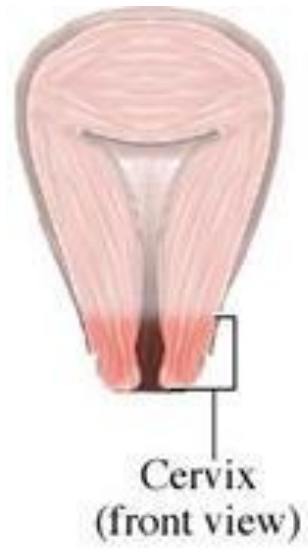
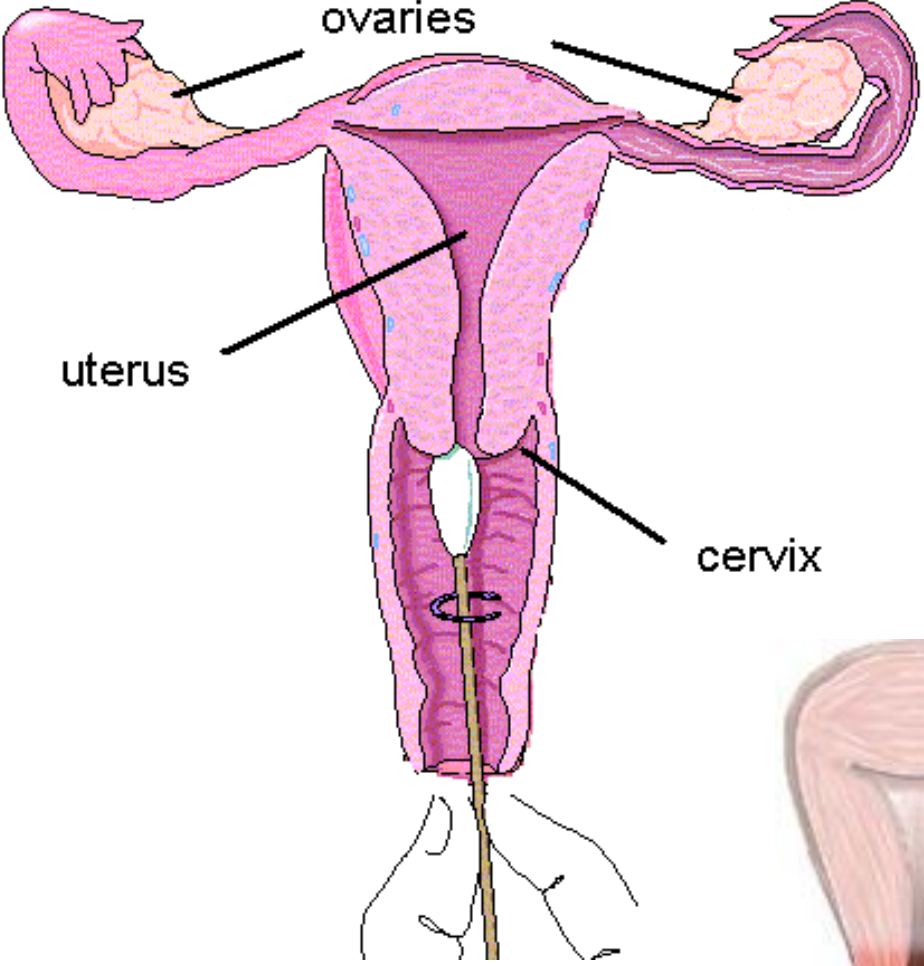
Hyperplasia & Dysplasia

Hyperplasia: Cell number is increased, but structure & arrangement are normal. It can be a normal, reversible response, e.g., a callus.

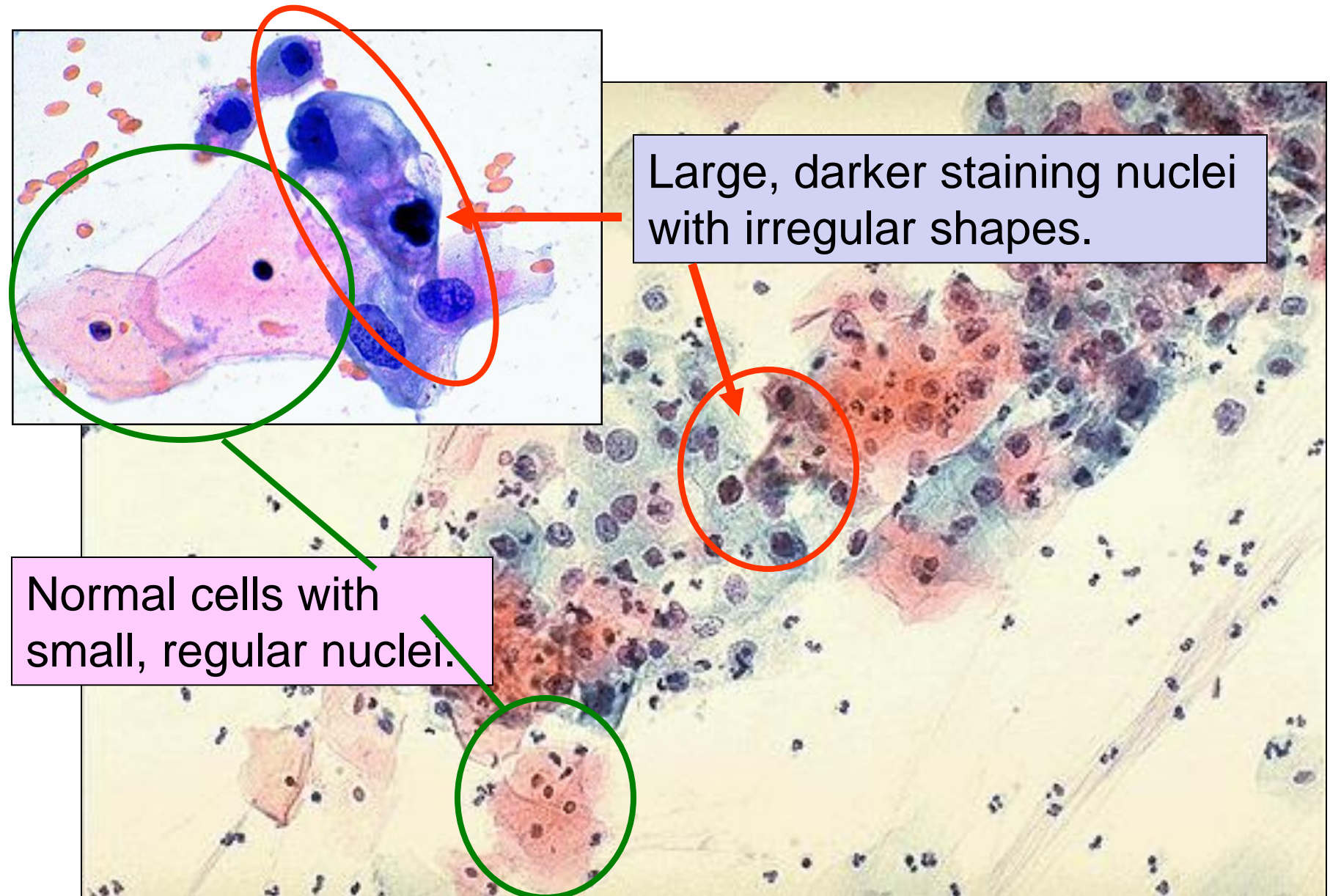
Dysplasia (precancerous) involves both excess proliferation AND loss of normal tissue arrangement & cell structure. Dysplasias can revert back to normal, but they may become malignant. Therefore, dysplasia should be carefully monitored or treated.



Pap Smear



Dysplasia On A Pap Smear



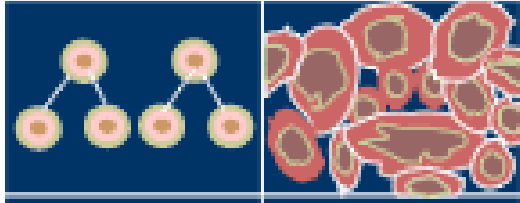
Large, darker staining nuclei with irregular shapes.

Normal cells with small, regular nuclei.

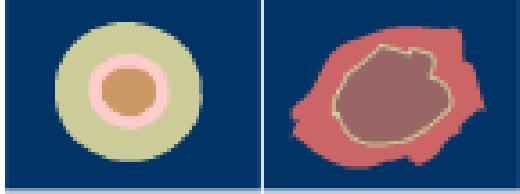
NORMAL

CANCER

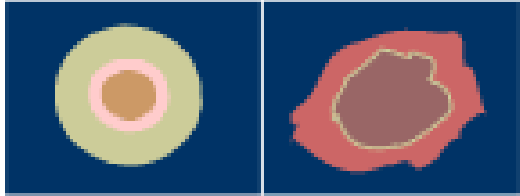
Characteristics of Cancer Cells



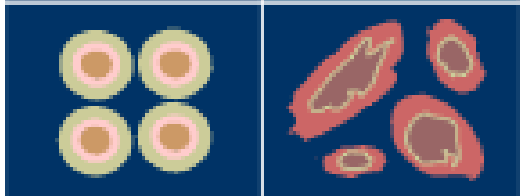
Large # of dividing cells



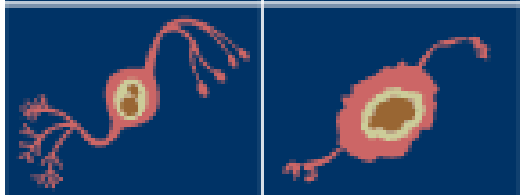
Large, variably shaped nuclei



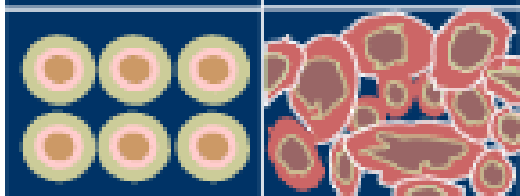
Large nucleus to cytoplasm ratio



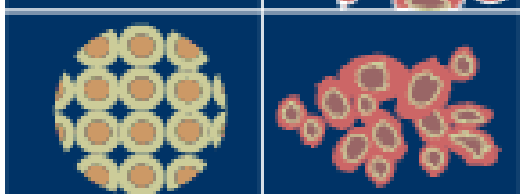
Variation in size and shape



Loss of normal cell features



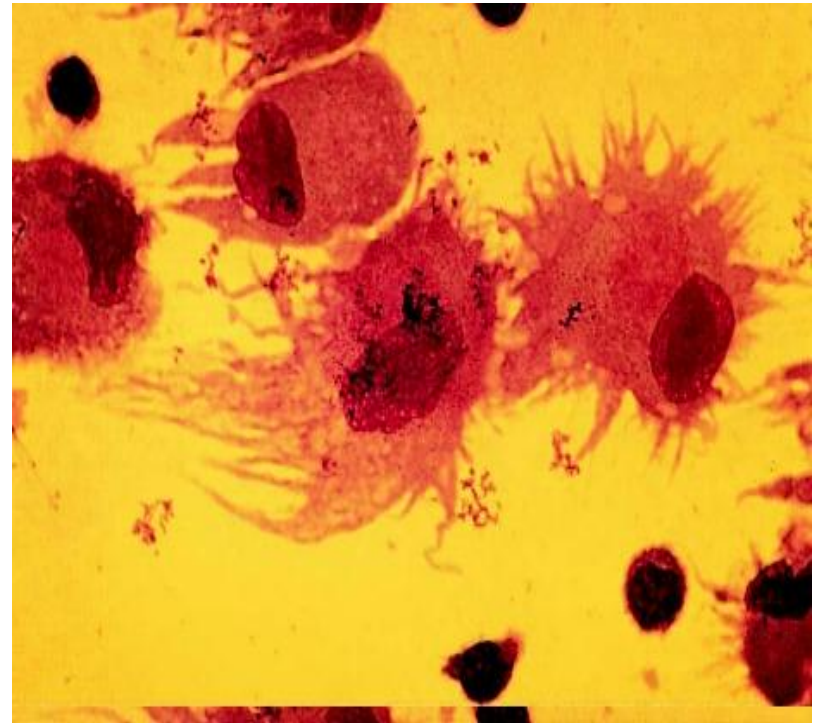
Disorganized arrangement



Poorly defined tumor boundary

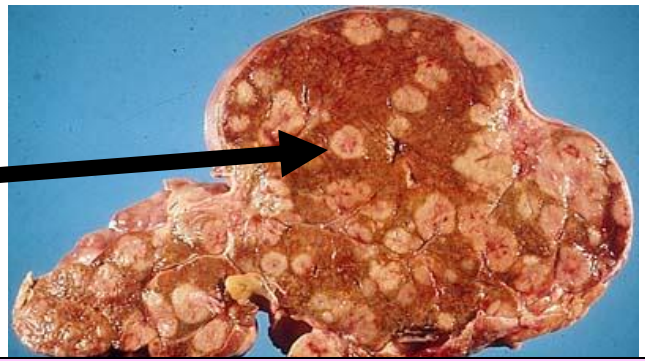
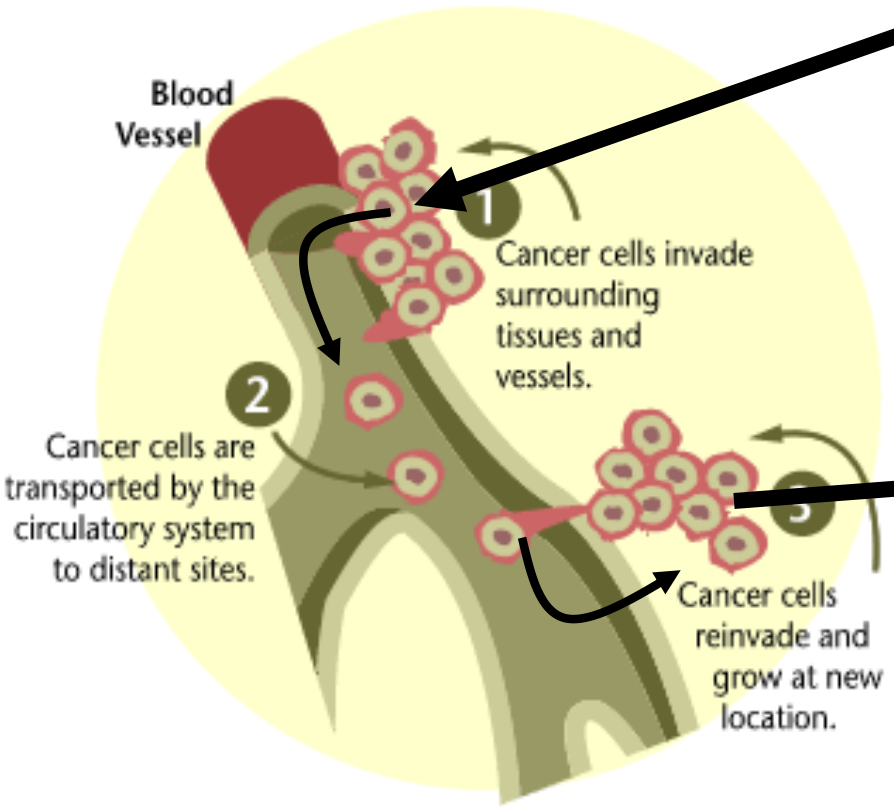
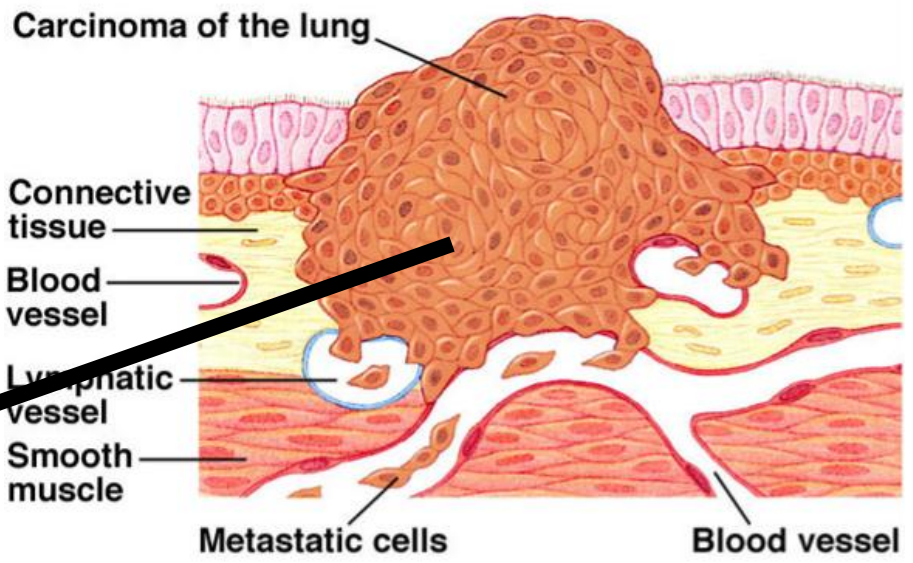
Primary Characteristics of Cancer

1. Abnormally rapid growth & replication; less differentiated. Overcrowding of cells. Membrane proteins are lost or abnormal.
2. Disfigured cells: abnormal cytoskeleton & membrane.
3. Cancers can spread by:
 - **Metastasis** (travel via blood, lymph) to establish colonies in distant tissues.
 - **Local invasion.**



Metastasis

Cancer



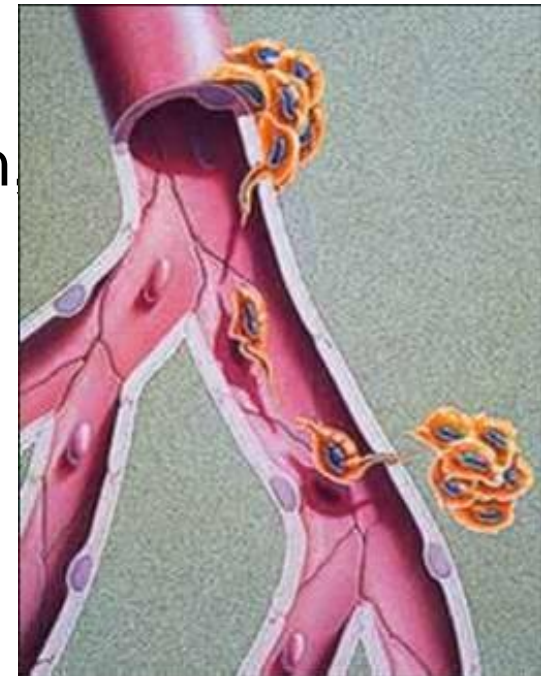
Multiple nodules of a colon cancer that has metastasized to liver.

Metastasis Video

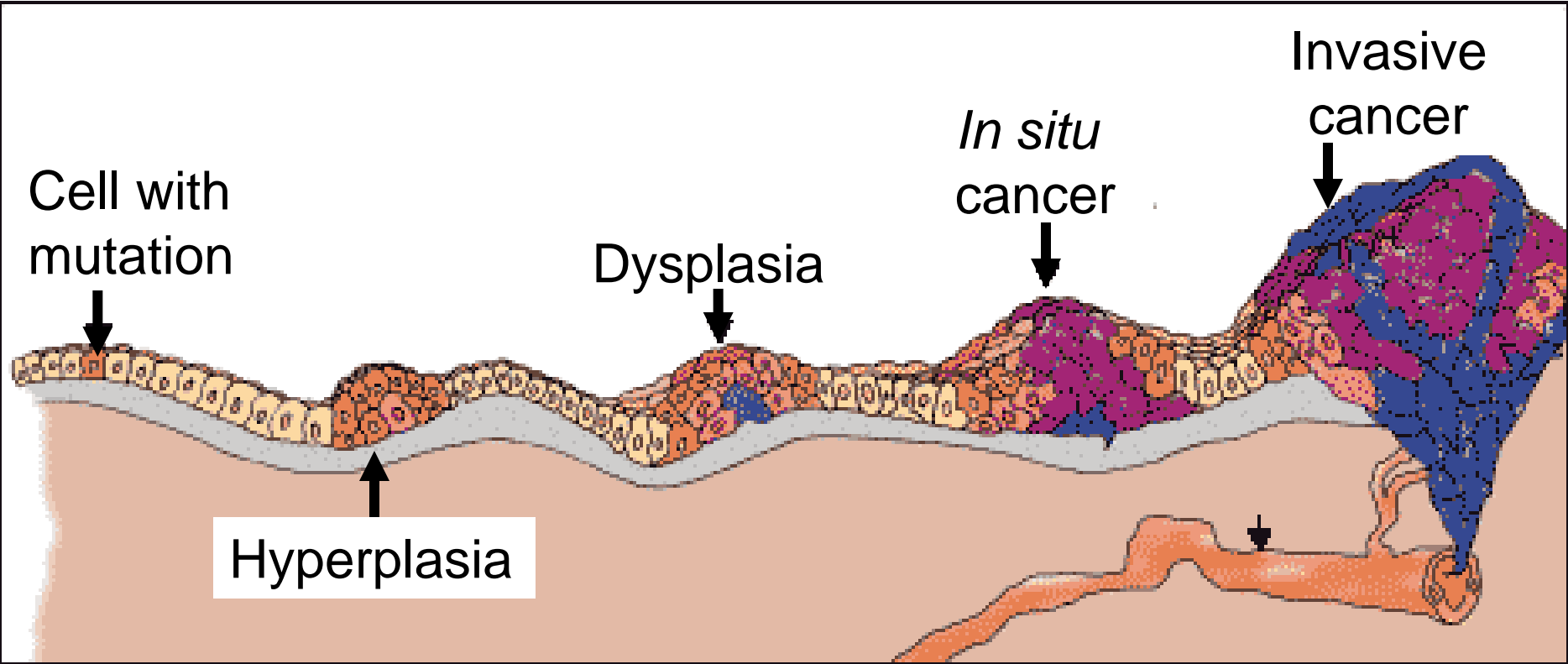
http://youtu.be/rrMq8uA_6iA

How Do Cancers Harm or Kill Us?

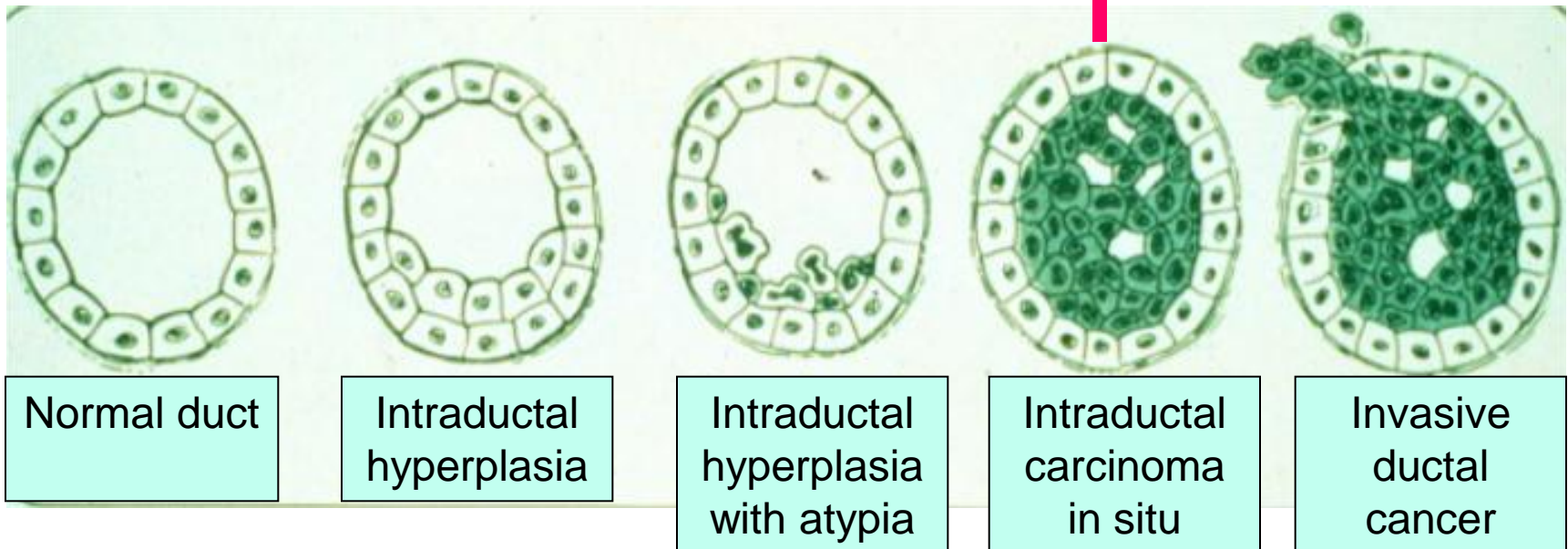
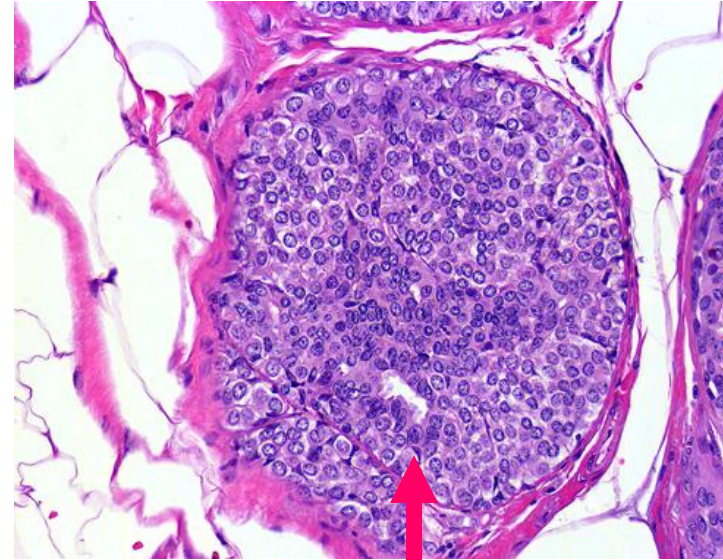
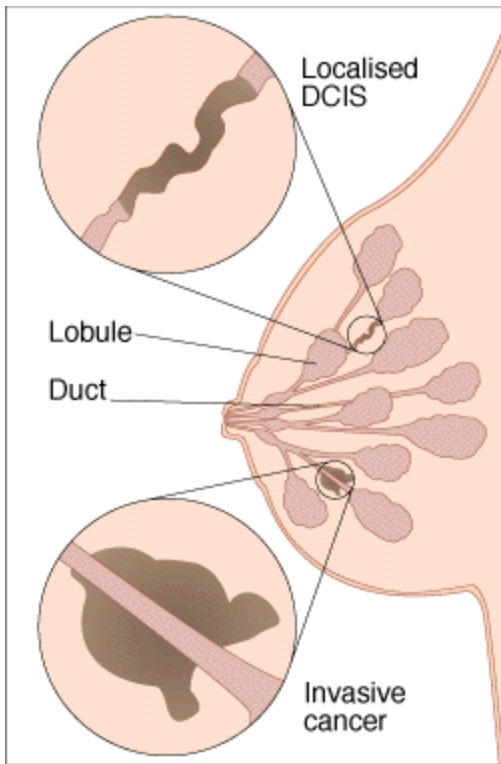
- Use nutrients, but do not contribute to function.
- Expand causing pressure on other organs, distorting them, or interfering with their blood, lymphatic, or nervous access.
- Invade and weaken bone.
- Produce chemicals that disrupt function (anorexia, inflammation, coagulation, pain, blood pressure)

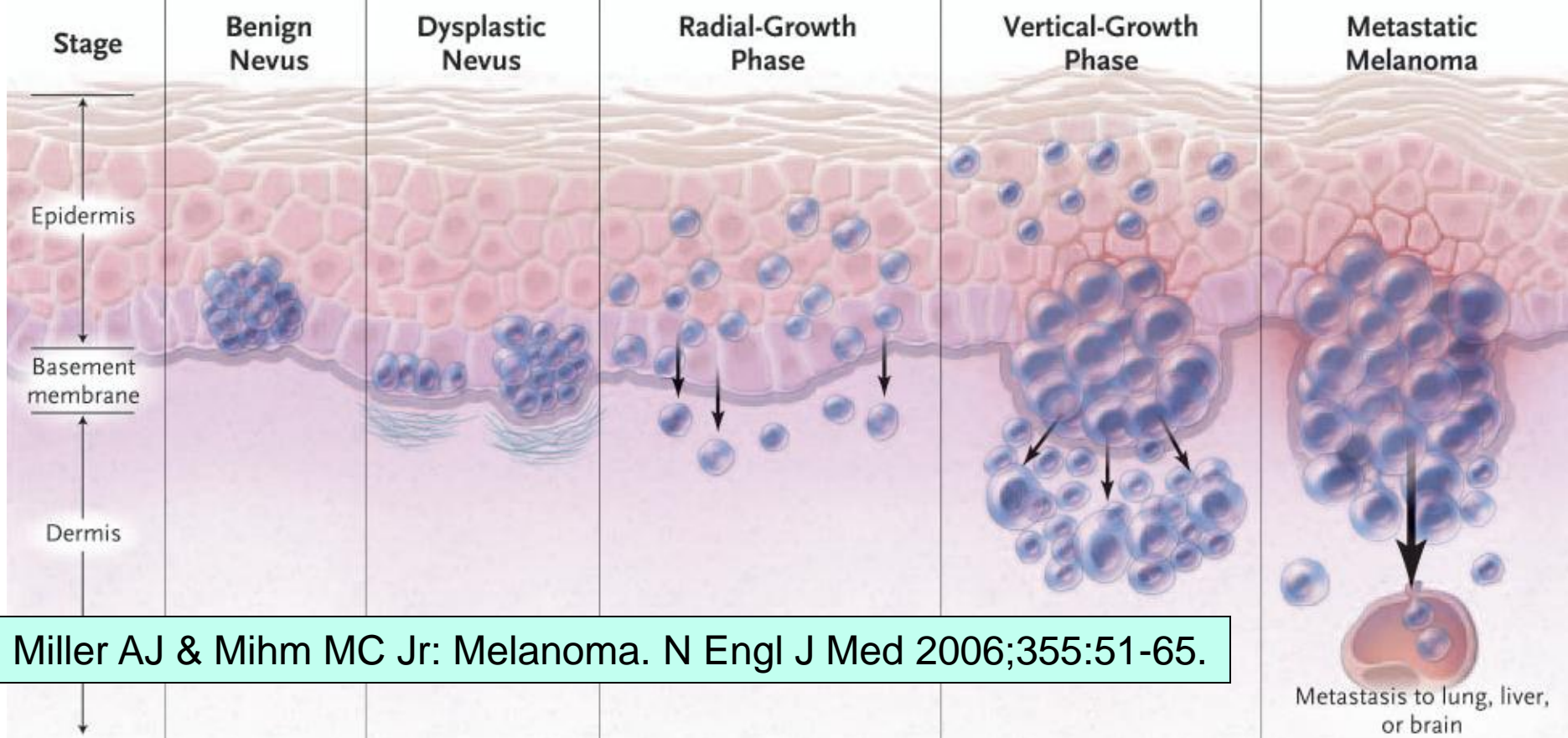


Evolution of a Cancer



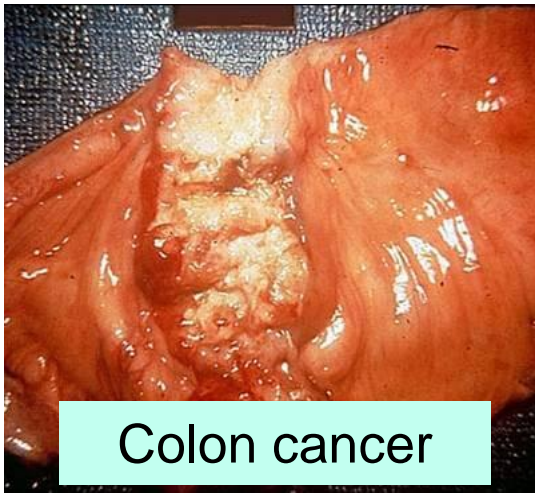
Stages in Progression to Breast Cancer





In the benign nevus, *BRAF* mutation and activation of the mitogen-activated protein kinase (MAPK) pathway occur. Atypia in dysplastic nevi reflect lesions within the cyclin-dependent kinase inhibitor 2A (CDKN2A) and phosphatase and tensin homologue (PTEN) pathways. Progression is associated with loss of differentiation. The vertical-growth phase and metastatic melanoma are notable for striking changes in the control of cell adhesion.

Cancer Staging



Colon cancer



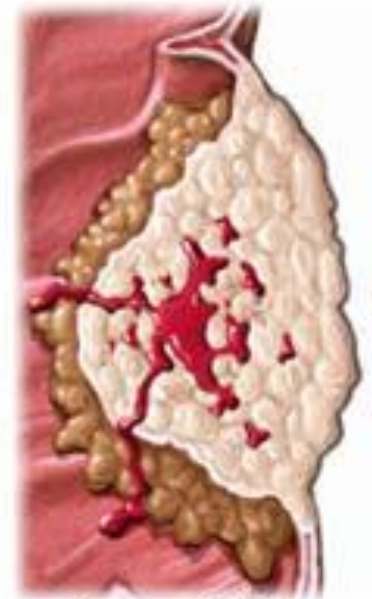
Treatment of colon cancer depends on the stage, or extent, of disease



Stage I



Stage II

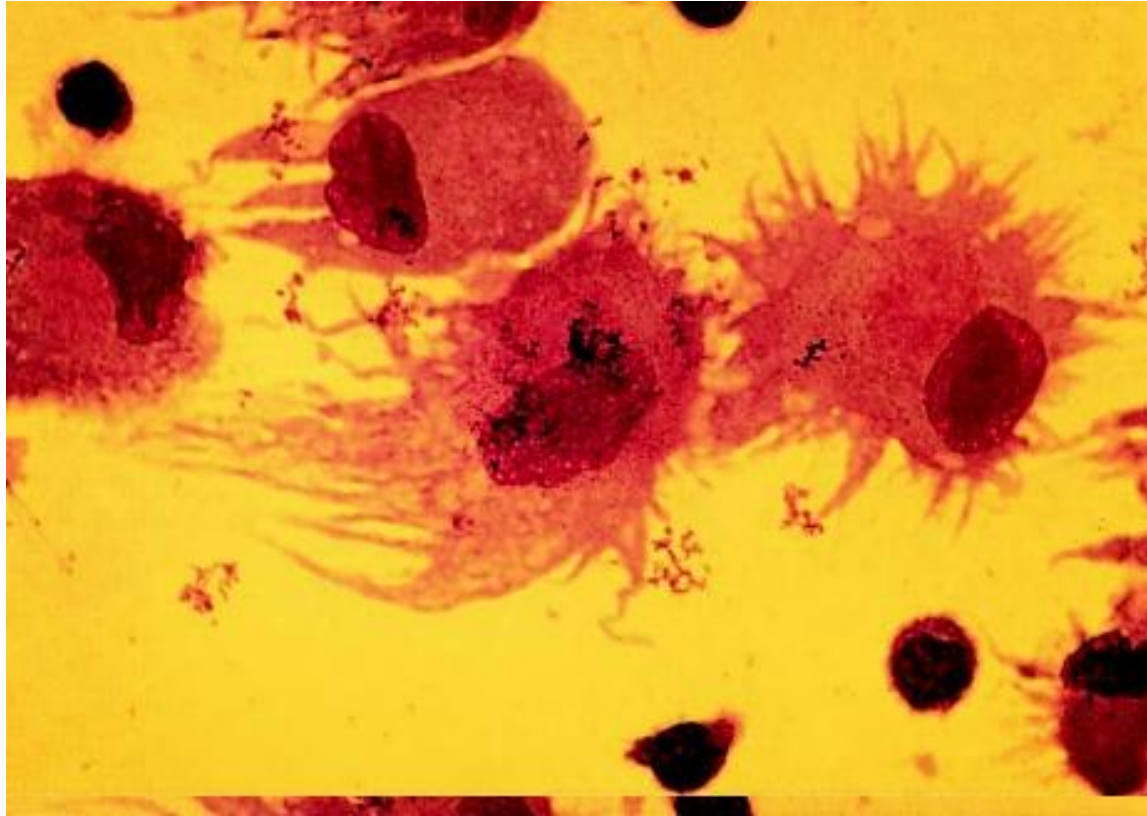


Stage III

Cancers are also assigned a “**stage**” based on **size & spread**:

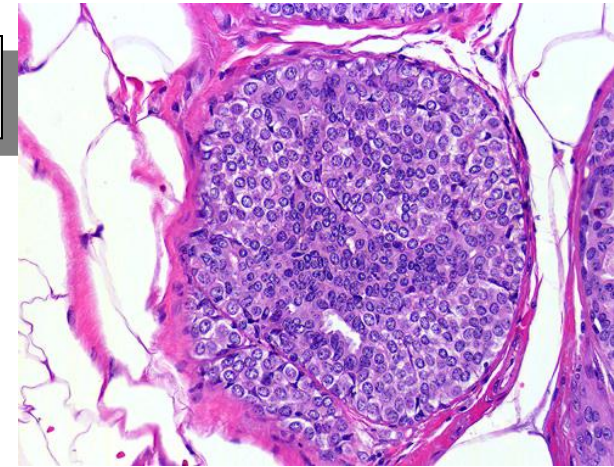
1. Size & how far it has invaded into surrounding tissues.
2. Whether it has spread to regional lymph nodes.
3. Whether it has metastasized to other regions of the body.

Cancer Grading



Aggressive tumors might be described by a pathologist as “poorly differentiated;” in contrast, a “well-differentiated” adenocarcinoma of the colon would be less aggressive.

Cancer Grading



The microscopic appearance a cancer indicates its likely behavior and its responsiveness to treatment.

- Poorly differentiated cancers have highly abnormal cell appearance and large numbers of dividing cells and tend to grow more quickly, spread to other organs more frequently, and be less responsive to therapy than cancers whose cells have a more normal appearance.
- Based on these differences in microscopic appearance, doctors assign a numerical "grade" to most cancers.
- A low number grade (grade I or II) refers to cancers with fewer cell abnormalities than those with higher numbers (grade III, IV).

Types of Cancer

Carcinomas, the most common types of cancer, arise from the cells that cover external and internal body surfaces. Lung, breast, and colon are the most frequent cancers of this type in the United States.

Sarcomas are cancers arising from cells found in the supporting tissues of the body such as bone, cartilage, fat, connective tissue, and muscle.

Lymphomas are cancers that arise in the lymph nodes and tissues of the body's immune system.

Leukemias are cancers of the immature blood cells that grow in the bone marrow and tend to accumulate in large numbers in the bloodstream.

Naming Cancers

FYI

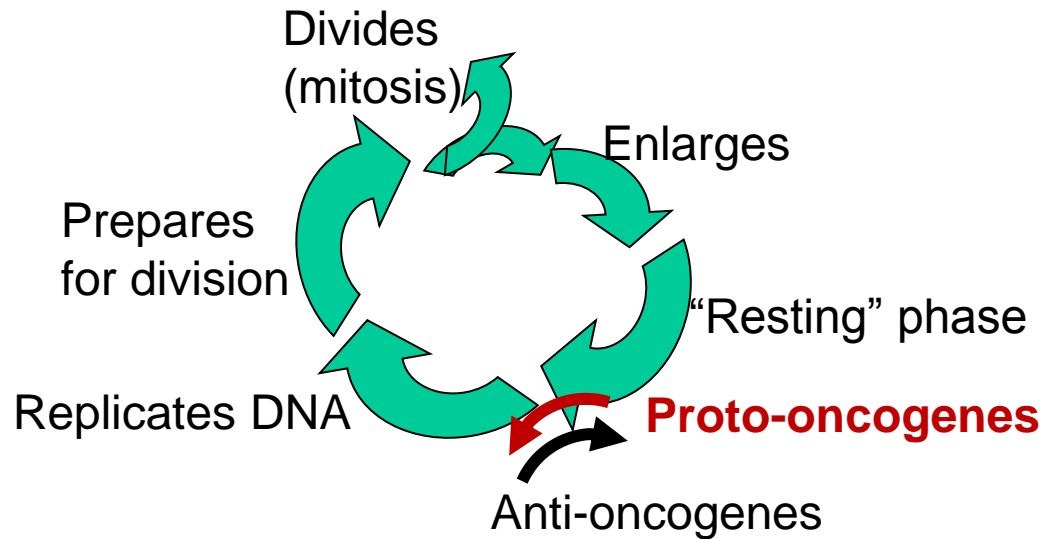
Names for specific cancers are created by using different prefixes that stand for the name of the cell type involved.

- “Osteo” means bone, so a bone cancer is called osteosarcoma.
- “Adeno” means gland, so a cancer of gland cells is an adenocarcinoma – e.g. a breast adenocarcinoma.

Some Prefixes Used in Naming Cancers

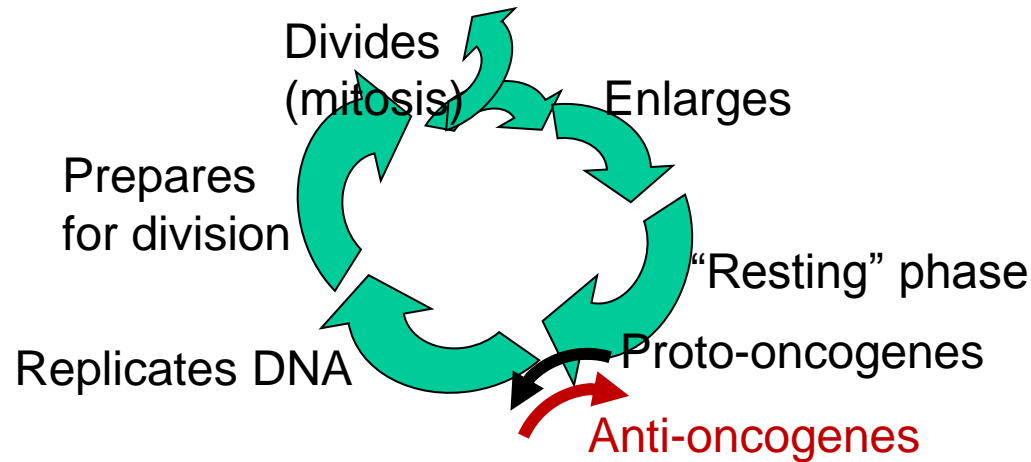
PREFIX	MEANING
adeno-	gland
chondro-	cartilage
erythro-	red blood cell
hemangio-	blood vessels
hepato-	liver
lipo-	fat
lympho-	lymphocyte
melano-	pigment cell
myelo-	bone marrow
myo-	muscle
osteo-	bone

Proto-oncogenes



Proto-oncogenes: normal genes that code for proteins involved in cell division. These “growth factors” or hormones bind to receptors on the cell surface & activate enzymes inside the cell, which in turn activate protein transcription factors in the nucleus. The activated transcription factors turn on genes required for cell growth and proliferation.

Tumor Suppressor Genes (Anti-oncogenes)



Anti-oncogenes (tumor suppressor genes): encode for protein signals that halt division or promote differentiation. If a pair of tumor suppressor genes are lost from a cell or inactivated by mutation, their functional absence can cause cancer. Individuals with familial retinoblastoma are born with one defective copy of the tumor suppressor gene "Rb". This will not cause cancer as long as the other copy of the gene is functional, but if the 2nd copy mutates, the suppressor is knocked out.

Damaged DNA

"DNA repair genes" code for proteins that correct errors arising when DNA is duplicated prior to cell division. Mutations in DNA repair genes can lead to a failure to repair mutations in tumor suppressor genes and proto-oncogenes.

- **Xeroderma pigmentosum** is an inherited defect in a DNA repair gene. One cannot repair DNA damage that occurs when skin cells are exposed to sunlight, & they have very high rates of skin cancer.
- Certain forms of hereditary colon cancer also involve defects in DNA repair.



Apoptosis

If damaged DNA cannot be repaired, “suicide genes” are activated to initiate **apoptosis** or “**programmed cell death**,” a mechanism for eliminating defective cells.



One particular tumor suppressor gene codes for a protein called "**p53**" that can trigger cell suicide (apoptosis). In cells that have undergone DNA damage, the p53 protein suppresses cell growth and division. If the damage cannot be repaired, the p53 protein eventually initiates cell suicide, thereby preventing the genetically damaged cell from growing out of control.

Summary: Control Of Cell Division

Oncogenes: variants (mutants) of proto-oncogenes that provide a continual signal to divide.

- 50 known oncogenes.
- Several must be activated before a cell becomes cancerous.

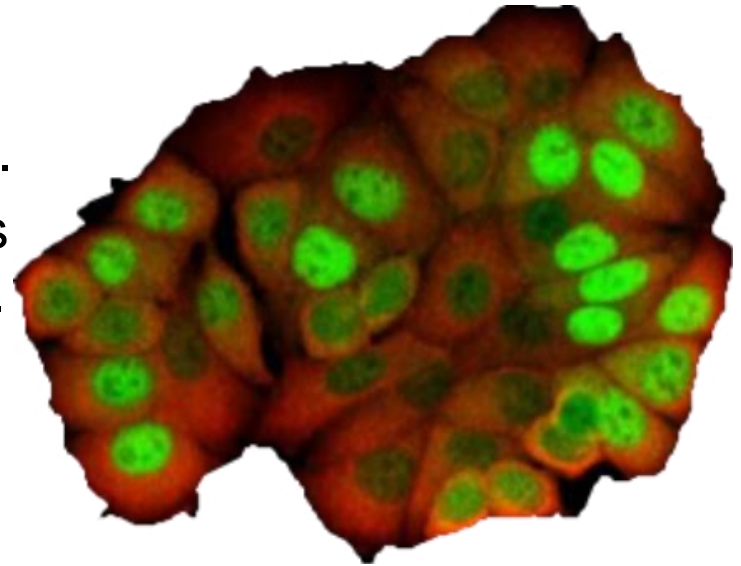
Tumor suppressor genes (anti-oncogenes) send signals to halt cell division or promote differentiation.

Apoptosis: programmed cell death (“suicide”) is a quality control mechanism for ridding the body of cells that have sustained irreparable DNA damage and might become cancerous.

Cancer Cell: A Failure of Cell Regulation

A cancer cell has multiple defects:

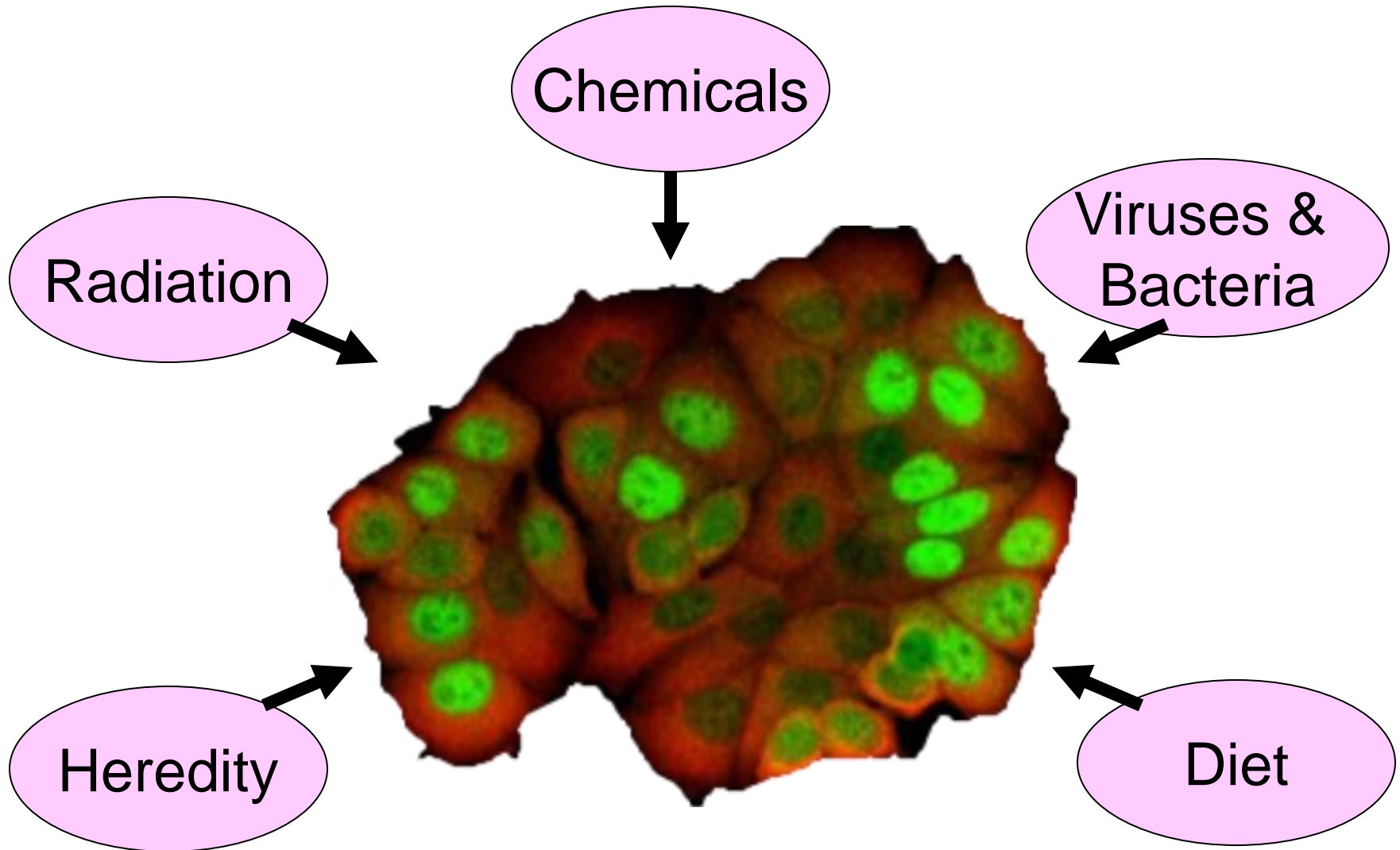
- Increased division due to oncogenes.
- Loss of negative control mechanisms that halt division (tumor suppressors).
- Have defective mechanism for eliminating irreparably damaged cells (apoptosis).



Cancer is due to **accumulation of mutations** involving oncogenes, tumor suppressor genes, and DNA repair genes.

For example, **colon cancer** can begin with a defect in a tumor suppressor gene that allows excessive cell proliferation. The proliferating cells then tend to acquire subsequent mutations involving a DNA repair gene, an oncogene, and several other tumor suppressor genes.

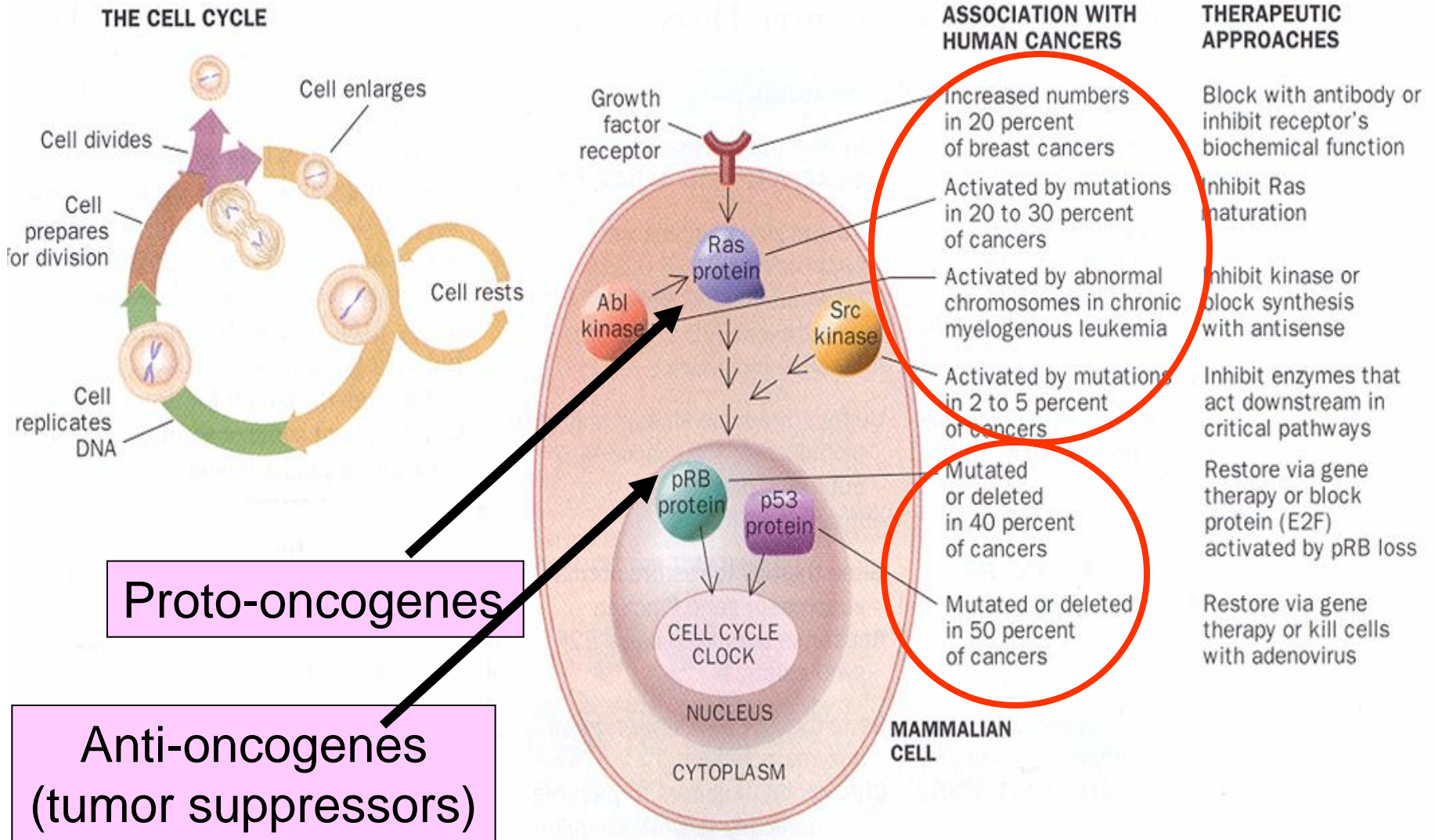
What Causes Cancer?



Mutations and Cancer

- Mutations in genes that control normal cell proliferation can lead to cancer. These mutations can be created by DNA-damaging **carcinogens** (e.g., radiation or chemicals & by products of tobacco)
- Viruses (e.g., Rous sarcoma virus, Kaposi's sarcoma herpes virus)
- However, some cancer-causing mutations are simply **spontaneous errors** that appear in normal DNA molecules when cells duplicate their DNA prior to cell division.
- The mutations that contribute to the development of cancer affect three general classes of gene:
 - Oncogenes
 - Tumor suppressor genes
 - DNA repair genes & genes controlling apoptosis.

Mutations in Any of the Links in the Chain of Control Can Promote Cancer



Tumor Viruses

One group of RNA viruses (retroviruses) and several types of DNA viruses can induce tumors if their nucleic acids are **incorporated into host DNA**.

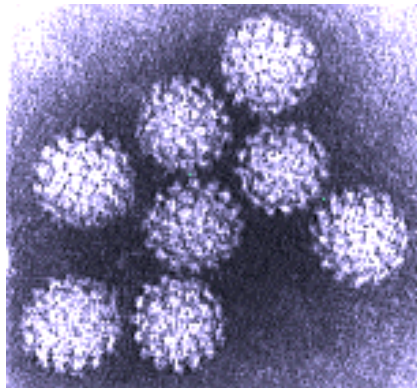
Examples: cervical cancer, liver cancer, and certain lymphomas, leukemias, and sarcomas.

The risk of cervical cancer is increased in women with multiple sexual partners (& very high in women who marry men whose previous wives had it). Transmission of human papillomavirus (HPV) during sexual relations is involved.

Human Papilloma Virus

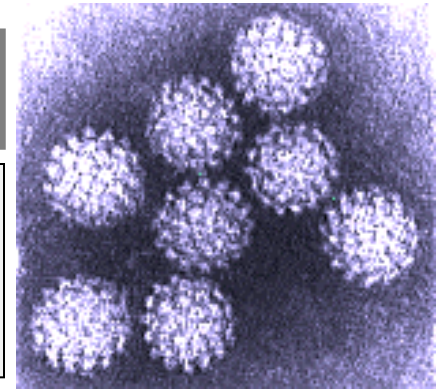
Papilloma viruses were recognized years ago as the cause of warts on the hands and feet or condyloma accuminata on the pubic area (penis and urethra in males or vulva and vagina in females).

For years, warts were considered just an ugly nuisance, rather than a forerunner of cancer. Warts on fingers and toes usually are not dangerous, but virus types that target the face can make skin cancer more likely.



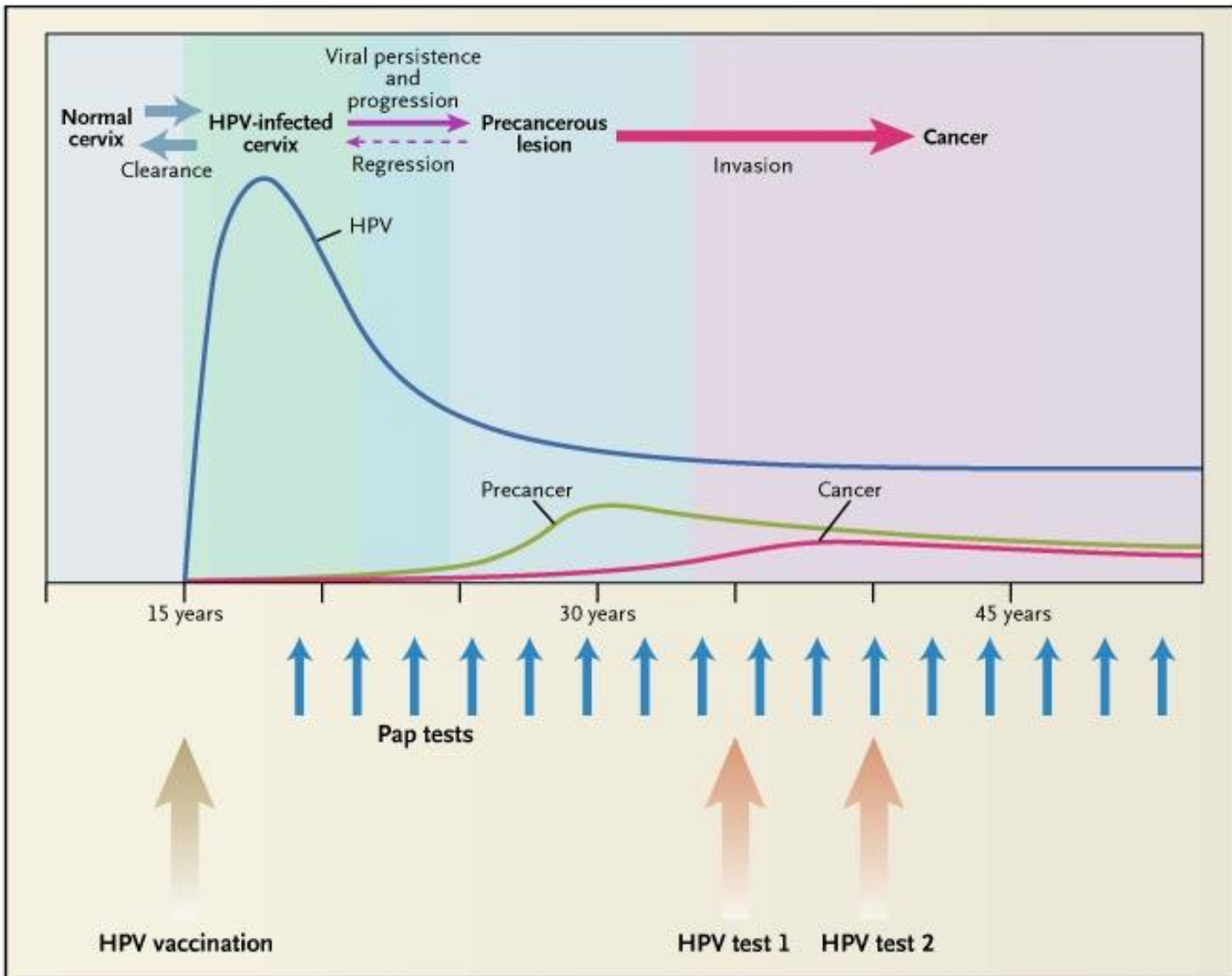
Human Papilloma Virus

HPV is the most prevalent sexually transmitted infection in the world, occurring in up to 75% of sexually active women, although few have any symptoms.



- Cervical cancer: 99.7% due to infection with one of a group of oncogenic HPVs.
- Men & women are infected shortly after becoming sexually active, but progression to cervical cancer takes 10-20 years.
- Nearly 100 types of papilloma virus have been identified. It is unknown why certain HPV types target skin on the hands or feet while others attack cells lining the mouth, and yet others the genitalia.
- **Two genes in HPV (E6 & E7) produce proteins that block Rb and p53 proteins (tumor suppressors).**

Natural History of HPV Infection



Estimate #1

Natural History of HPV Infection

100,000 women
infected with HPV

➤ **Cervical dysplasia** (pre-malignant):
With time the cells expand, become distorted, and their arrangement in rows & columns on the surface of the cervix is destroyed.

➤ **Carcinoma in situ:** In some women the pre-malignant cells will slowly replace the normal cells on the surface of the cervix and carcinoma *in situ* will develop.

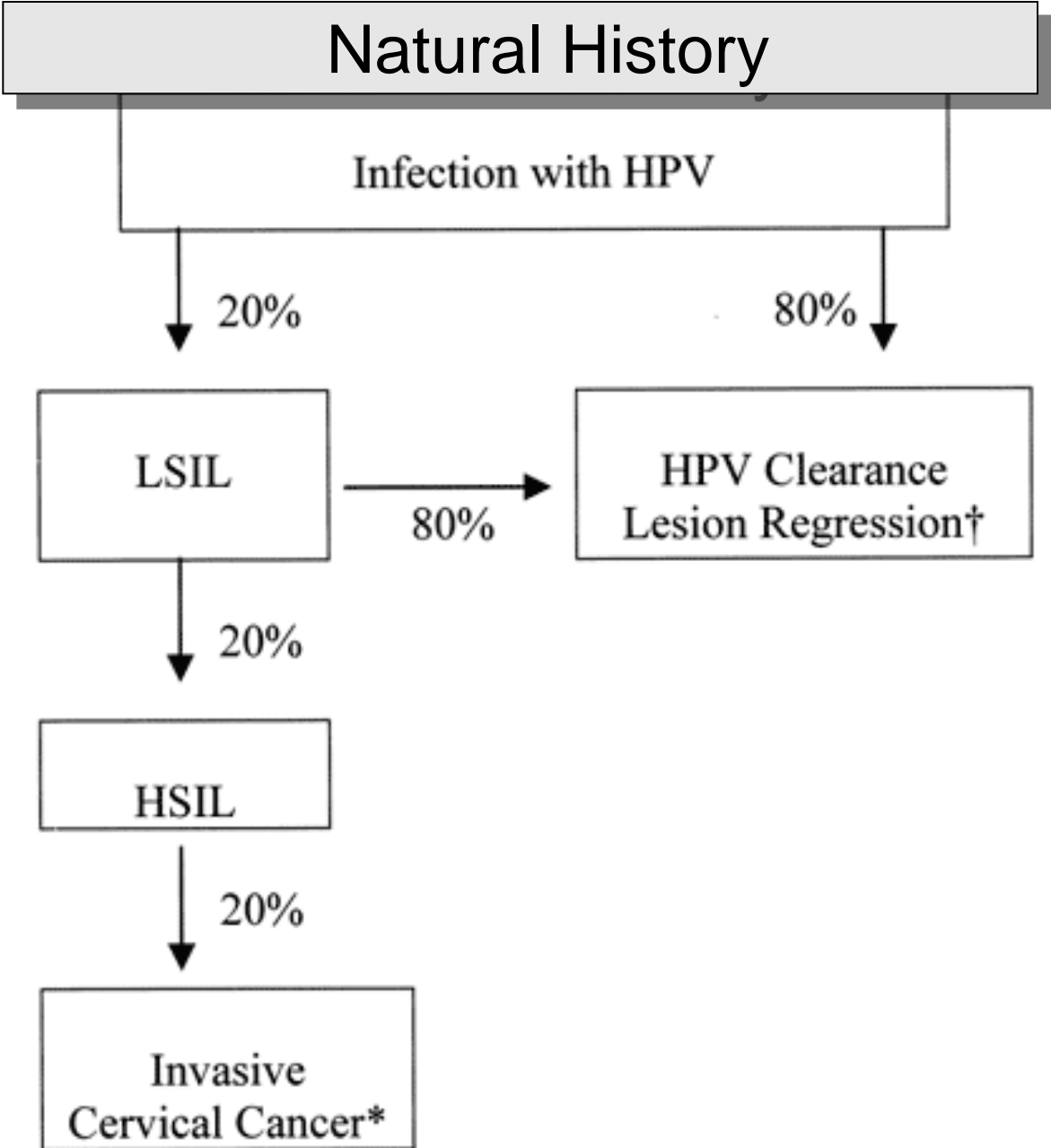
➤ **Cervical cancer:** Occurs when cells grow through the normal surface layer into the muscle and deeper tissues.

↓
10,000 (10%) develop
precancerous
changes (dysplasia)

↓
800 (8%) develop CIS

↓
160 develop invasive
cancer if not treated

Risk of dysplasia is higher if the woman smokes.



Estimate #2

100,000

Natural History

Infection with HPV

20%

80%

20,000

LSIL

80%

HPV Clearance
Lesion Regression†

20%

4,000

HSIL

20%

800

Invasive
Cervical Cancer*

Molly C. Fey, FNP, MSN; Margaret W. Beal, CNM, PhD: The Role of Human Papilloma Virus Testing in Cervical Cancer Prevention. J Midwifery Womens Health 49(1):4-13, 2004.

The American Cancer Society, US (2006):

9,700 women diagnosed with cervical cancer

3,700 deaths

A Vaccine for HPV

The Basics about Genital HPV and Cervical Cancer [CDC]

<http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine.htm#hpvvac6>

In June 2006, the Advisory Committee on Immunization Practices (ACIP) voted to recommend the first vaccine developed to prevent cervical cancer and other diseases in females caused by certain types of genital human papillomavirus (HPV). The vaccine, Gardasil®, protects against four HPV types, which together cause 70% of cervical cancers and 90% of genital warts.

The Food and Drug Administration (FDA) recently licensed this vaccine for use in girls/women, ages 9-26 years. The vaccine is given through a series of three shots over a six-month period.

Cost (\$120/shot + \$80 administration) x 3 shots x 100,000 = \$6 million

MA: 700,000 females age 9-26 = \$42 million

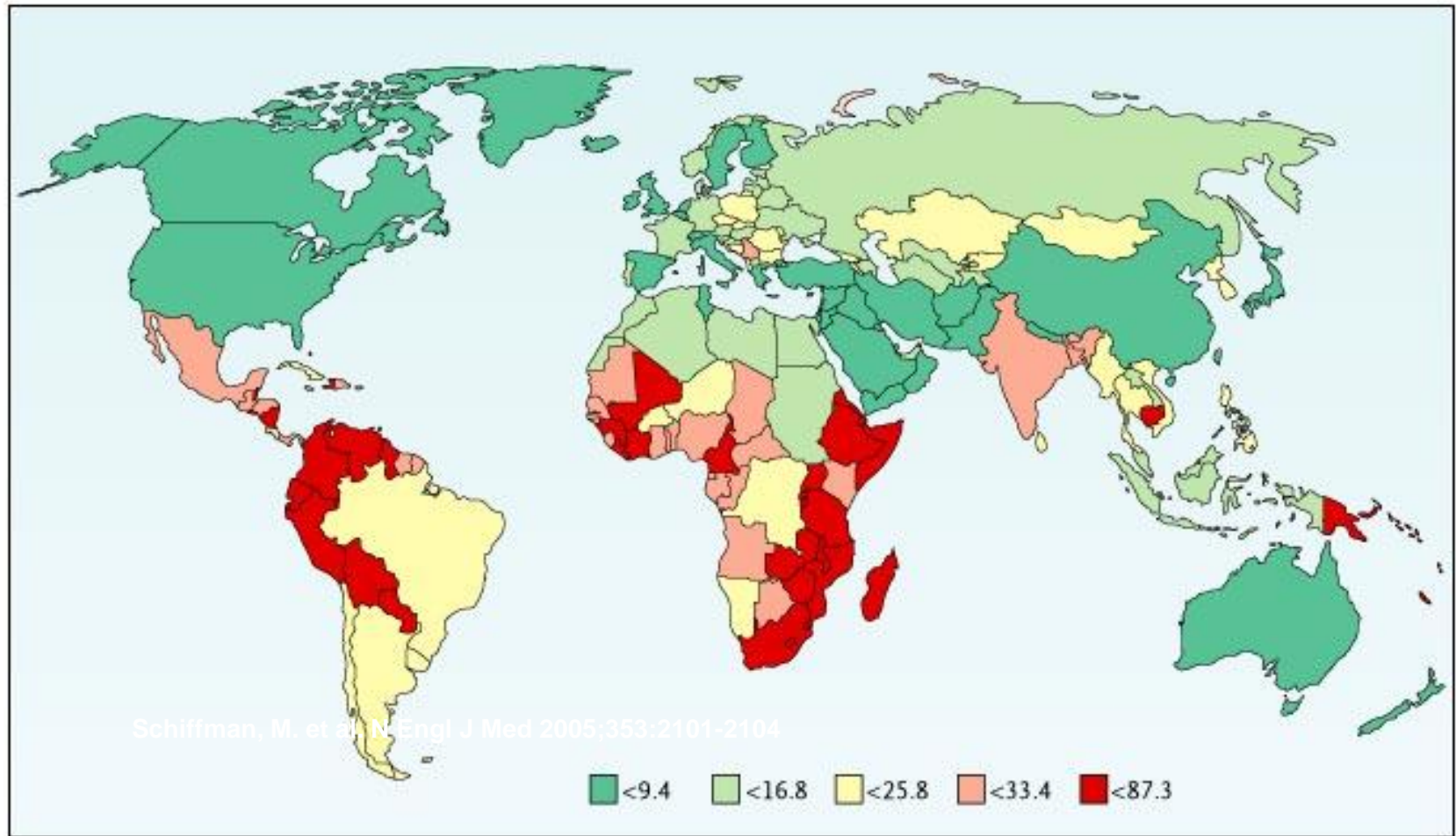
Cost (\$120/shot + \$80 administration) x 3 shots x 100,000 = \$6 million

MA: 700,000 females age 9-26 = \$42 million

Lives saved?

Money saved?

Incidence of Cervical Cancer Worldwide



HPV In Developing Countries

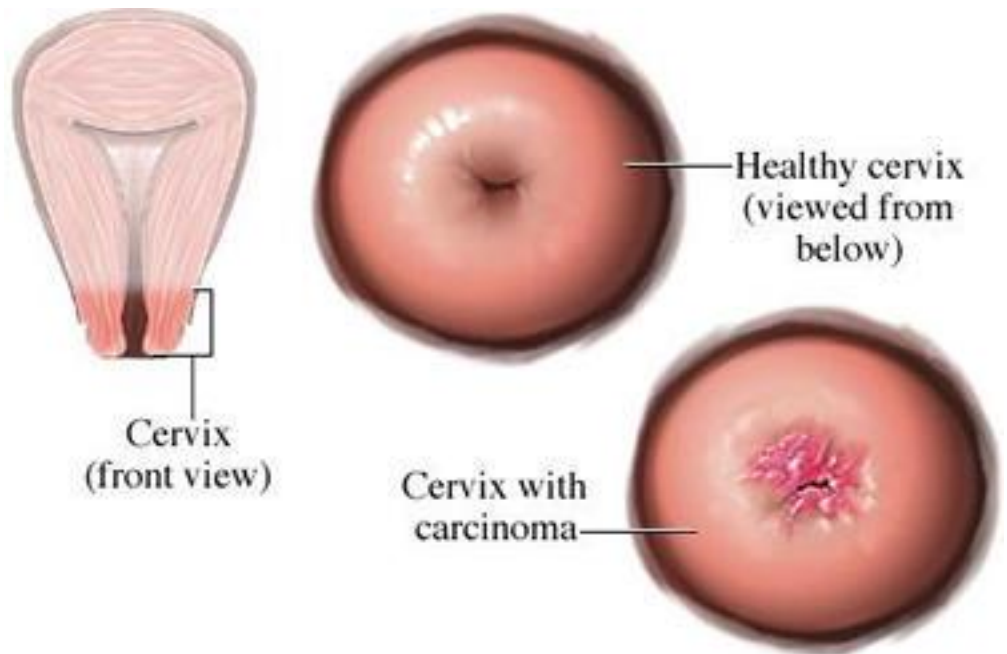
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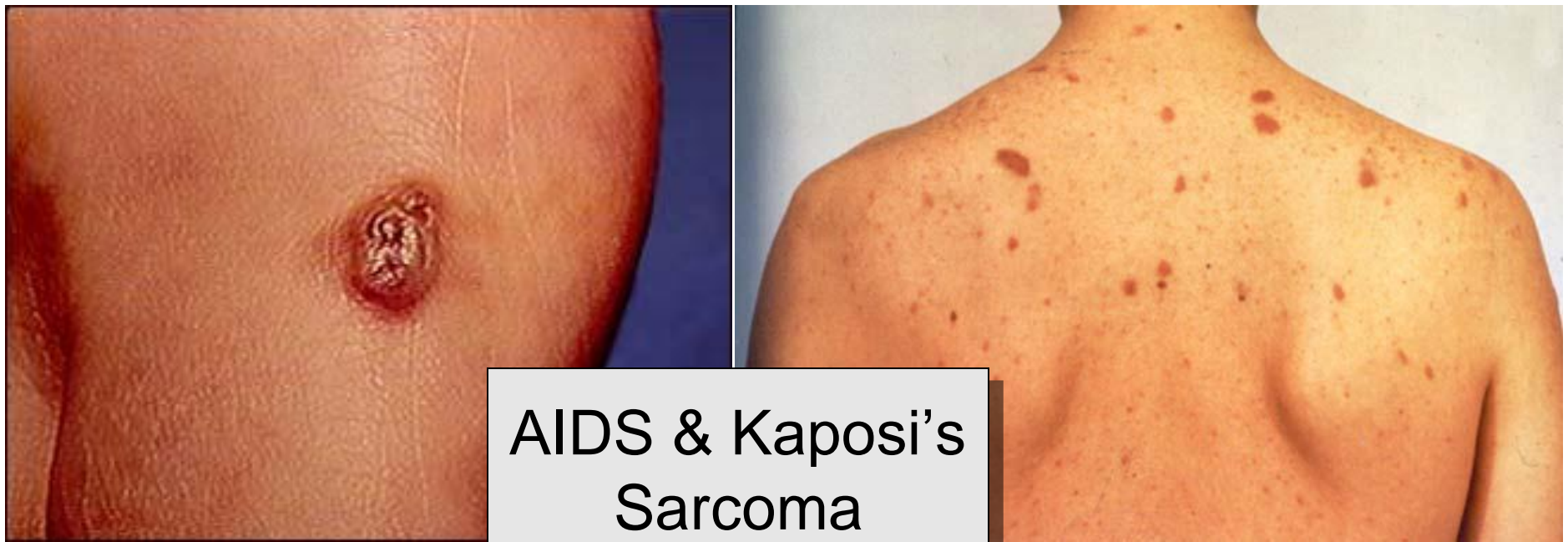
In developing countries many women do not receive timely treatment for cervical dysplasia & CIS.

- There are barriers to Pap testing.
- Lack of trained providers and equipment.
- There are long delays in reading & reporting results.
- It may be difficult to locate the patient once the report is available.
- Treatment is not affordable for many women.

An Alternative To Pap Smear

- A dilute solution of acetic can be applied to the cervix for unmagnified (naked eye) visual inspection to detect dysplasia (VIA).
- Results are immediate and treatment or referral can be initiated at the same visit.
- *The Lancet* reported 77% sensitivity and 64% specificity (comparable to Pap).
- Nurse-midwives quickly learned the test.





AIDS & Kaposi's Sarcoma

- Those with AIDS are at high risk for developing Kaposi's sarcoma, a malignant tumor of blood vessels in the skin.
- Kaposi's is not directly caused by HIV infection. Instead, the immune deficiency makes people more susceptible to other viral infections. Infection by KSHV (Kaposi's sarcoma-associated herpes virus) initiates development of Kaposi's sarcoma.

Mutagenic Ionizing Radiation

- Protons, neutrons, x-rays, & gamma rays have highly energetic wavelengths that can damage DNA with a direct hit. However, more often they damage DNA indirectly by striking other molecules and creating free radicals by stripping away electrons to create a highly reactive “ion”. In turn, the resulting **free radicals** damage other molecules by stealing their electrons.
 - Free radicals can break phosphate bonds in DNA. Breaks in a single strand can be repaired easily, but sometimes double strand breaks are not.
 - Ionizing radiation is very dangerous because its high energy allows it to penetrate deeply into tissue leaving a trail of free radicals in its path.
 - It also has a cumulative mutagenic effect.
 - Lead shields block these forms of radiation.
- **Examples:** cancer caused by nuclear fallout (Chernobyl; Hiroshima & Nagasaki); tongue and jaw cancer from exposure to radioactive chemicals.

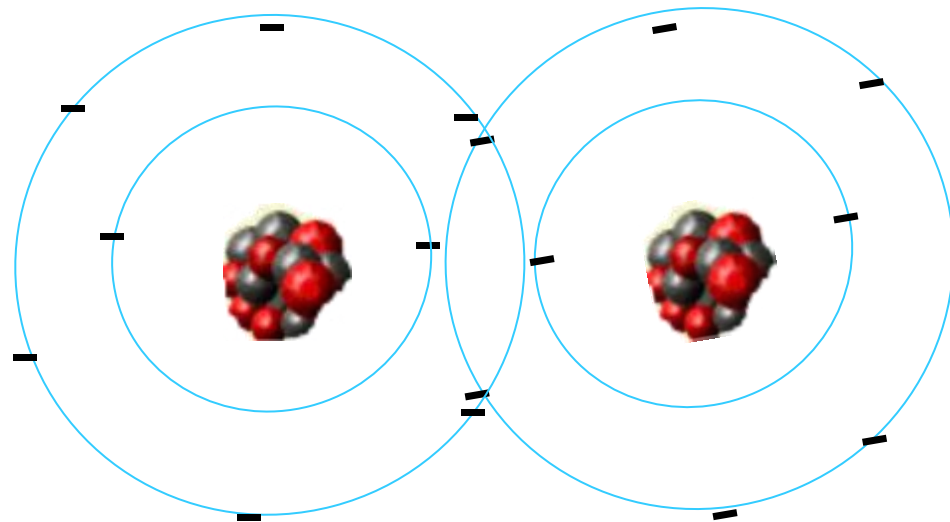
Free Radicals: Chemicals with Unpaired Electrons

Free radicals seek electrons to complete their unpaired electrons. When they steal electrons from normal molecules, it is called “oxidation”.

Lipid peroxidation: A free radical can pull off a hydrogen atom (with its only electron) from polyunsaturated fatty acids, so the fatty acid has an unpaired electron and becomes a *peroxyl radical*, which can attack another fatty acid setting off a chain reaction.

Free radicals are part of life, e.g. the immune system produces free radicals to fight bacteria and viruses, and cells use free radicals to communicate, but large quantities are damaging.

Oxygen gas (O_2) sharing 2 pairs of electrons.



Radon

Radon, a potential hazard in the home, is a radioactive gas that can seep into houses from underground rock formations. Simple test kits for radon are available.

[EPA: A Citizen's Guide to Radon - The Guide to Protecting Yourself and Your Family From Radon](#)

FYI

How Does Radon Get Into Your Home?

How to Test Your Home

How to use a test kit

What Your Test Results Mean

Radon and Home Sales

Radon in Water

How to Lower the Radon Levels in Your Home

The Risk of Living With Radon

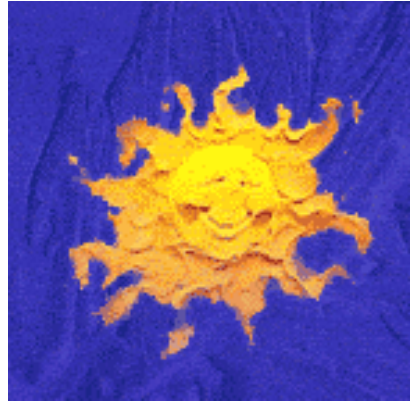
Radon Risk Charts

Radon Myths

For Further Information

Hotlines

Mutagenic Non-ionizing Radiation (Ultraviolet Light)

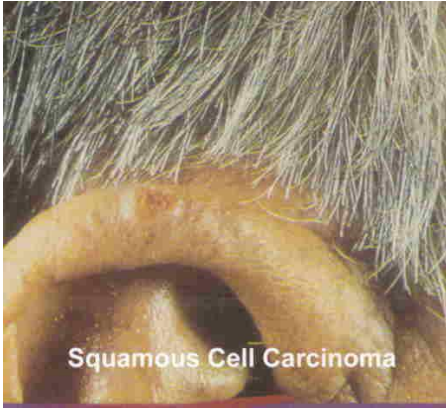
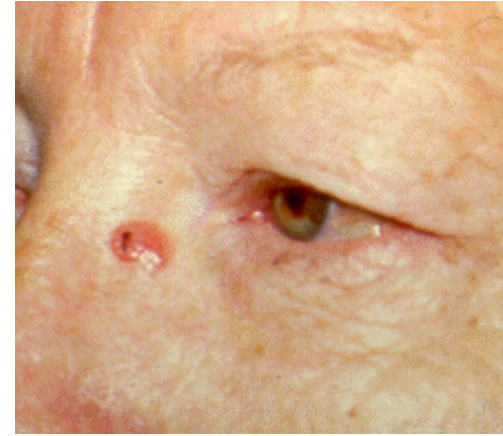


Non-ionizing radiation is not energetic enough to penetrate deeply or to create free radicals. It only penetrates single-celled organisms and the superficial cell layers of multicellular organisms. Its energy is sufficient to boost the energy of electrons in molecules.

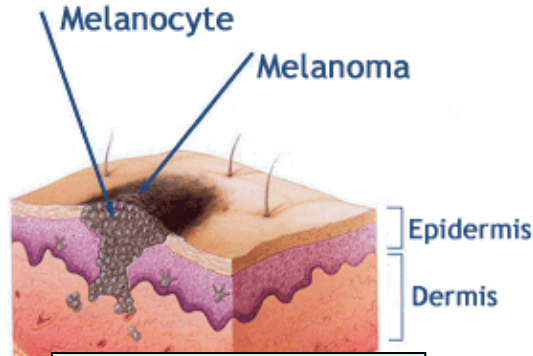
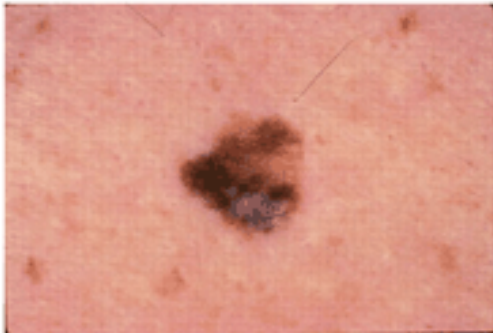
- Nucleotides of DNA absorb this energy (maximum mutagenesis occurs at 234 nm). Excitation of nucleotides can induce abnormalities such as formation of bulky thymine dimers that cause mutations by interfering with proper base pairing during replication.
- UV light is the most significant source of mutagenic non-ionizing radiation and is responsible for most skin cancers.



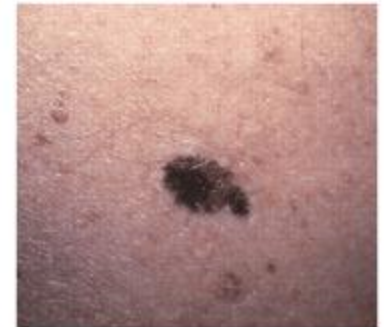
Basal Cell Carcinomas



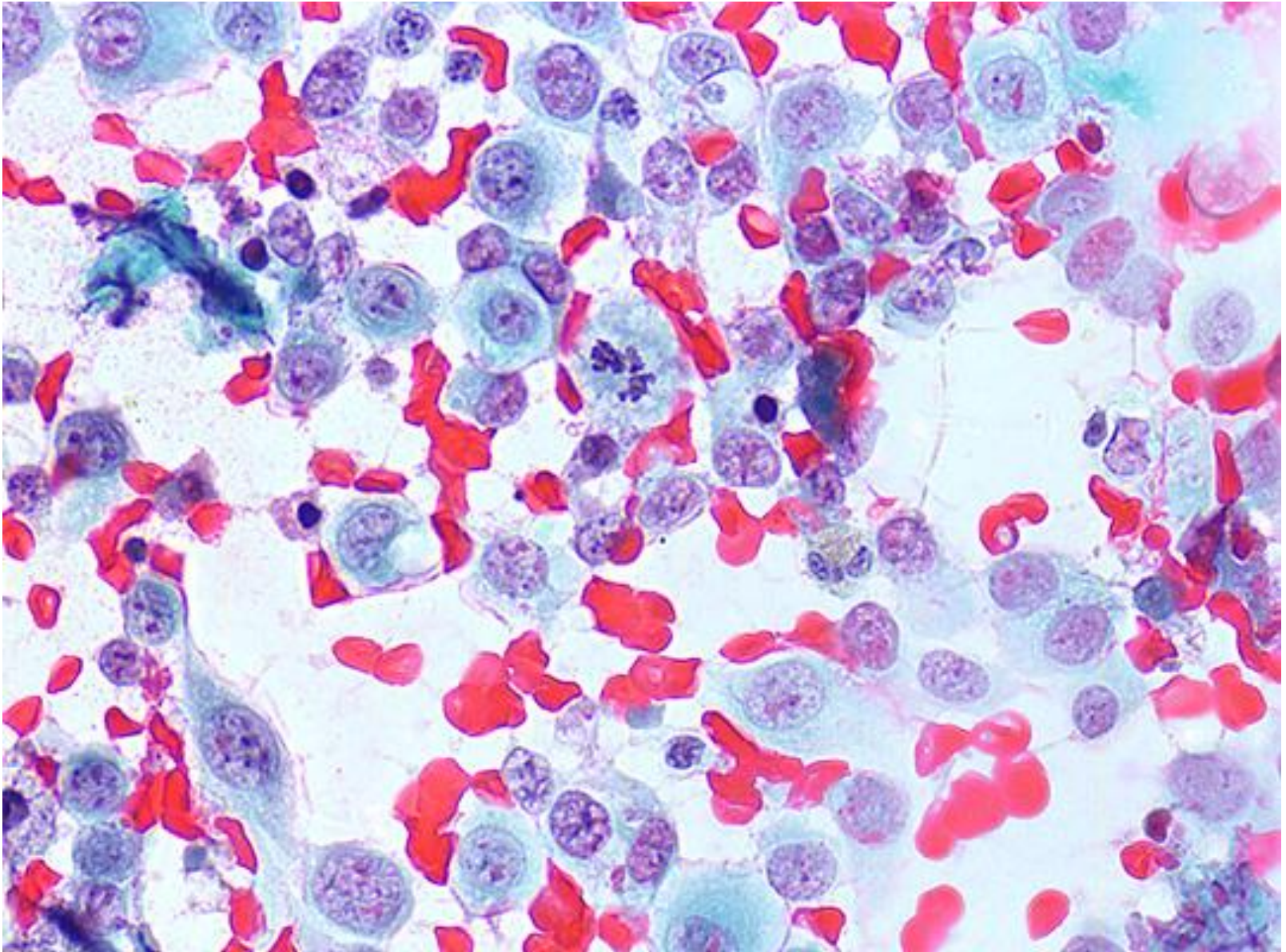
Squamous Cell Carcinomas



Melanomas



Malignant Melanoma



Chemical Carcinogens

- Cigarette smoke contains more than two dozen different chemicals capable of causing cancer.
- Cigarette smoking is the main cause of lung cancer and contributes to many other kinds of cancer (mouth, larynx, esophagus, stomach, pancreas, kidney, and bladder).
- Current estimates suggest that smoking cigarettes is responsible for at least one out of every three cancer deaths, making it the largest single cause of death from cancer.

Industrial Pollutants & Cancer

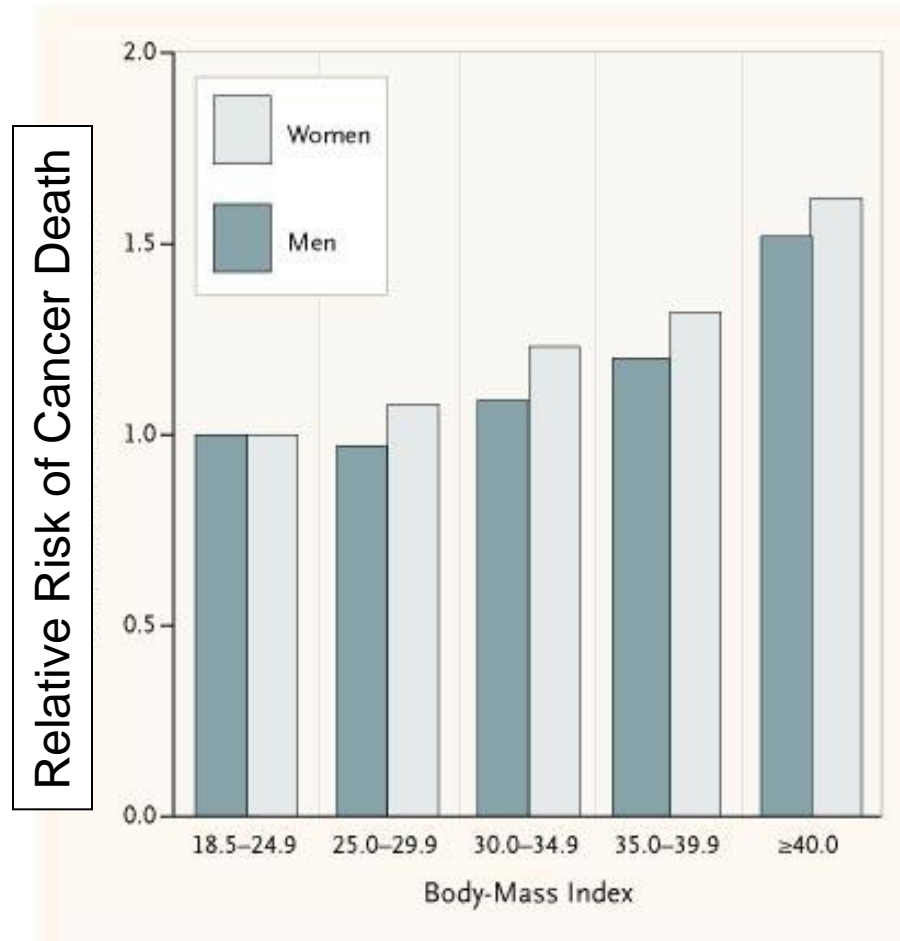
“The fact that many environmental chemicals can cause cancer has fostered the idea that industrial pollution is a frequent cause of cancer. However, the frequency of most human cancers (adjusted for age) has remained relatively constant over the past half century, in spite of increasing industrial pollution. Hence, in spite of evidence that industrial chemicals can cause cancer in people who work with them or in people who live nearby, industrial pollution does not appear to be a major cause of most cancers in the population at large.” - Source: **NIH**

However, some occupational carcinogens have been identified.

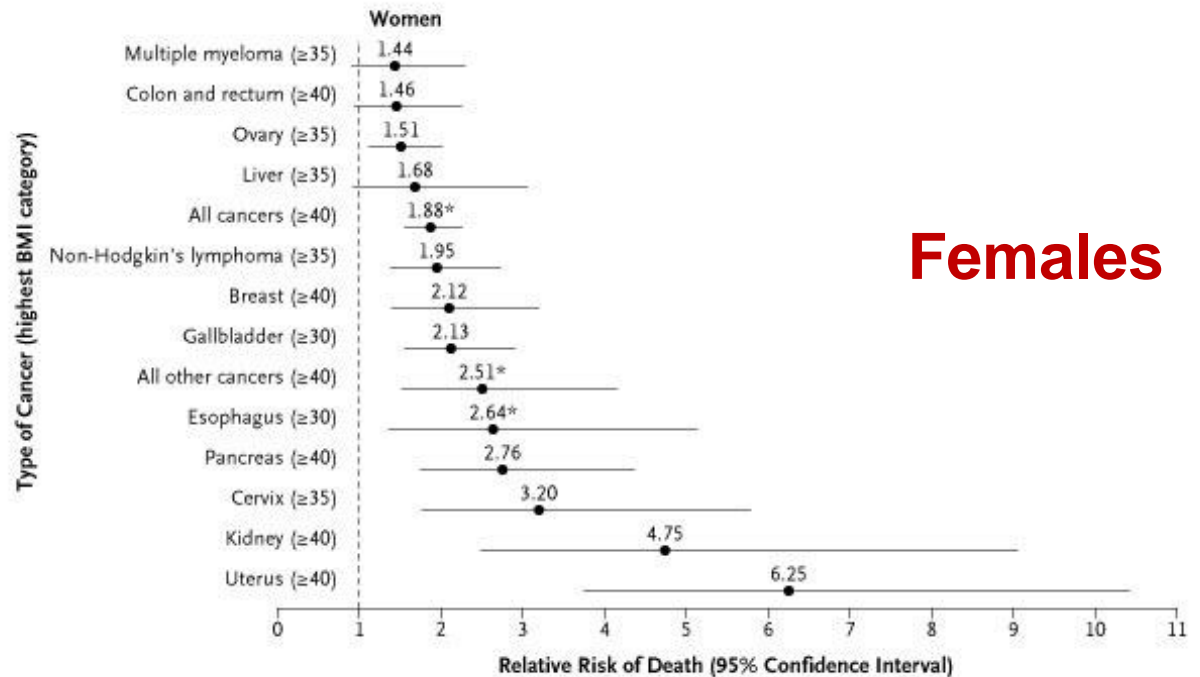
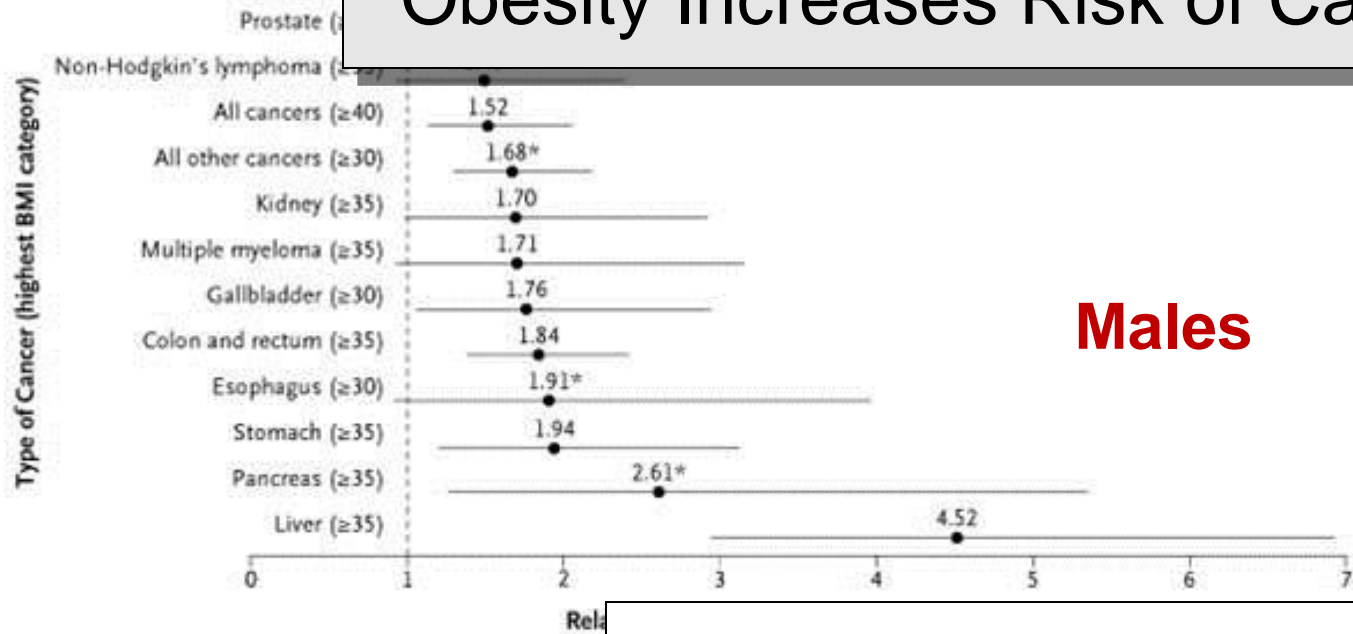
- Example: Occupational exposure to **asbestos** increase cancer risk increases by 10 times.

BMI & Cancer Mortality

Animals with energy intake 60% of ad lib have a considerably lower incidence of cancer. This holds true for viral, chemical, and spontaneous cancer.



Obesity Increases Risk of Cancer



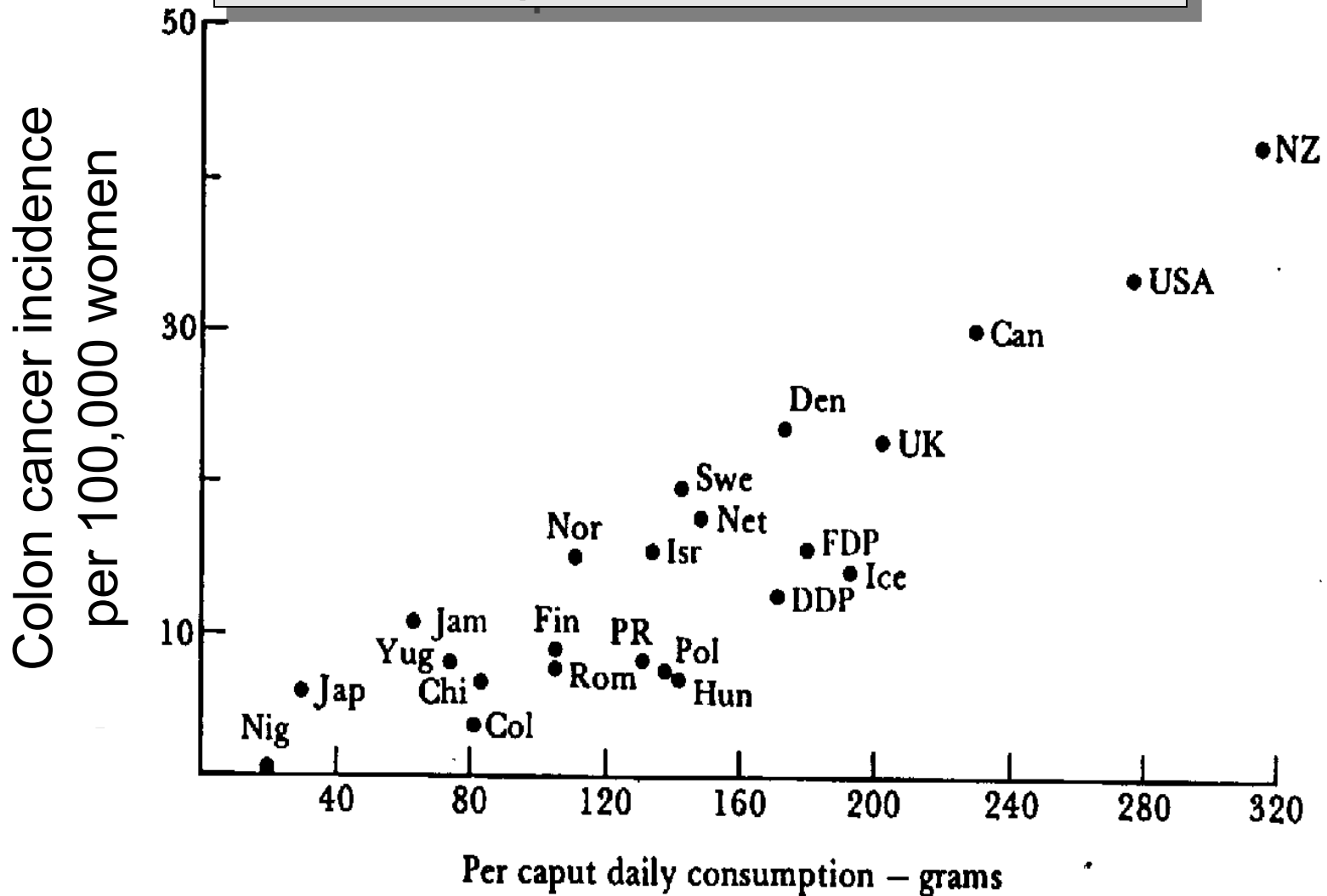
Free Radicals?

Diet and Cancer

Diet may also play a role in determining cancer risk, but unlike tobacco and sunlight, the exact dietary components that influence cancer risk are unclear.

- **Limiting fat & calorie intake** may decrease risk of some cancers (e.g. breast and colon cancer).
- **Consumption of fruits & vegetables** correlates with a reduction in cancer risk. The responsible components remain unknown, but many recommend at least 5 servings/day.

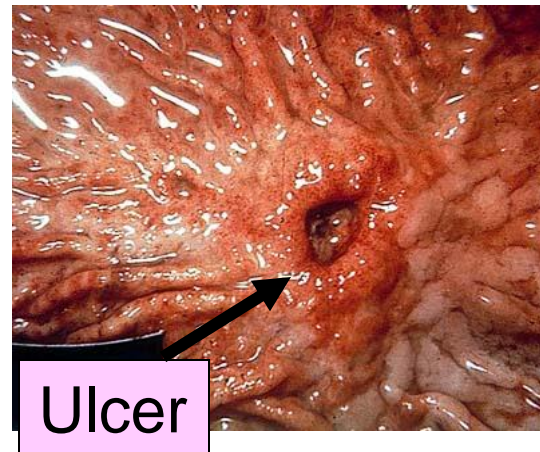
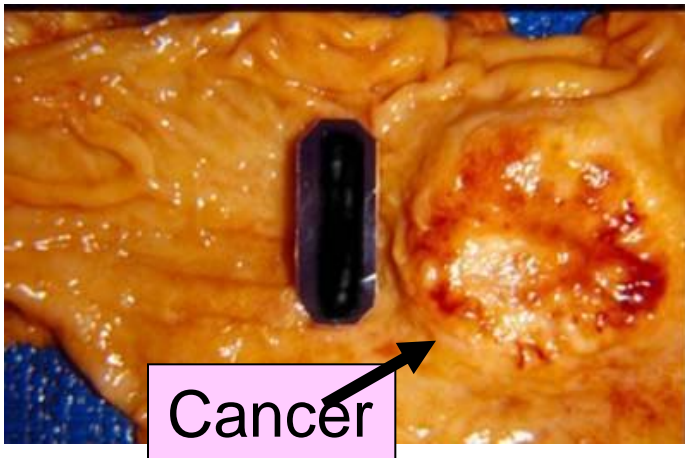
Correlation Between Meat Consumption & Colon Cancer



Average Meat consumption (in many people)

Helicobacter pylori & Stomach Cancer

The bacterium **H. pylori**, which can cause stomach ulcers, has been associated with the development of stomach cancer (but decreased esophageal cancer?). People infected with H. pylori are at increased risk of developing stomach cancer.



Stomach Cancer Mortality in Japanese

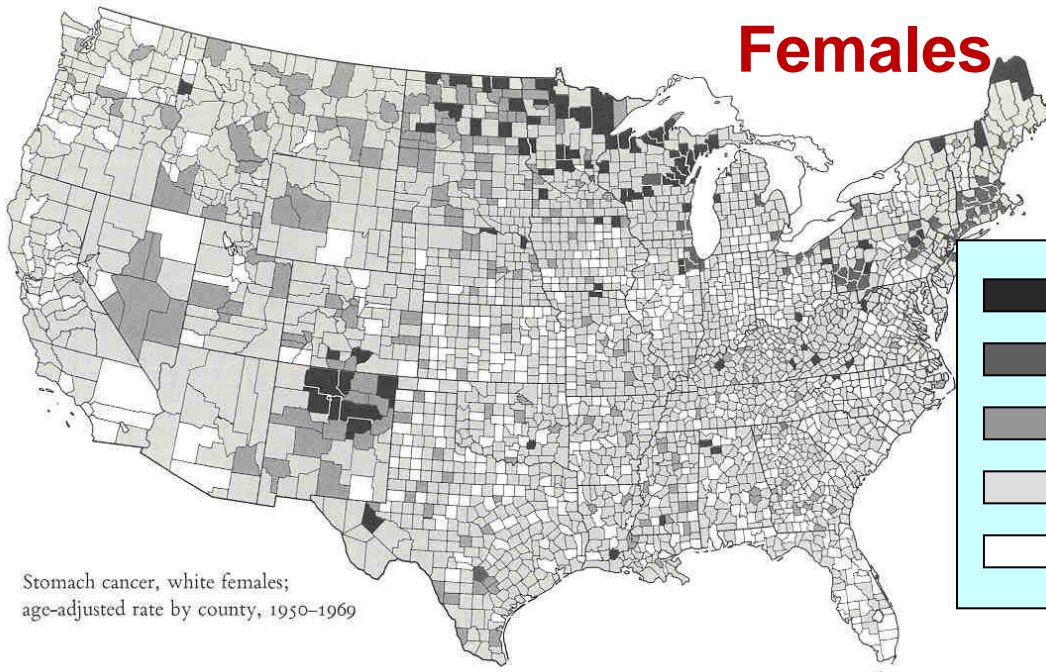
*Mortality /100,000 pop.
due to Stomach Cancer*

Japanese in Japan	58.4
Japanese immigrants to California	29.9
Sons of Japanese immigrants	11.7
Native Californians (Caucasians)	8.0

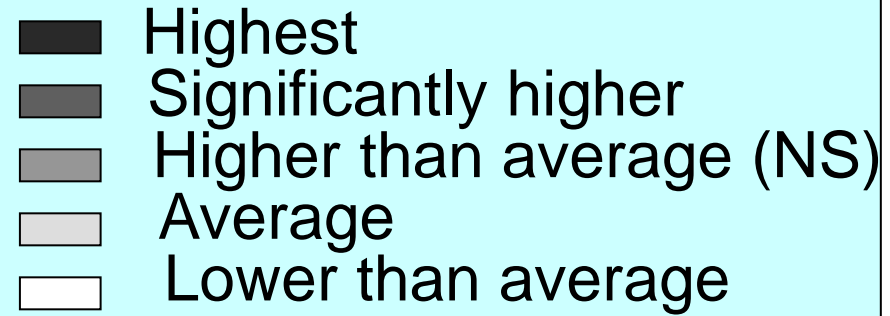
The highest rates of gastric (stomach) cancer are seen in Japan, Chile, and Iceland.

Stomach Cancer

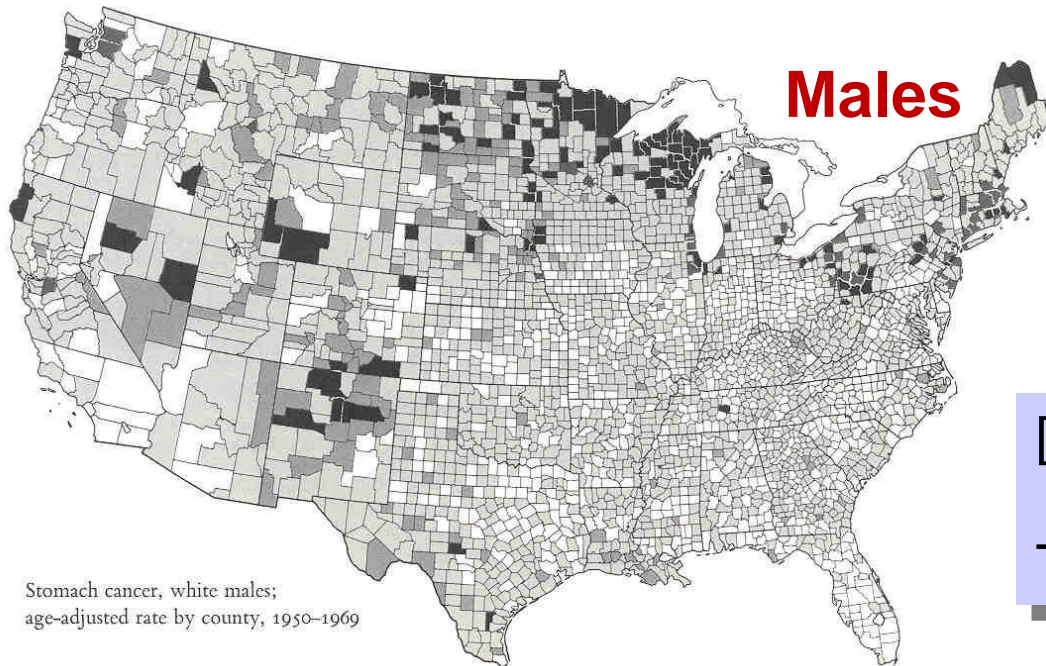
Females



Stomach cancer, white females;
age-adjusted rate by county, 1950-1969



Males



Stomach cancer, white males;
age-adjusted rate by county, 1950-1969

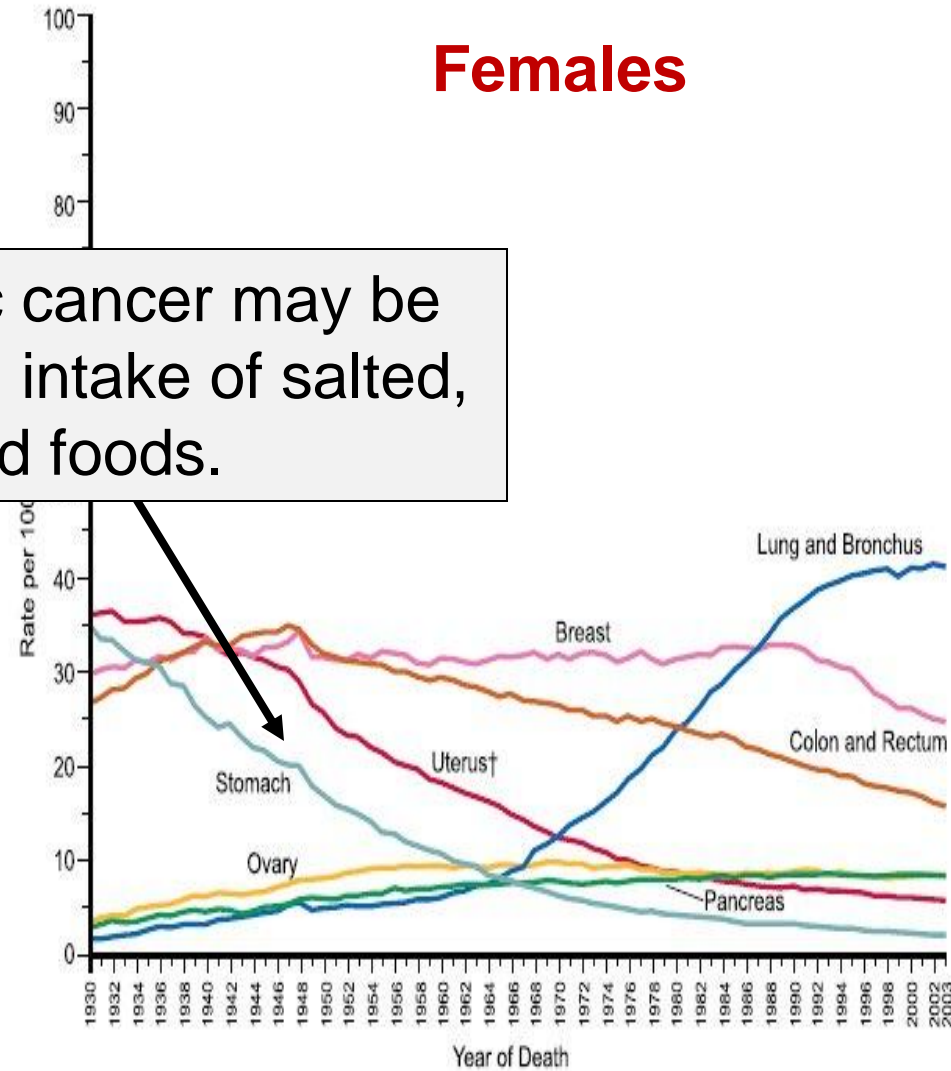
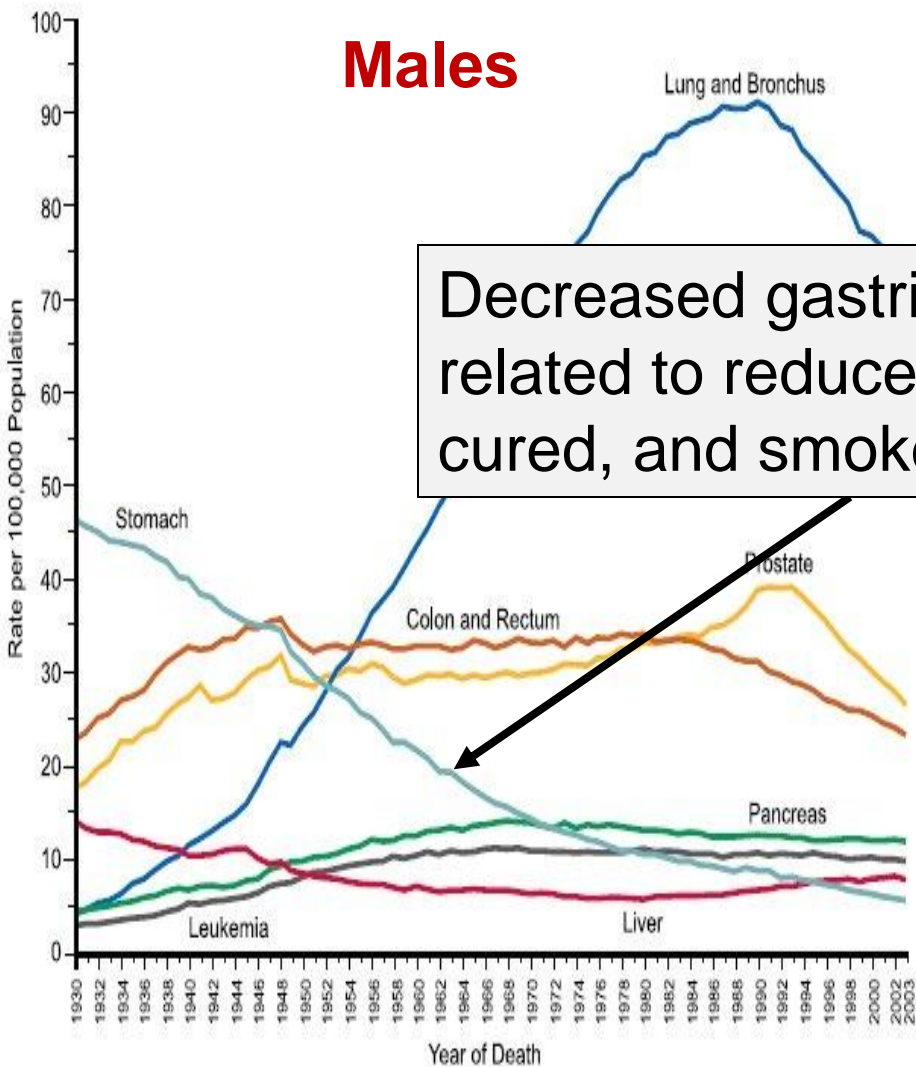
[from *Atlas of Cancer Mortality for
U.S. Counties: 1950-1969*,
TJ Mason et al, PHS, NIH, 1975

Cancer Rates

Males

Females

Decreased gastric cancer may be related to reduced intake of salted, cured, and smoked foods.



Risk Factors For Stomach Cancer

Mutations in the p53 tumor suppressor gene are found in 50-60% of gastric carcinomas.

- Age > 55 (most patients are in their 60s or 70s)
- Helicobacter pylori infection
- Diet that includes:
 - large amounts of smoked foods
 - salted fish and meat
 - foods high in starch and low in fiber
 - pickled vegetables
 - foods and beverages that contain nitrates and nitrites (nitrosamines)
- Tobacco
- Alcohol abuse
- Pernicious anemia (caused by vitamin B12 deficiency)
- 2x more in males
- Blood type A

Heterocyclic Amines

Heterocyclic amines (HCAs) are a family of carcinogenic chemicals formed from the cooking of muscle meats (beef, pork, fowl, and fish); other sources of protein have not been associated with HCAs (e.g. eggs, tofu).

HCAs form when amino acids and creatine (a chemical found in muscles) react at high cooking temperatures. Frying, broiling, and barbecuing produce the largest amounts of HCAs because the meats are cooked at very high temperatures. They have been associated with an increased risk of stomach, colorectal, and pancreatic cancer.

- People eating well-done beef had 3x risk of stomach cancer compared to those who ate beef rare or medium-rare.
- People who ate beef 4+ times/week had 2x the risk of stomach cancer than those consuming beef less frequently.
- Also, increased risk of colorectal, pancreatic, and breast cancer in those with high intakes of well-done, fried, or barbequed meats.

FYI

Alcohol & Cancer

- Excessive alcohol consumption is associated with increased risk for cancers of the mouth, throat, esophagus, and breast.
- The combination of alcohol and tobacco appears to be especially dangerous for oral and esophageal cancer.
 - For example, in heavy smokers or heavy drinkers, the risk of developing cancer of the esophagus is 6x greater than that for nonsmokers/nondrinkers, but those who smoke **and** drink have >40 times the risk of nonsmokers/nondrinkers. (effect modification; synergism; interaction)

Hormones and Cancer

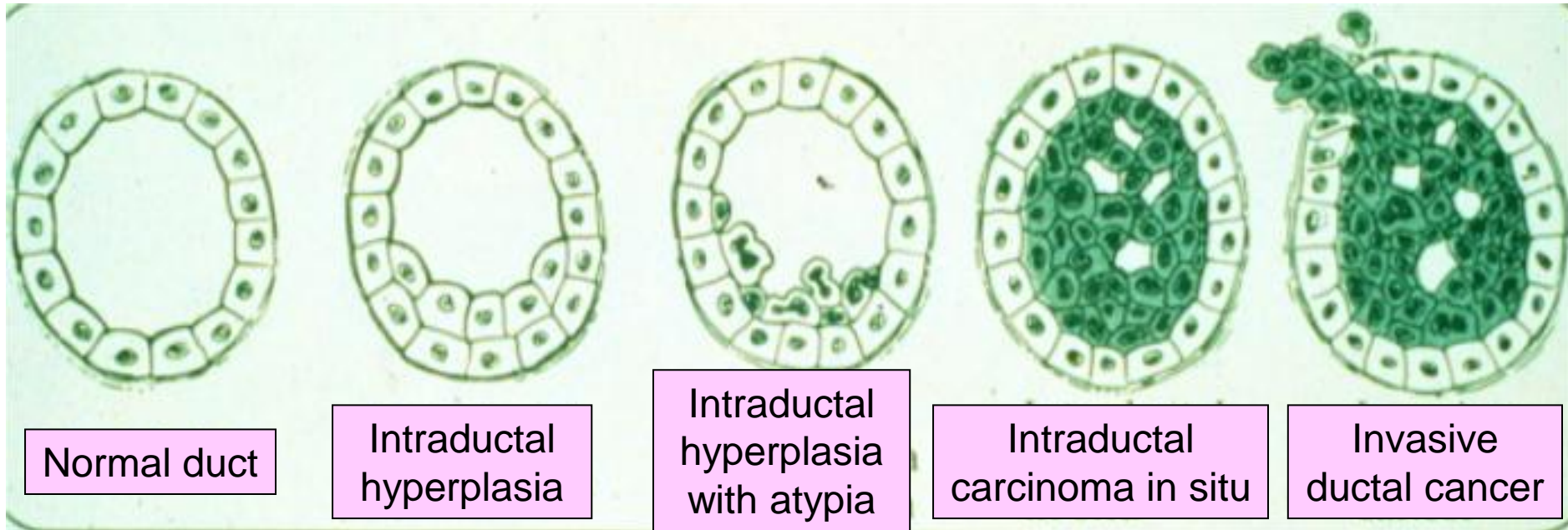
Estrogens stimulate growth of breast tissue and appear to have a role in the development & growth of breast cancer.

- Estrogens promote the development of mammary cancer in rodents.
- They also stimulate proliferation of human breast cancer cells grown in cell culture.

Tumor formation may result from excessive hormonal stimulation of cells whose normal growth and function are under endocrine control.

- Tumor initiation may occur directly via activation of oncogenes ...
- or indirectly by stimulating secretion of other hormones (e.g. prolactin) and production of growth factors (e.g., transforming growth factor and epidermal growth factor).

Normal...Hyperplasia... Neoplasia



Cumulative exposure of breast tissue to estrogen may increase risk of breast cancer by accelerating progression from normal to hyperplasia to cancer.

Predicting Risk Of Breast Cancer: 6 Key Factors

- Age
- Age at menarche (onset of menstrual cycle)
- Age at first live birth
- # of 1st degree relatives (mother, sister(s), and/or daughters) with breast cancer
- # of previous breast biopsies (whether + or -)
- Previous biopsy with atypical hyperplasia

Other risk factors such as age at menopause, dense breast tissue on a mammogram, use of birth control pills or hormone replacement therapy, high-fat diet, alcohol, physical activity, obesity, or environmental exposures are not included on this list either because evidence is inconclusive or the increased risk they pose is small and has not been accurately calculated.

Tamoxifen

Tamoxifen is a drug that has an **estrogen-blocking effect in the breast**, but *estrogen-like* effects on some other tissues, e.g. uterus & bone.

The Breast Cancer Prevention Trial studied effect of Tamoxifen for 5 years in a large group of women at increased risk. Women ages 35 and older who took a daily dose of 20 mg Tamoxifen for up to 5 years had 50% reduction in risk of breast cancer.

- In women ages 35-49, risk of serious side effects was similar to placebo.
- Over age 50 there was increased risk of uterine cancer and blood clots when taking Tamoxifen.

Perspective: The Risk Of Breast Cancer

TABLE 1. LIFE TABLE FOR A BIRTH COHORT OF 1000 WOMEN ACCORDING TO FIVE-YEAR AGE INTERVALS.*

AGE (YR)	NO. ALIVE AT BEGINNING OF INTERVAL	NO. OF INCIDENT BREAST CANCERS	NO. OF DEATHS FROM BREAST CANCER	NO. OF DEATHS FROM CARDIOVASCULAR CAUSES†	NO. OF DEATHS FROM OTHER CAUSES
0-4	1000	0	0	0	6
5-9	994	0	0	0	1
10-14	993	0	0	0	1
15-19	992	0	0	0	1
20-24	991	0	0	0	1
25-29	990	0	0	0	2
30-34	988	1	0	0	2
35-39	986	3	0	0	3
40-44	983	5	1	1	4
45-49	977	8	2	1	6
50-54	968	11	3	2	11
55-59	952	12	3	5	15
60-64	929	12	3	9	25
65-69	892	14	4	16	36
70-74	836	13	5	28	51
75-79	752	11	6	52	70
80-84	624	9	6	89	95
≥85	434	5	7	224	203

Consider risk in the context of competing risks.

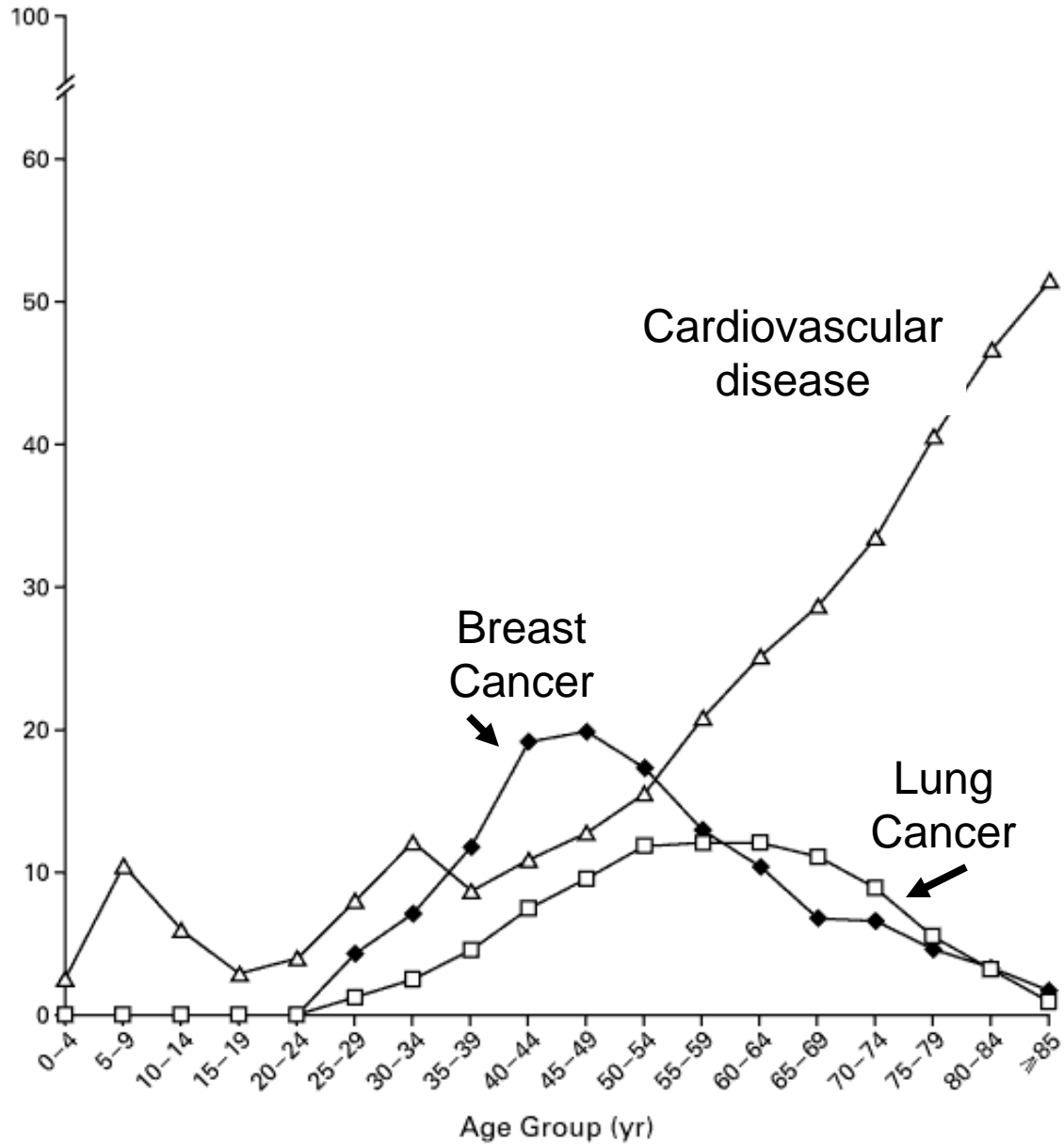
* 1995 incidence and mortality rates in the Ontario Cancer Registry.

† Includes deaths from all causes except breast cancer.

104 40 427 533

FYI

% of Women Dying



For each group, the value is the % of the total number of deaths among women in that age group. The proportion of deaths due to breast cancer never exceeded 20%.

Heredity & Cancer

Risk of cancer can be influenced by inheritance, but, overall, 85-90% of cancers occur in people with no family history.

Breast cancer:

- 85% of breast cancers are 'sporadic' i.e. non-familial, non-hereditary.
- Women with a family history have increased risk for breast cancer & increased risk of early cancer.
- 50% of *familial* breast cancer is linked to inherited mutation in one of two oncogenes" (**BRCA1 & BRCA2**). BRCA1 also linked to increased risk of ovarian cancer.

- Other inherited mutations increase risk of colon, kidney, bone cancer, or skin cancer, but all together these probably account for less than 10% of cancers.
- Genetic testing: Genetic tests are complex and difficult to interpret, & the decision to undergo genetic testing is a difficult one that should be made with appropriate genetic counseling.
 - E.g., women with a family history of breast cancer can be tested for BRCA1. A negative test would decrease anxiety but

Aging and Cancer

Chances of developing cancer increase with age because

- Mutations accumulate over time.
- Mechanisms for DNA repair are less effective with increasing age.

The perception of a “cancer epidemic” is probably primarily due to the fact that people are living longer and have longer exposures to risk factors and more time to accumulate mutations in somatic cells.

Overview of Carcinogenesis

