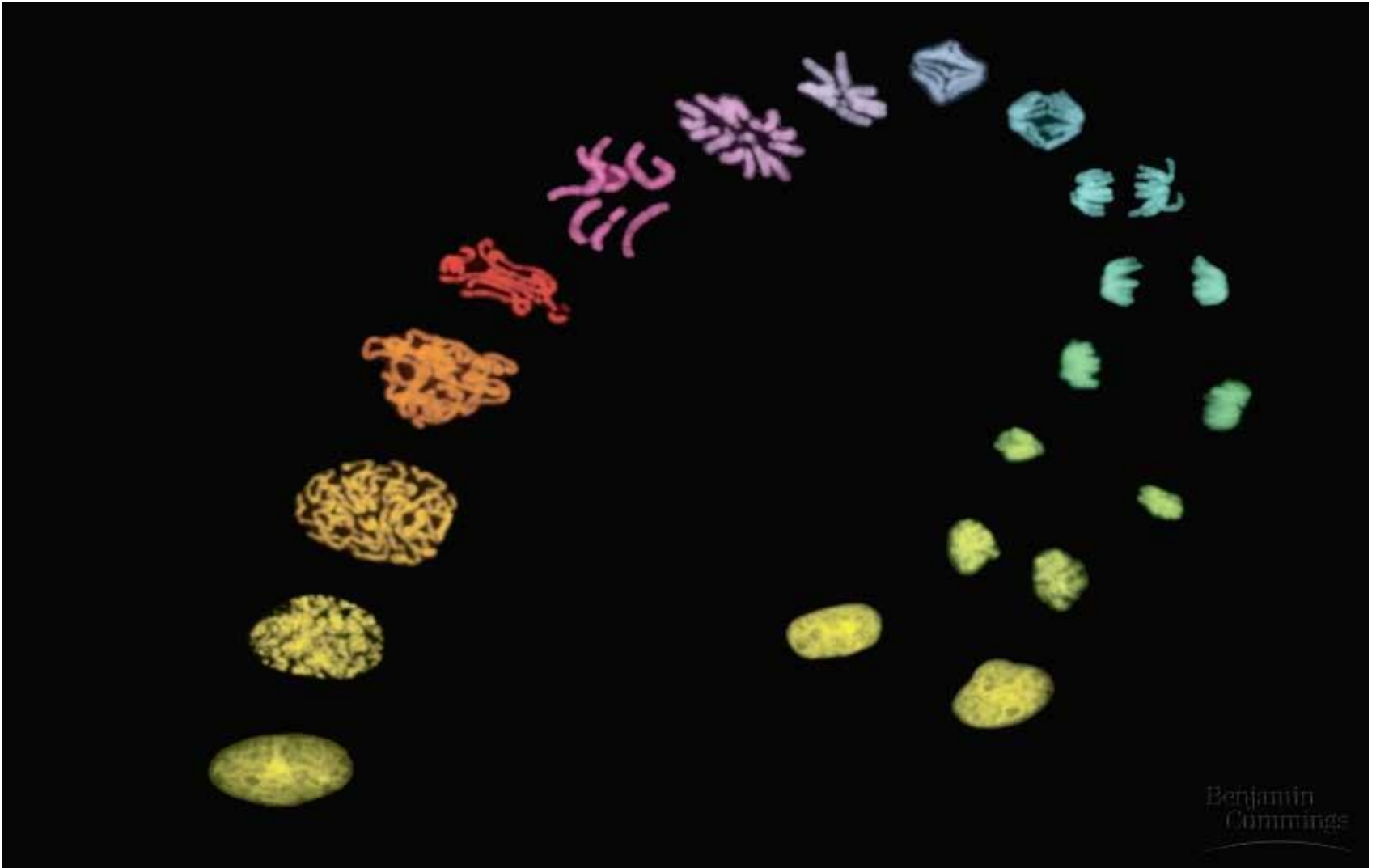


Cancer and the cell cycle, Origins of cancerous cells

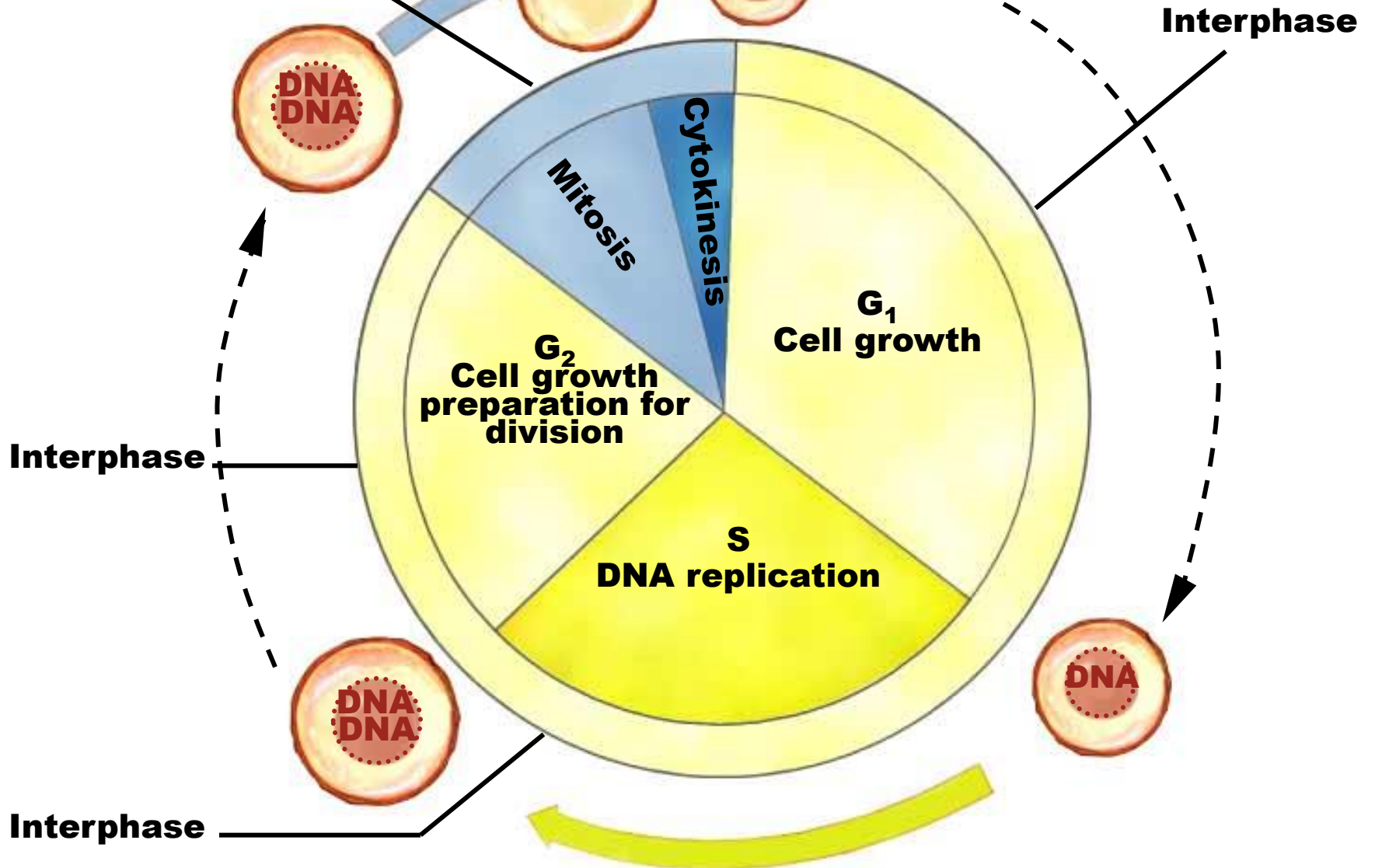


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Cummings



1. Cancer and the cell cycle
checkpoints, reqmts to advance
oncogenes
tumor suppressor genes
2. 6 Traits of cancerous cells
3. Origins of cancerous cells

Mitotic Phase (M)



- Proteins within the cell control the cell cycle
 - Signals affecting critical checkpoints determine whether the cell will divide (cyclins, kinases)

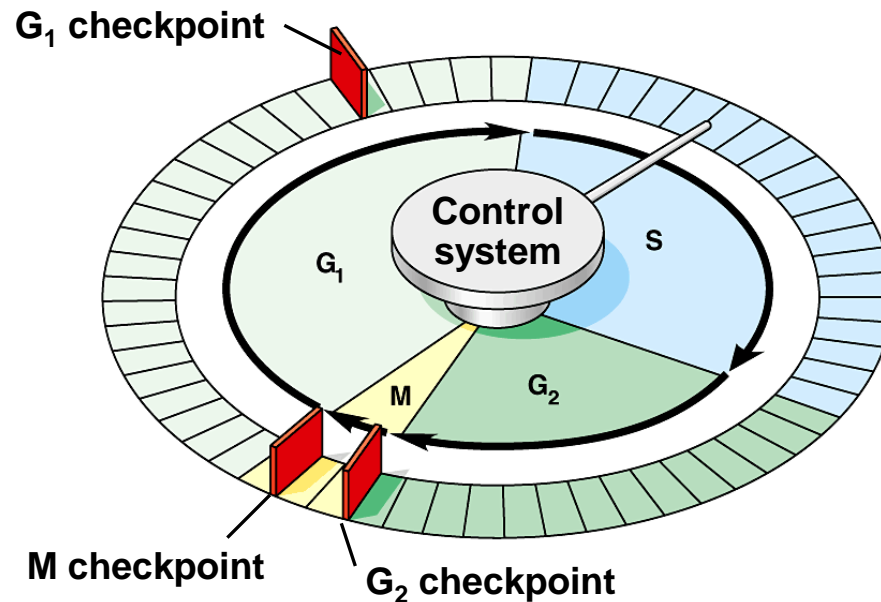


Figure 8.9A

Anchorage, cell density, and chemical growth factors affect cell division

- In laboratory cultures, normal cells divide only when attached to a surface
= anchorage dependent

- Cells continue dividing until they touch one another
= density-dependent inhibition

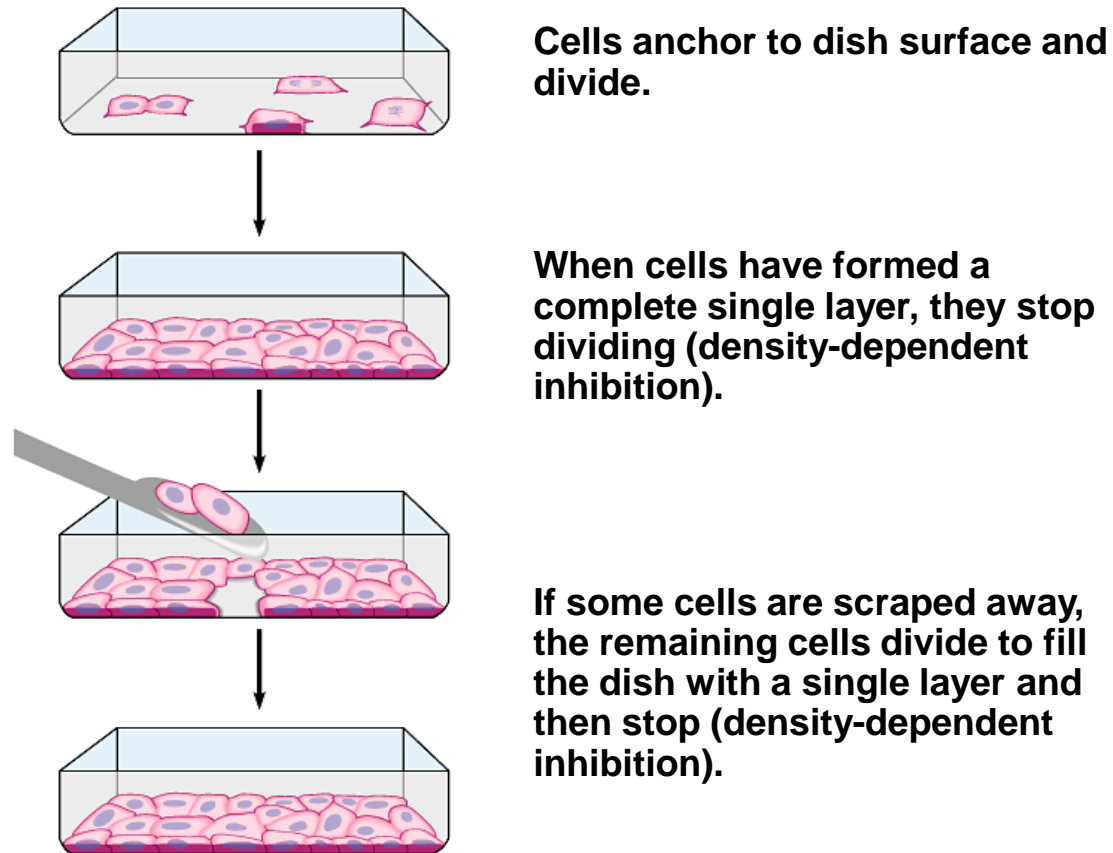
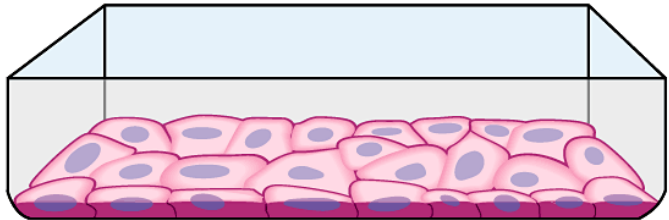
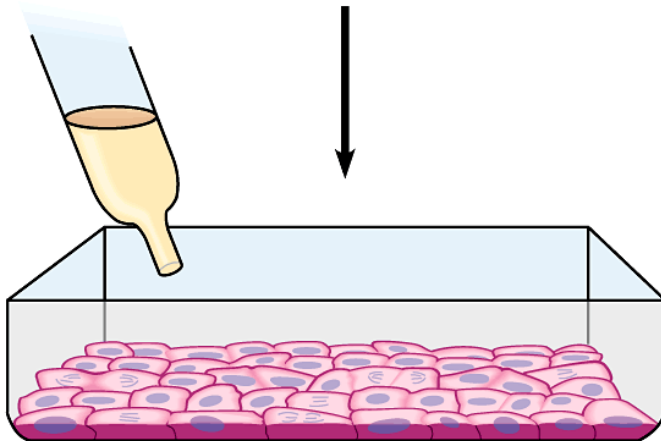


Figure 8.8A

- Growth factors are proteins secreted by cells that stimulate other cells to divide



After forming a single layer, cells have stopped dividing.



Providing an additional supply of growth factors stimulates further cell division.

Figure 8.8B

- Growth factors bind to specific receptors on the plasma membrane to trigger cell division

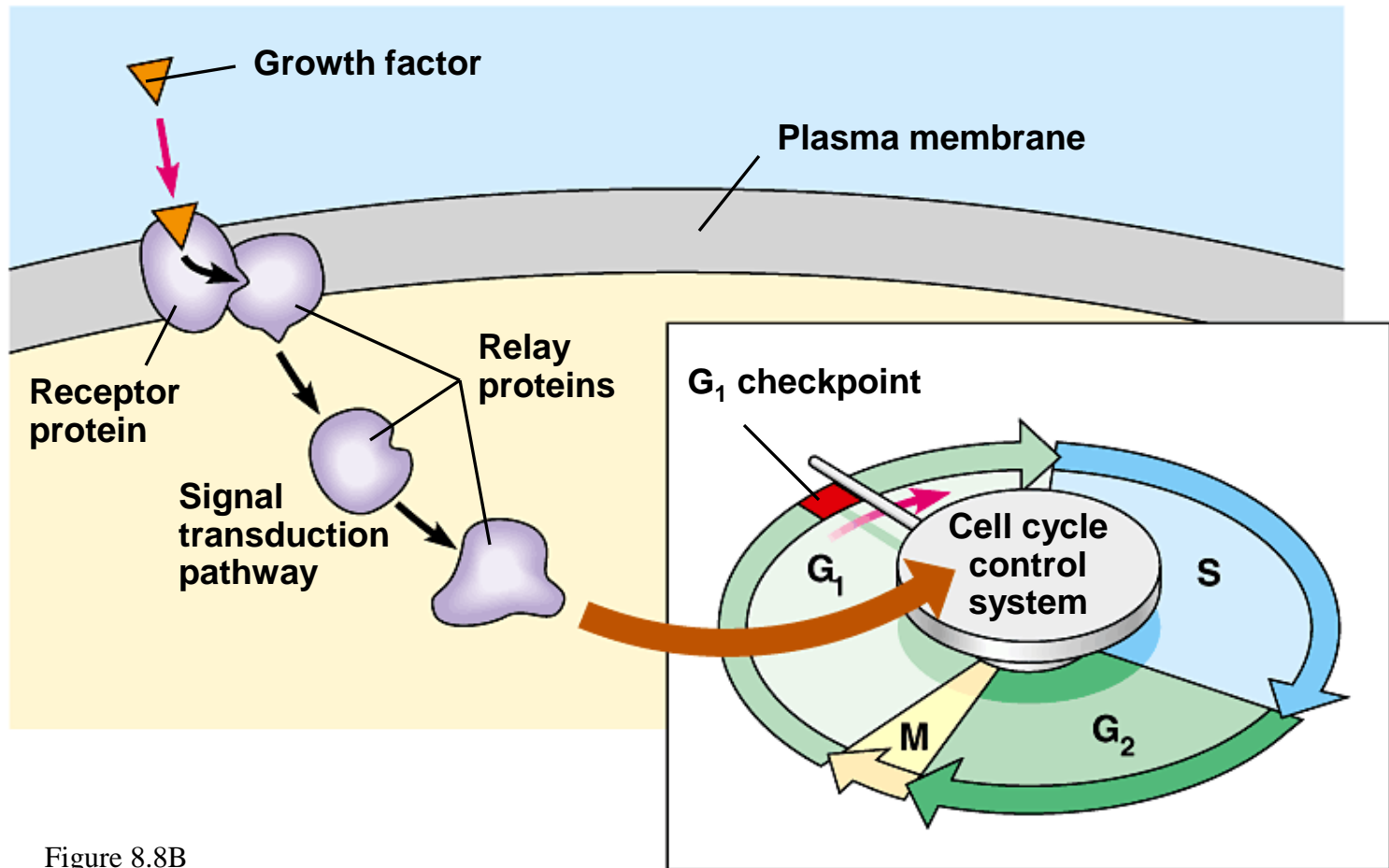
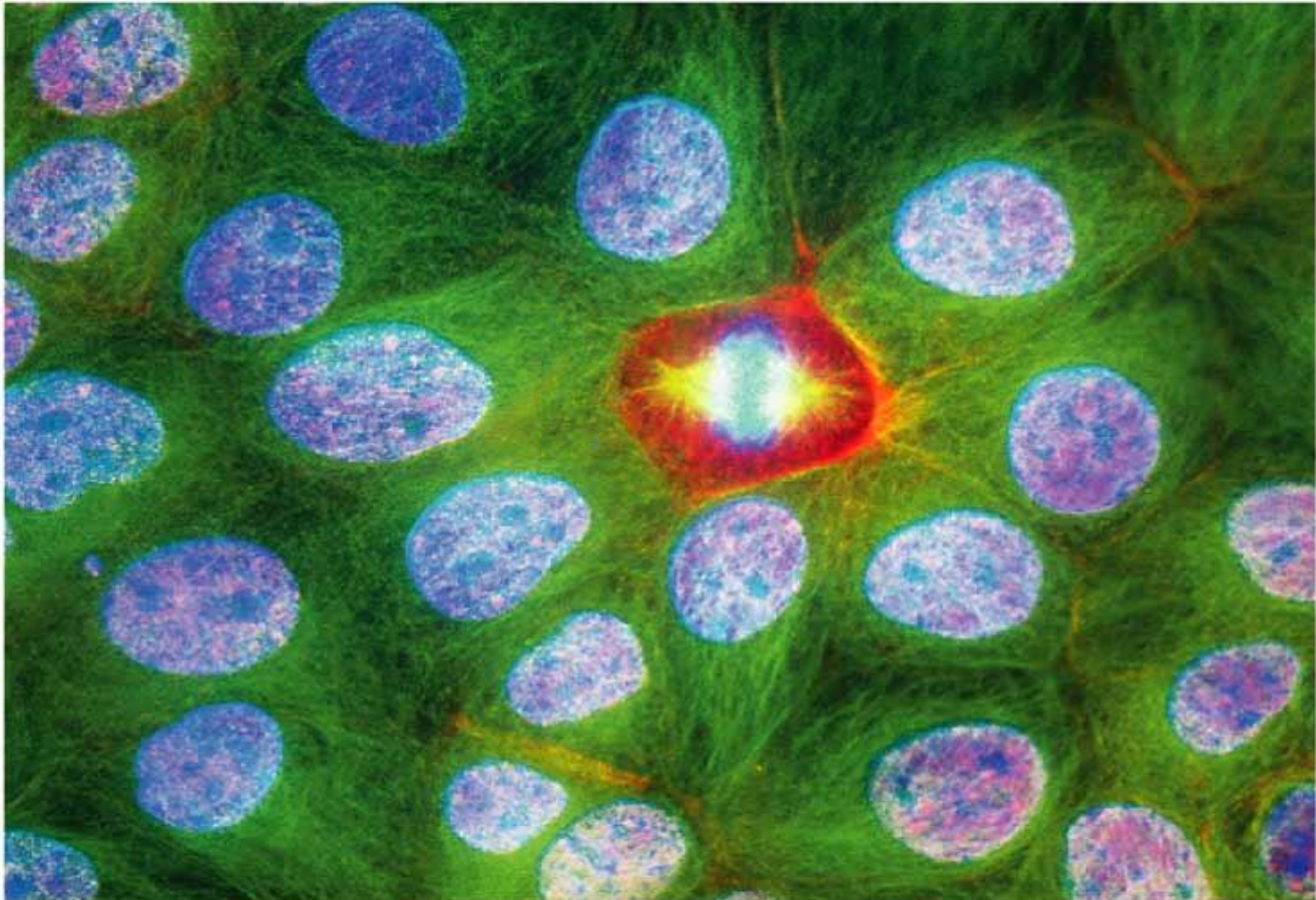


Figure 8.8B

- Cancer cells have abnormal cell cycles
 - divide excessively and form tumors



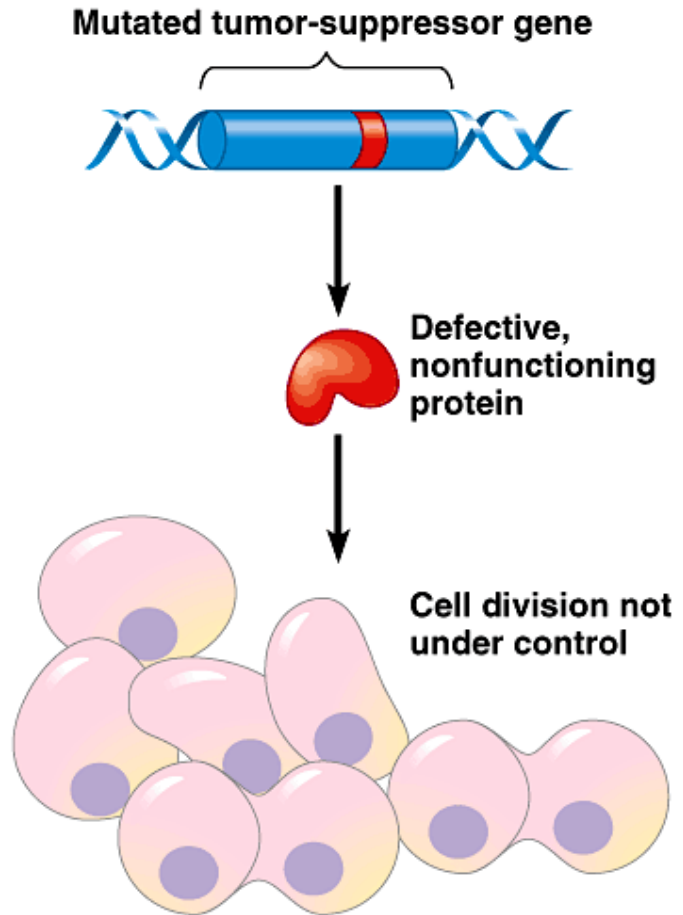
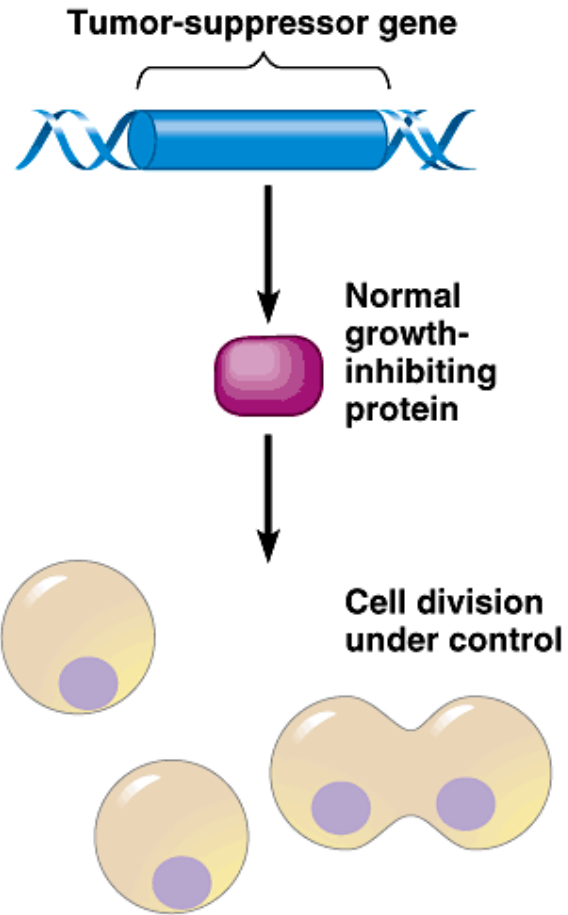
- Breast cancer cell - altered morphology



Figure 8.10x1

Traits of cancer cells

- 1. Independent of GROW signal from other cells often, oncogenes. Ex. *ras*
- 2. Ignores STOP signal
 defective damage control, so problems not corrected.
 Often, tumor suppressor genes. Ex. *p53*



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Traits of cancer cells, continued

- 3. No cell suicide (apoptosis)
If this occurs, treatments which damage dividing cells may not work.
- 4. No limit to cell divisions
telomeres rebuilt on ends of chromosomes
new treatment target: telomerase

Traits of cancer cells, continued

- 5. Angiogenesis - formation of blood vessels
- 6. Metastasis - ability to move to other tissues
benign: do not move from tumor site
malignant: invasive cells, can travel in blood and lymph system

- Malignant tumors can invade other tissues and may kill the organism

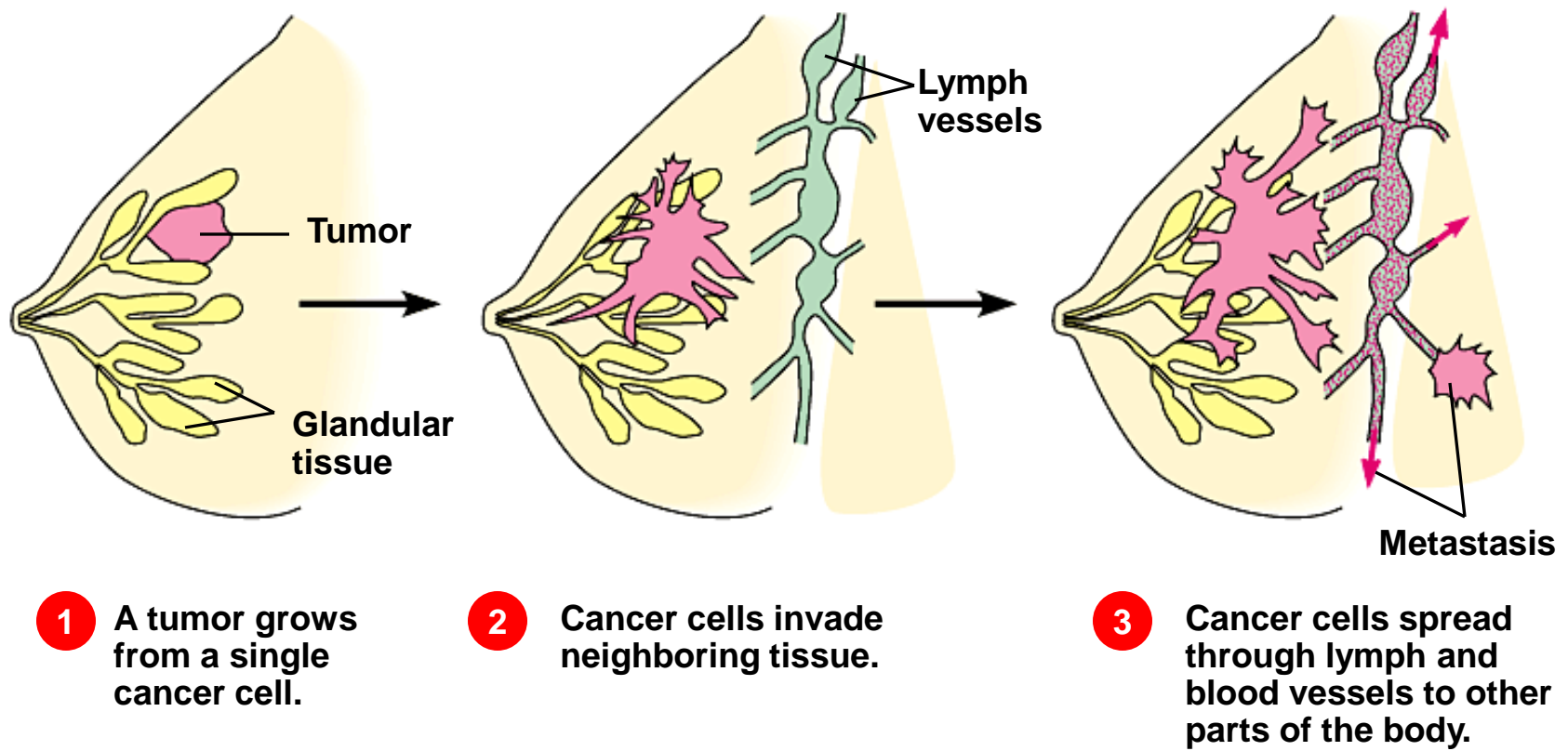
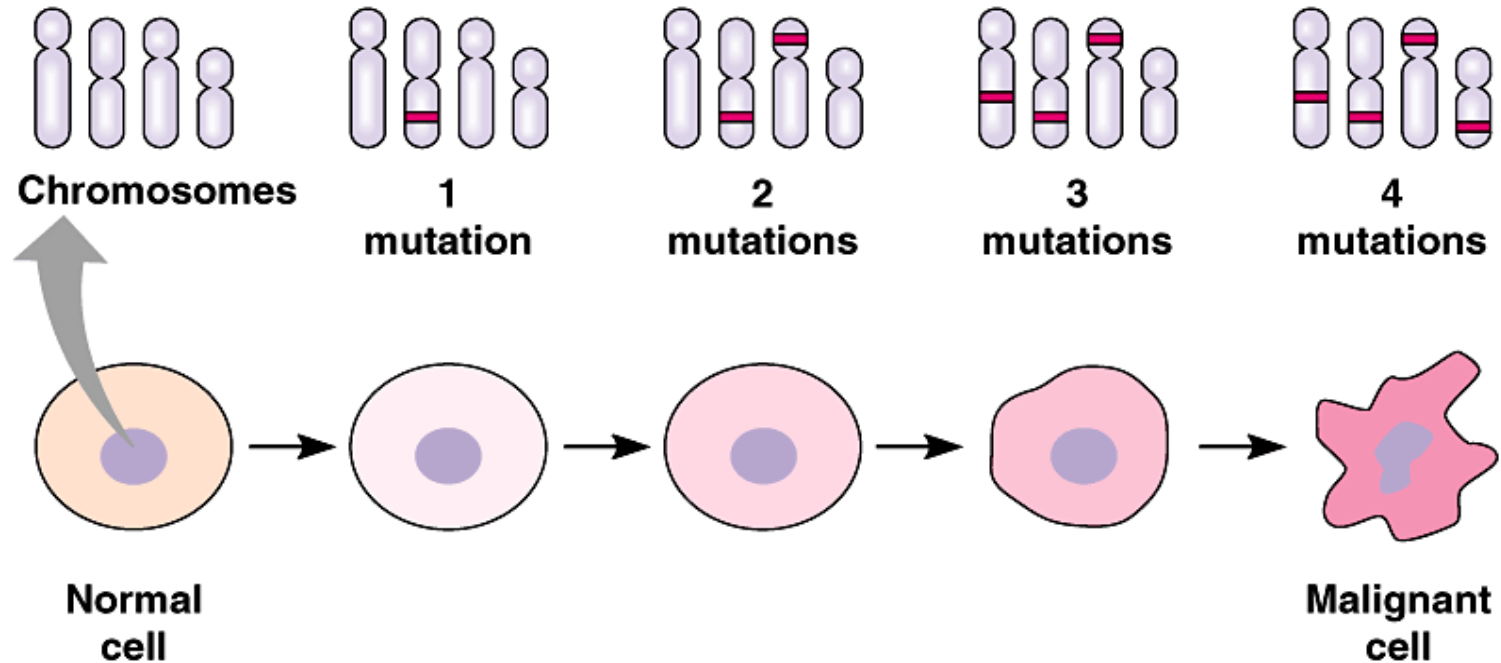


Figure 8.10

How do normal cells become cancerous?



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Selection within tumor for
“most cancerous” cells

What is the source of oncogenes?

- Mutation of a normal gene = change in DNA sequence
- UV light, Xrays, natural or synthetic chemicals
- Virus (ex. HPV and cervical cancer)

- Xsomal changes can be large or small

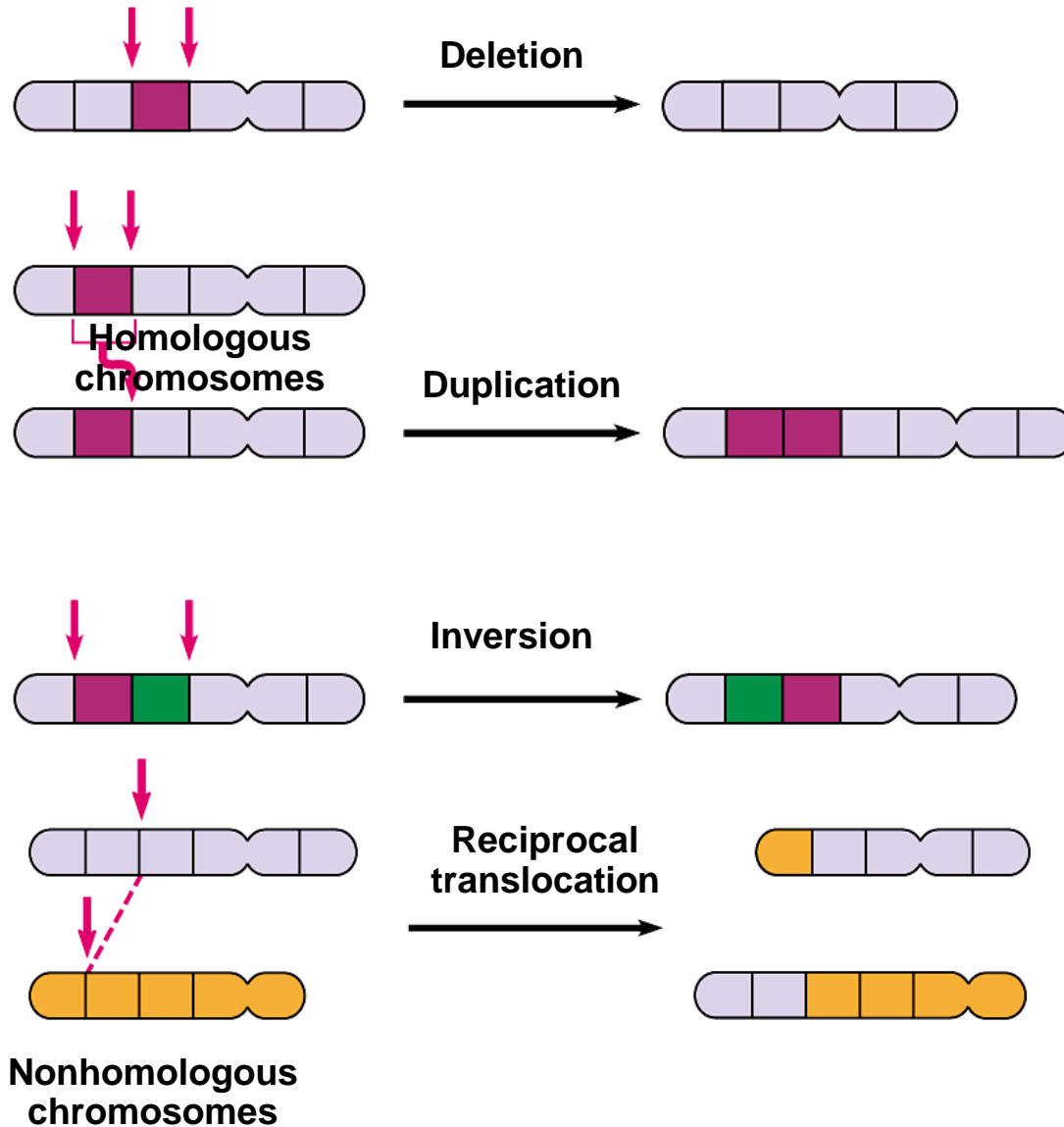
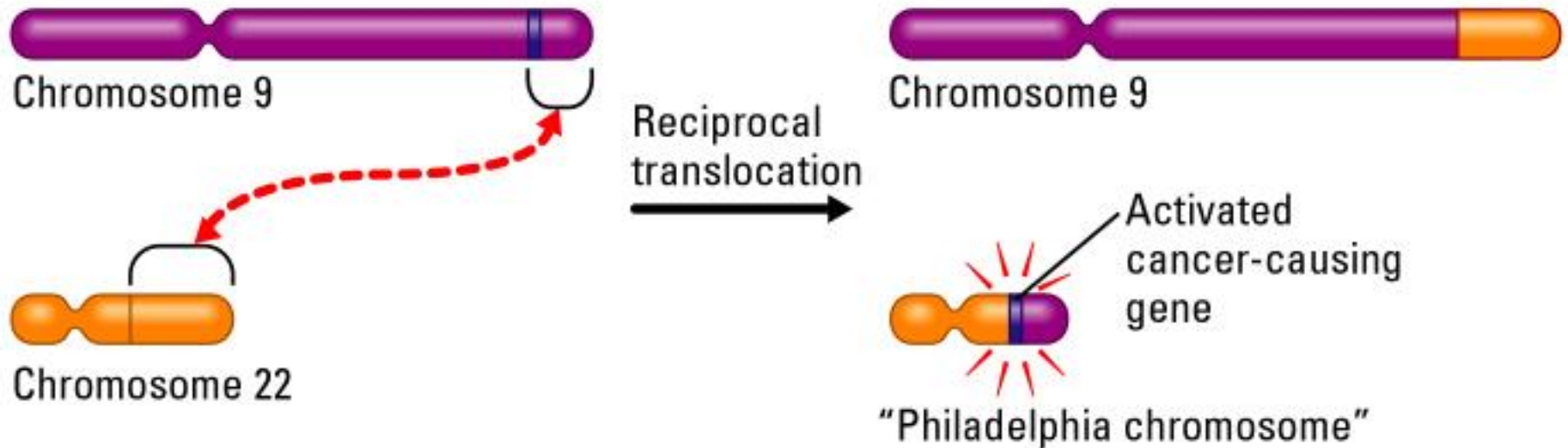


Figure 8.23A, B

Xsomal translocation can activate an oncogene



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A chromosomal translocation in the bone marrow is associated with chronic myelogenous leukemia

CANCER IN THE UNITED STATES

Cancer	Examples of Known or Likely Carcinogens	Estimated Number of Cases in 2002
Breast	Estrogen; possibly dietary fat	205,000
Prostate	Testosterone; possibly dietary fat	189,000
Lung	Cigarette smoke	169,000
Colon, rectum, and anus	High dietary fat; low dietary fiber	152,200
Lymphomas	Viruses (for some types)	60,900
Bladder	Cigarette smoke	56,500
Melanoma of skin	Ultraviolet light	53,600
Uterus	Estrogen	39,300
Kidney	Cigarette smoke	31,800
Leukemias	X-rays, benzene; virus (for one type)	30,800
Pancreas	Cigarette smoke	30,300
Mouth and throat	Tobacco in various forms; alcohol	28,900
Ovary	(Large number of ovulation cycles)	23,300
Stomach	Table salt; cigarette smoke	21,600
Brain and nerve	Trauma; X-rays	17,000
Liver	Alcohol; hepatitis viruses	16,600
Cervix	Viruses; cigarette smoke	13,000
All others		145,700

Cancer

- Cancer is one of the most common diseases in the developed world:
- 1 in 4 deaths are due to cancer
- 1 in 17 deaths are due to **lung cancer**
- Lung cancer is the most common cancer in men
- Breast cancer is the most common cancer in women
- There are over 100 different forms of cancer

Cancer

- The division of normal cells is precisely controlled. New cells are only formed for growth or to replace dead ones.
- Cancerous cells divide repeatedly out of control even though they are not needed, they crowd out other normal cells and function abnormally. They can also destroy the correct functioning of major organs.

What causes cancer?

- Cancer arises from the **mutation** of a normal gene.
- Mutated genes that cause cancer are called **oncogenes**.
- It is thought that several mutations need to occur to give rise to cancer
- Cells that are old or not functioning properly normally self destruct and are replaced by new cells.
- However, cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.

- A factor which brings about a mutation is called a **mutagen**.
- A mutagen is **mutagenic**.
- Any agent that causes cancer is called a **carcinogen** and is described as **carcinogenic**.
- So some mutagens are carcinogenic.

Carcinogens

- **Ionising radiation** – X Rays, UV light
- **Chemicals** – tar from cigarettes
- **Virus infection** – papilloma virus can be responsible for cervical cancer.
- **Hereditary predisposition** – Some families are more susceptible to getting certain cancers. Remember you can't inherit cancer its just that you maybe more susceptible to getting it.

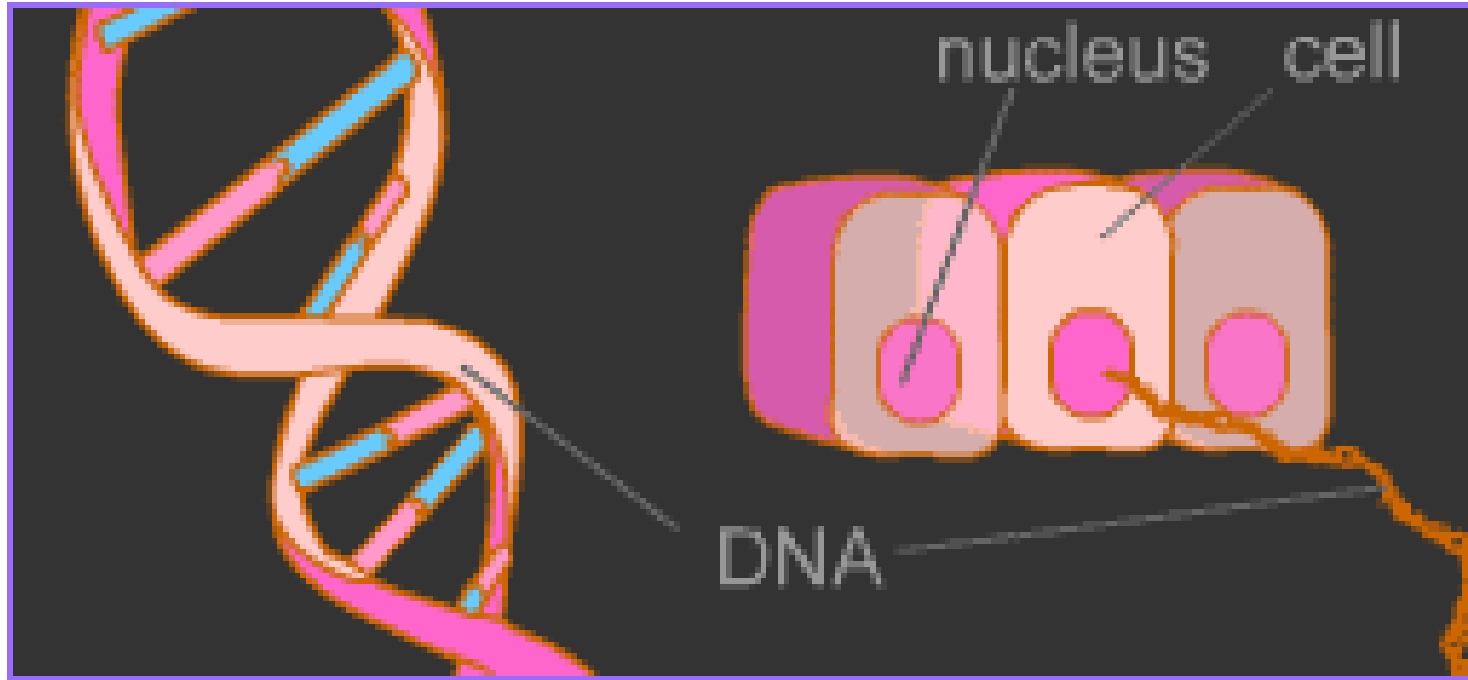
Types of tumour are Benign or malignant

- **Benign tumours** do not spread from their site of origin, but can crowd out (squash) surrounding cells eg brain tumour, warts.
- **Malignant tumours** can spread from the original site and cause secondary tumours. This is called metastasis. They interfere with neighbouring cells and can block blood vessels, the gut, glands, lungs etc.
- Why are secondary tumours so bad?
- Both types of tumour can tire the body out as they both need a huge amount of nutrients to sustain the rapid growth and division of the cells.

The Development of Cancer

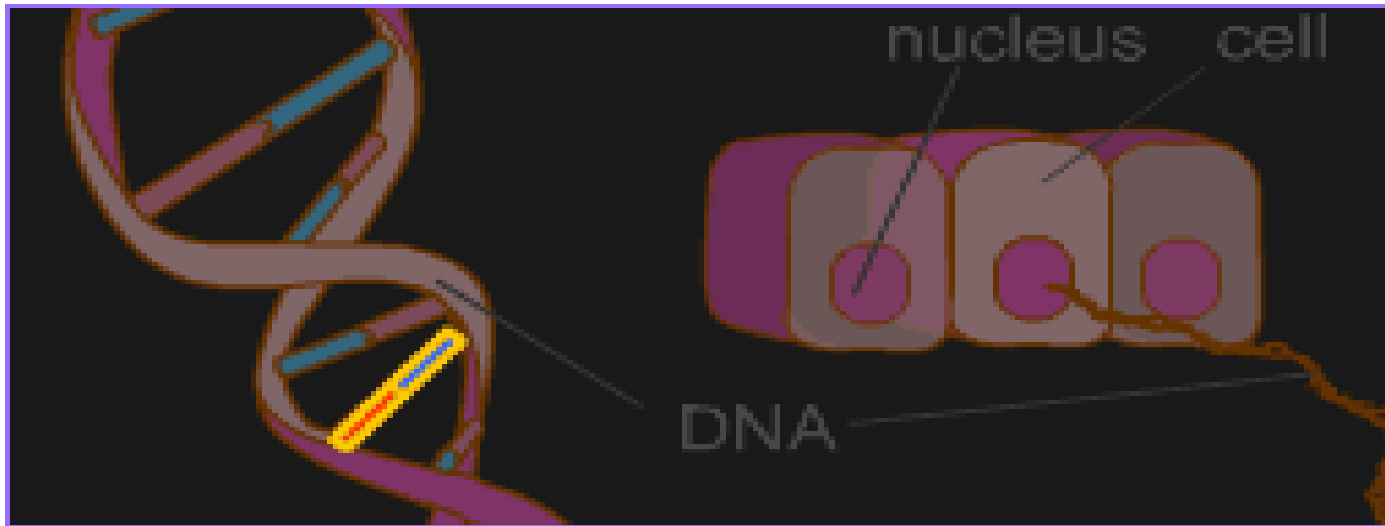
- Within every nucleus of every one of the human body's 30 trillion cells exists DNA, the substance that contains the information needed to make and control every cell within the body. Here is a close-up view of a tiny fragment of DNA.

1. DNA of a normal cell



- This piece of DNA is an exact copy of the DNA from which it came. When the parent cell divided to create two cells, the cell's DNA also divided, creating two identical copies of the original DNA.

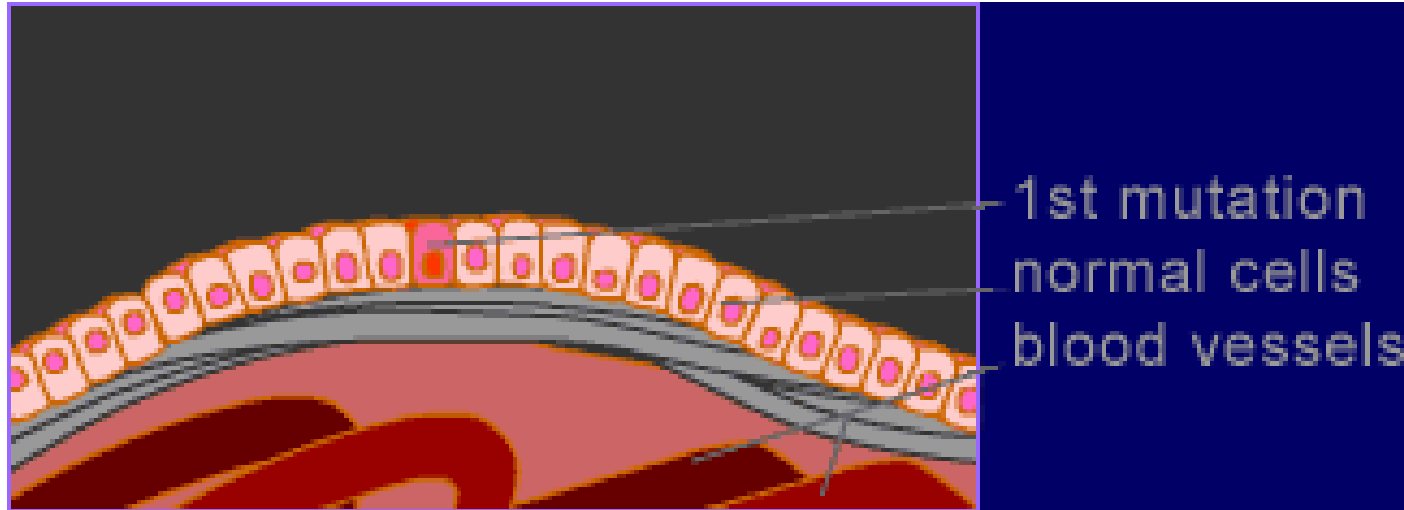
2. Mutation of DNA



- Here is the same section of DNA but from another cell. If you can imagine that DNA is a twisted ladder, then each rung of the ladder is a pair of joined molecules, or a base pair. With this section of DNA, one of the base pairs is different from the original.

This DNA has suffered a **mutation**, either through mis-copying (when its parent cell divided), or through the damaging effects of exposure to **radiation or a chemical carcinogen**.

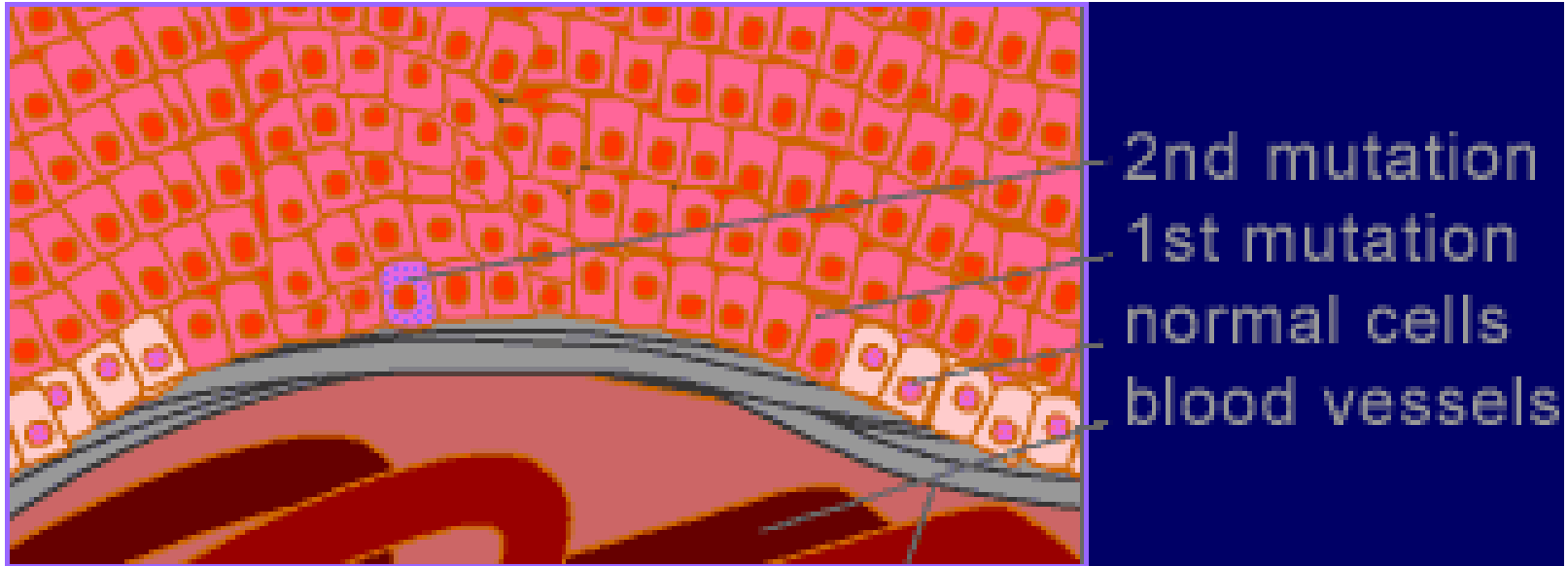
3. Genetically altered cell



- Body cells replicate through mitosis, they respond to their surrounding cells and replicate only to replace other cells. Sometimes a **genetic mutation** will cause a cell and its descendants to reproduce even though replacement cells are not needed.

The DNA of the cell highlighted above has a **mutation** that causes the cell to replicate even though this tissue doesn't need replacement cells at this time or at this place.

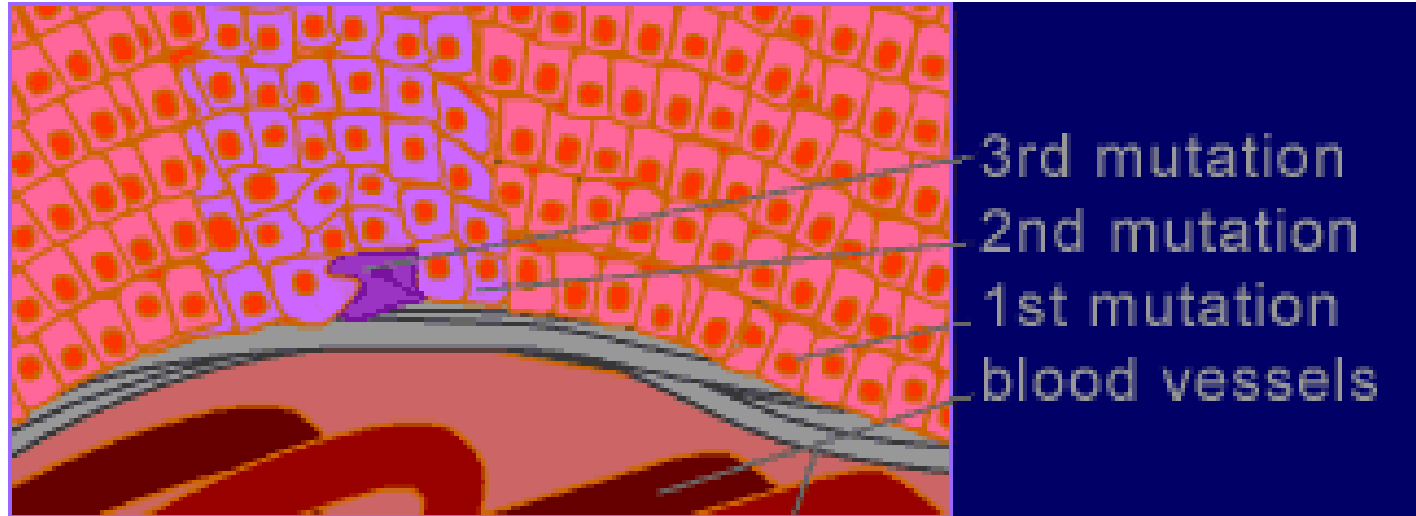
4. Spread and second mutation



- The genetically altered cells have, over time, **reproduced unchecked**, crowding out the surrounding normal cells. The growth may contain one million cells and be the size of a pinhead. At this point the cells continue to look the same as the surrounding healthy cells.

After about a million divisions, there's a good chance that one of the new cells will have **mutated further**. This cell, now carrying two **mutant genes**, could have an **altered appearance** and be even more prone to reproduce unchecked.

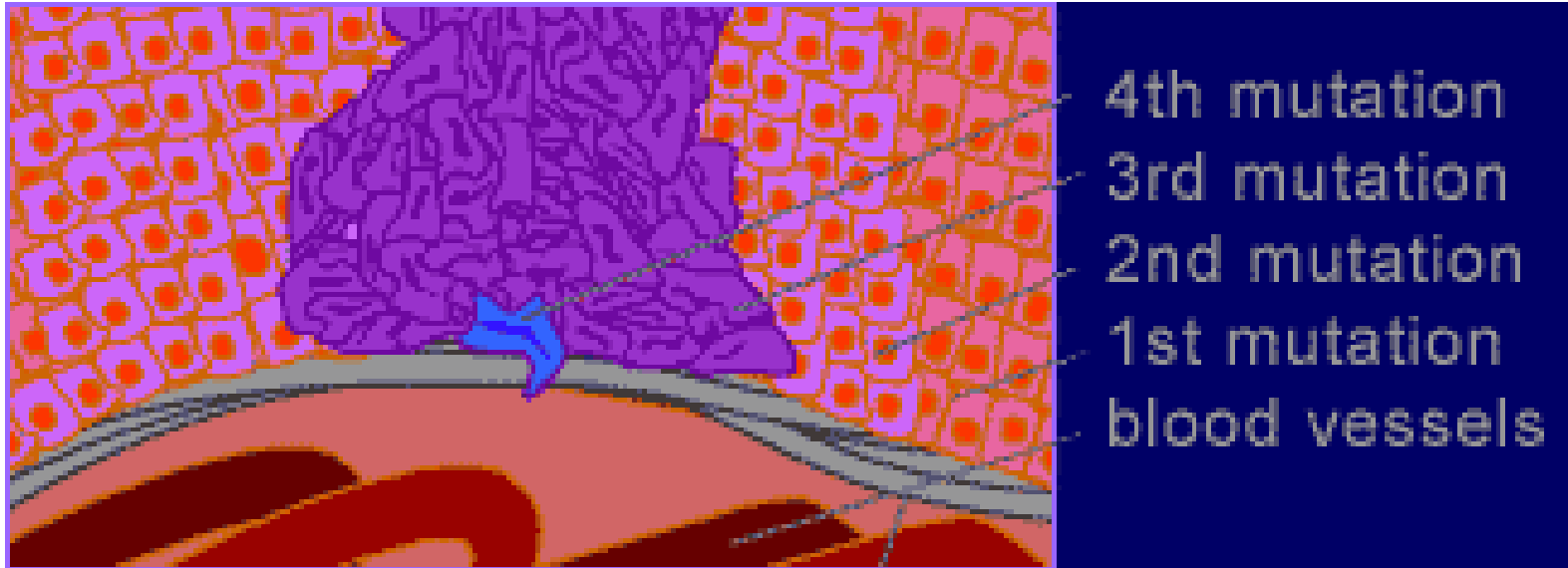
5. Third mutation



- Not all mutations that lead to cancerous cells result in the cells reproducing at a faster, more uncontrolled rate. For example, a mutation may simply cause a cell to keep from self-destructing. All normal cells have surveillance mechanisms that look for damage or for problems with their own control systems. If such problems are found, the cell destroys itself.

Over time and after many cell divisions, a **third mutation** may arise. If the mutation gives the cell some further advantage, that cell will grow more vigorously than its predecessors and thus speed up the **growth of the tumour**.

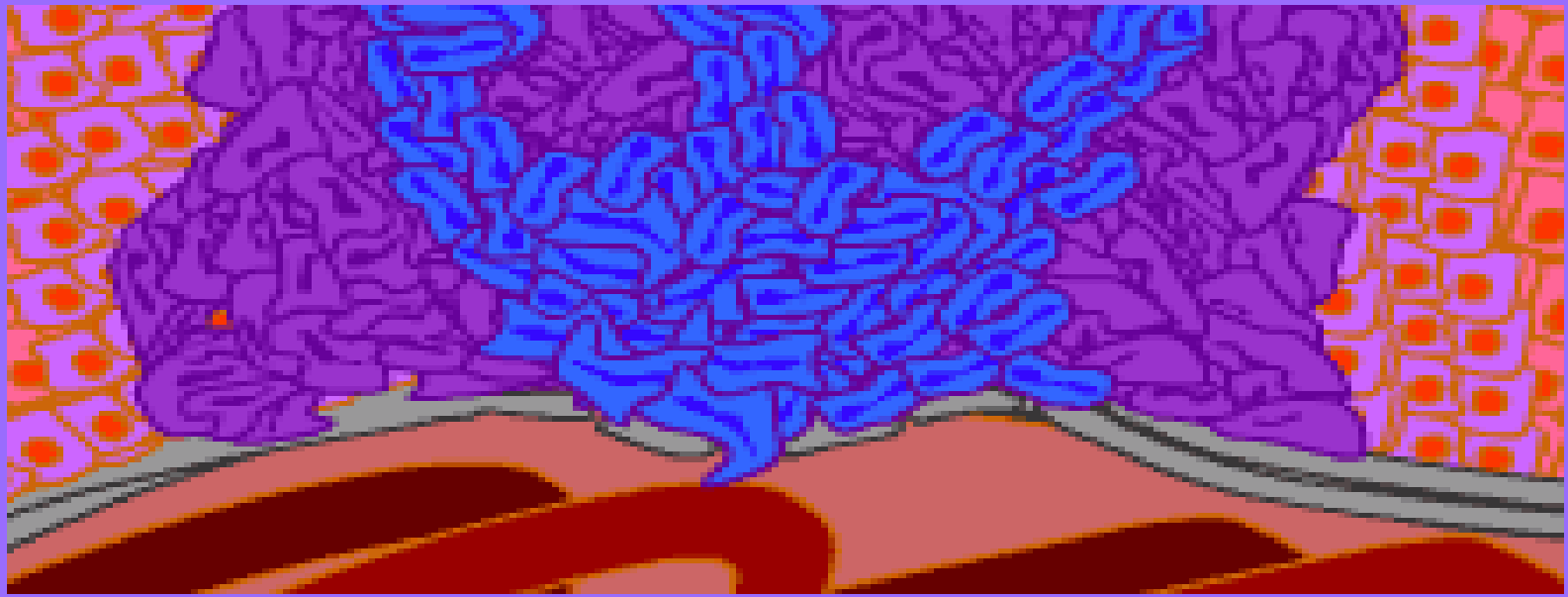
6. Fourth mutation



- The new type of cells grow rapidly, allowing for more opportunities for mutations. The next mutation paves the way for the development of an even more **aggressive cancer**.

At this point the tumour is still contained.

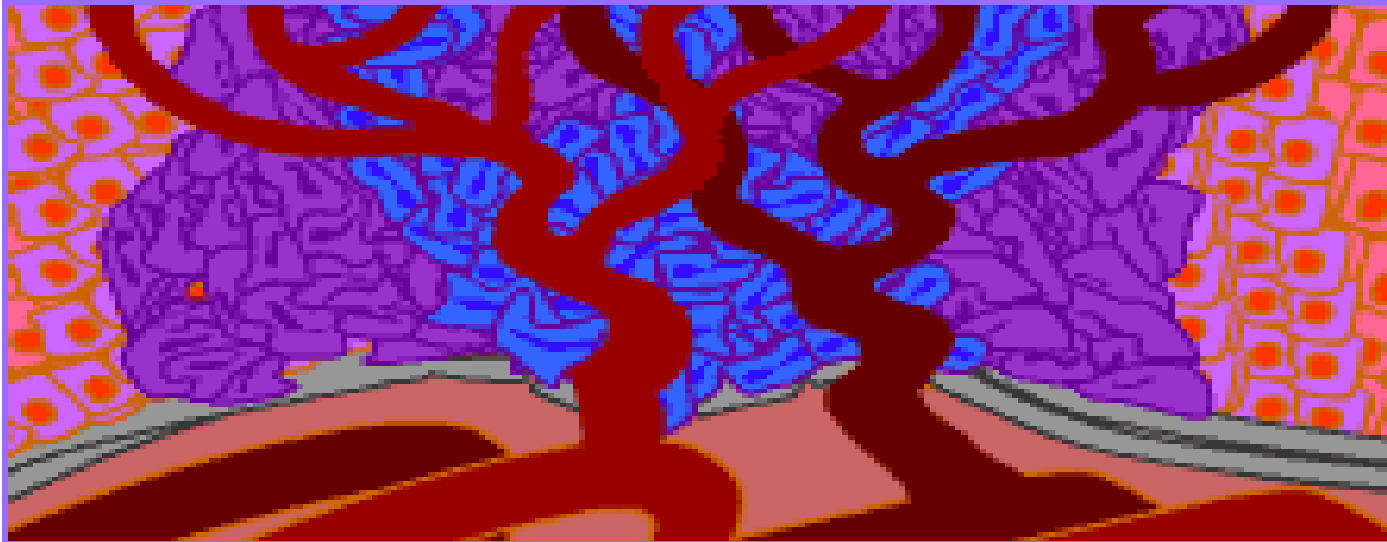
7. Breaking through the membrane



- The newer, wilder cells created by another mutation are able to **push their way through the epithelial tissue's basement membrane**, which is a meshwork of protein that normally creates a barrier. The invasive cells in this tumour are **no longer contained**.

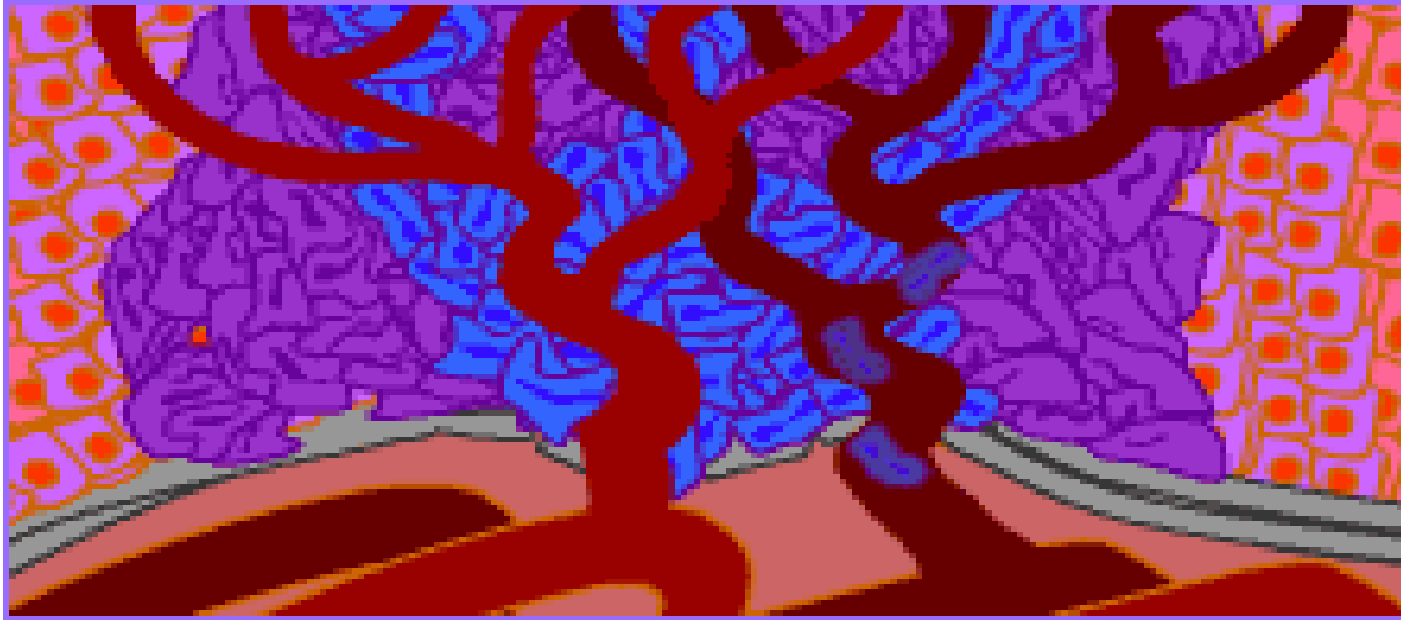
At this point the cancer is still **too small to be detected**.

8. Angiogenesis



- Often during the development of earlier stages of the tumour, or perhaps by the time the tumour has broken through the basement membrane (as pictured above), **angiogenesis** takes place. **Angiogenesis is the recruitment of blood vessels from the network of neighbouring vessels.**
- Without blood and the nutrients it carries, a tumour would be unable to continue growing. With the new blood supply, however, the **growth of the tumour accelerates**; it soon contains **thousand million cells** and, now the size of a small grape, is large enough to be detected as a lump

9. Invasion and dispersal



- The tumour has now **invaded the tissue** beyond the basement membrane.

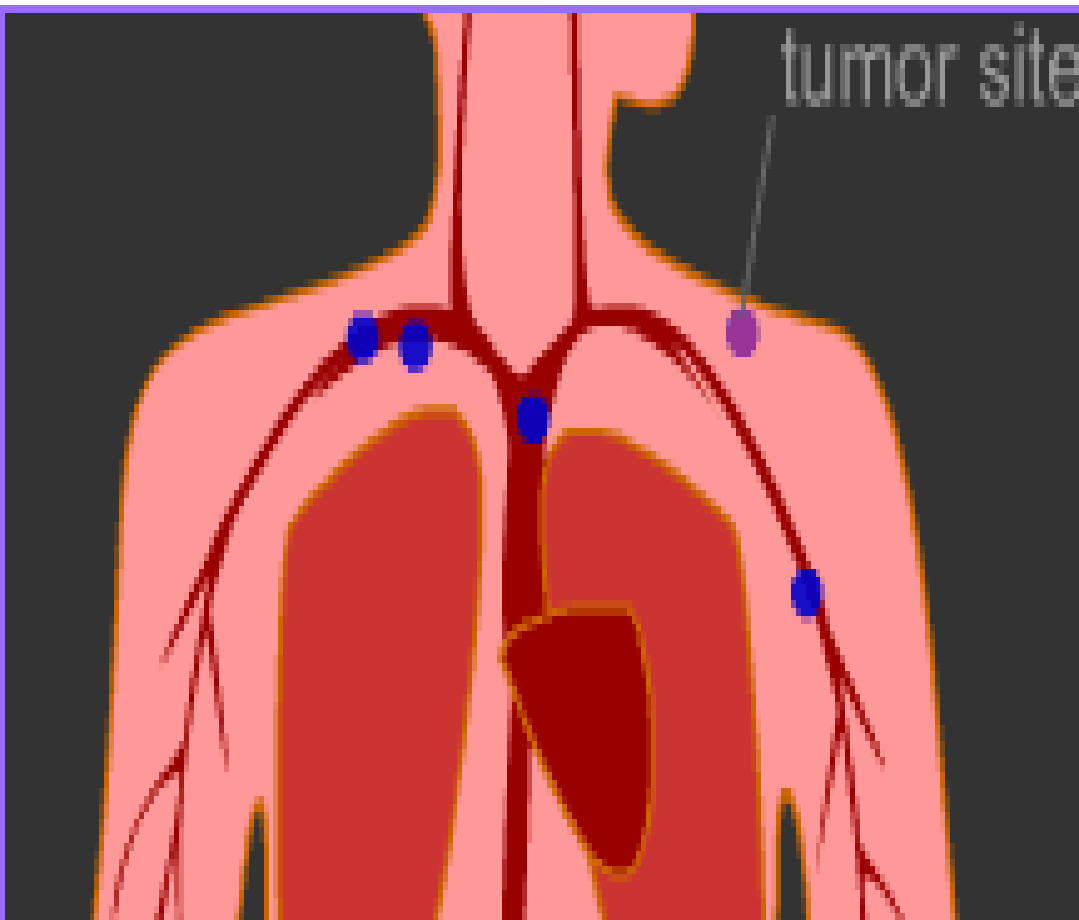
Individual cells from the tumour enter into the network of newly formed blood vessels, using these vessels as highways by which they can move to other parts of the body. A tumour as small as a gram can send out a million tumour cells into blood vessels a day.

10. Tumour cells travel - metastasis

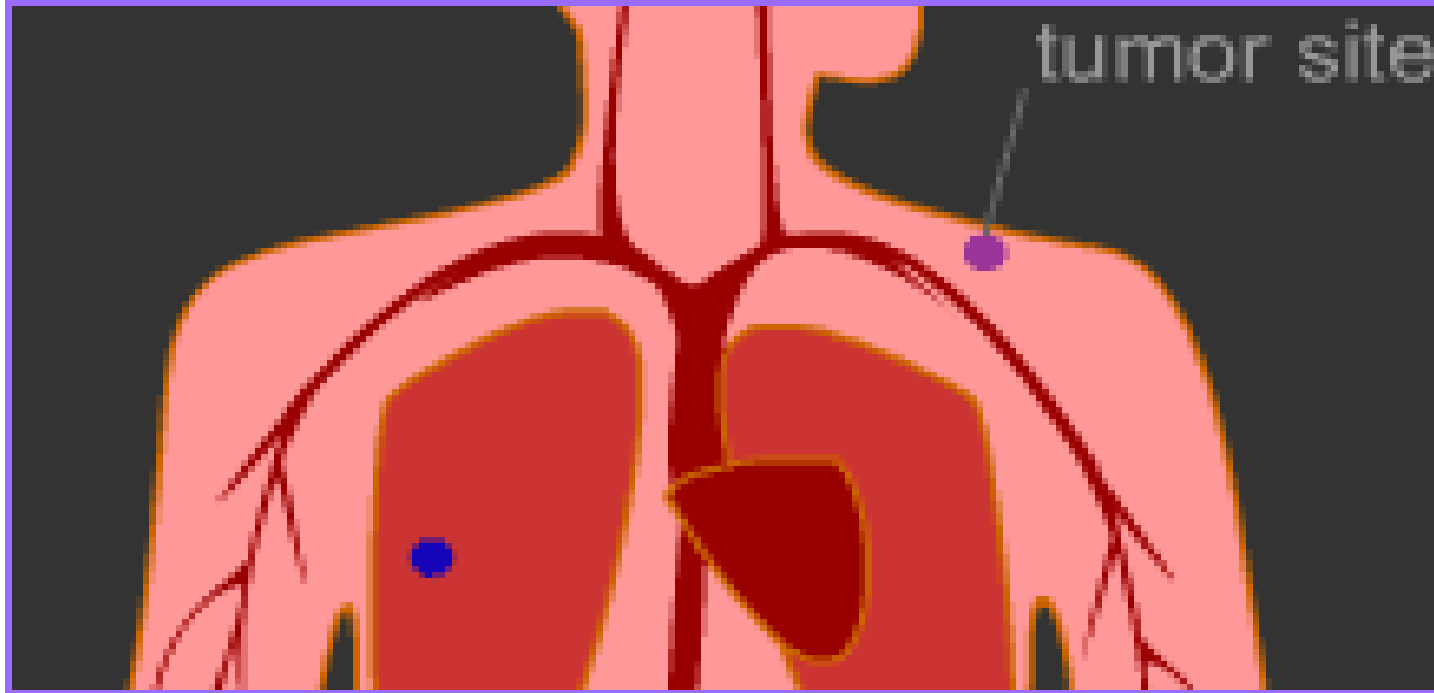
- What makes most tumours so lethal is their ability to **metastasize** -- that is, establish new tumour sites at other locations throughout the body.

Secondary tumours.

Metastasis is now underway, as tumour cells from the original cancer growth travel throughout the body. Most of these cells will die soon after entering the blood or lymph circulation.



11. Metastasis



- To form a **secondary tumour**, a tumour cell needs to leave the vessel system and invade tissue. The cell must **attach itself** to a vessel's wall. Once this is done, it can work its way through the vessel and enter the tissue.

Although perhaps less than one in 10,000 tumour cells will survive long enough to establish a new tumour site, a few survivors can escape and initiate **new colonies** of the cancer.

Facts on Cancer

- 2006, approximately 564,830 Americans died of cancer
- 1.4 million new cases diagnosed
- 1/3 of cancers are related to poor nutrition, physical inactivity, and obesity – preventable causes

What Is Cancer?

- Cancer – a large group of diseases characterized by the uncontrolled growth and spread of abnormal cells
- Neoplasm – new growth of tissue that serves no physiological function
- Tumor – clumping of neoplastic cells
- Malignant - cancerous
- Benign - noncancerous
- Biopsy – microscopic examination of cell

What Is Cancer? – cont.

- Metastasis – malignant tumors that are not enclosed in a protective capsule have the ability to spread to other organs
- Mutant cells – disruption of RNA and DNA within normal cells may produce cells that differ in form, quality and function from the normal cell

Disparities In Cancer Rates

- African Americans have the highest death rates from cancer
- The gap in cancer mortality rates is greater now than in 1975
- African Americans with certain cancers are more likely to go unstaged and less likely to receive treatment
- Men from poorer census counties have a 22% higher death rate from prostate cancer than their affluent county comparison groups

Factors Believed to Contribute to Global Causes of Cancer

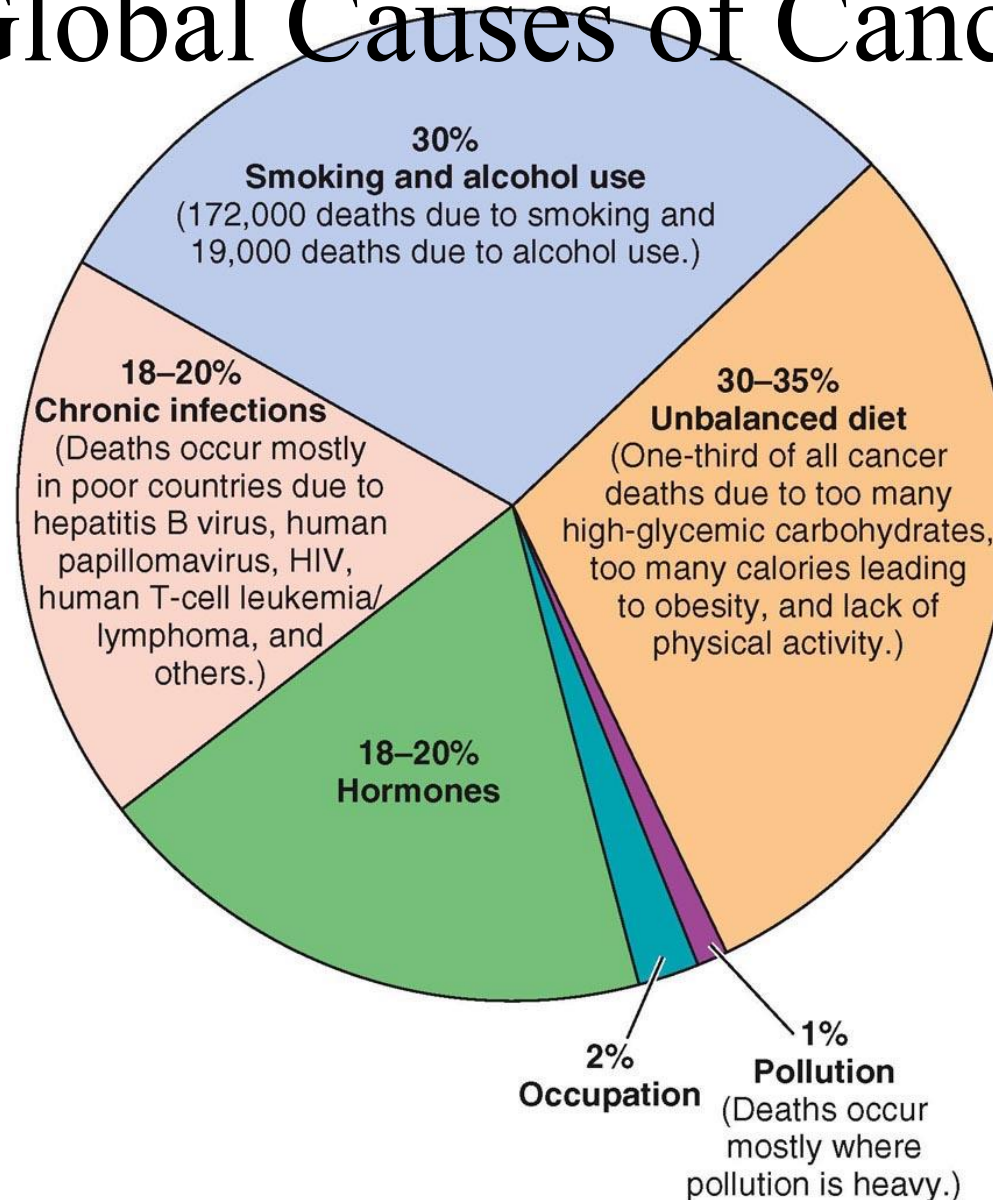


Figure 16.2

Risks For Cancer

- Lifetime risk – the probability that an individual, over the course of a lifetime, will develop cancer or die from it
- Relative risk – measure of the strength of the relationship between risk factors and a particular cancer
- Smoking – 30% of all cancer deaths, 87% of lung cancer deaths
- Obesity – 50% higher risk for breast cancer in postmenopausal women, 40% higher risk in colon cancer for men

TABLE 16.2 Preventing Cancer through Diet and Lifestyle

Type of Cancer	Factors that Decrease Risk	Factors that Increase Risk
Breast	Engage in physical activity for at least 4 hours per week; consume lots of fruits and vegetables	Obesity and weight gain; alcohol consumption; hormone replacement therapy
Colorectal	Engage in regular, moderate physical activity; consume lots of fruits and vegetables	High intake of red meat; smoking; alcohol consumption; obesity
Lung	Consume at least 5 servings of fruits and vegetables daily	Tobacco use; some occupations
Oral/Throat	Consume at least 5 servings of fruits and vegetables daily; engage in regular, moderate physical activity	Tobacco use; obesity; alcohol consumption; salted foods
Prostate	Consume at least 5 servings of fruits and vegetables daily	High intake of red meat and high-fat dairy products
Stomach	Consume at least 5 servings of fruits and vegetables daily; refrigerate food	Salted foods; <i>Helicobacter pylori</i> bacteria

Here are some additional tips issued by a panel of cancer researchers:

- Avoid being underweight or overweight, and limit weight gain during adulthood to less than 11 pounds.
- If you don't get much exercise at work, take a 1-hour brisk walk or similar exercise daily, and exercise vigorously for at least 1 hour a week.
- Eat 8 or more servings a day of cereals and grains (such as rice, corn, breads, and pasta), legumes (such as peas), roots (such as beets, radishes, and carrots), tubers (such as potatoes), and plantains (including bananas).
- Limit consumption of refined sugar.
- Limit alcoholic drinks to less than 2 a day for men and 1 for women.
- Limit intake of red meat to less than 3 ounces a day, if eaten at all.
- Limit consumption of salted foods and use of cooking and table salt. Use herbs and spices to season foods.

Sources: World Cancer Research Fund, American Institute for Cancer Research, "Food, Nutrition and the Prevention of Cancer," www.wecf-uk.org; American Cancer Society, "The Complete Guide: Nutrition and Physical Activity," www.cancer.org.

Biological Factors

- Some cancers such as breast, stomach, colon, prostate, uterus, ovaries and lung appear to run in families
- Hodgkin's disease and certain leukemia's show similar patterns
- University of Utah research suggests that a gene for breast cancer exists
- A rare form of eye cancer appears to be transmitted genetically from mother to child

Reproductive And Hormonal Risks For Cancer

- Pregnancy and oral contraceptives increase a woman's chances of breast cancer
- Late menarche, early menopause, early first childbirth, having many children have been shown to reduce risk of breast cancer

Occupational And Environmental Factors

- Asbestos
- Nickel
- Chromate
- Benzene
- Arsenic
- Radioactive substances
- Coal tars
- Herbicides/pesticides

Social And Psychological Factors

- Stress has been implicated in increased susceptibility to several types of cancers
- Sleep disturbances, diet, or a combination of factors may weaken the body's immune system

Chemicals In Foods

- Sodium nitrate when ingested forms a potential carcinogen, nitrosamine
- Sodium nitrate is still used because it is effective in preventing botulism
- Pesticide and herbicide residues

Viral Factors

- Herpes-related viruses may be involved in the development of leukemia, Hodgkin's disease, cervical cancer, and Burkitt's lymphoma
- Epstein-Barr virus, associated with mononucleosis, may contribute to cancer
- Human papillomavirus (HPV), virus that causes genital warts, has been linked to cervical cancer
- *Helicobacter pylori* causes ulcers which are a major factor in the development of stomach cancer

Medical Factors

- Some medical treatments actually increase a person's risk for cancer
- Diethylstilbestrol (DES) used 1940 to 1960 to control bleeding during pregnancy, the daughters of mothers that used DES were found to have an increased risk for cancers of the reproductive organs
- Estrogen supplementation
- Chemotherapy used to treat one form of cancer may increase risk for another type of cancer

Types Of Cancers

- Classification of cancers
 - Carcinomas
 - Sarcomas
 - Lymphomas
 - Leukemias

Colon And Rectal Cancers

- Third most common cancer in men and women with over 148,610 new cases diagnosed in 2006
- Risk factors: over 50 years old, obese, family history of colon or rectum cancer or polyps, diets high in fats, low in fiber, smoking, high alcohol consumption, lack of exercise
- 90% of colorectal cancers are preventable
- Treatment: radiation, surgery, and possible chemotherapy
- Prevention: regular exercise, a diet heavy in fruits and plant-origin foods, a health weight, and moderation in alcohol consumption

Prostate Cancer

- Most common cancer in American men, excluding skin cancer
- In 2006, 234,460 new cases diagnosed
- 1 in 3 men will be diagnosed in their lifetime
- Prostate is a muscular, walnut-sized gland that surrounds part of the urethra. Its primary function is to produce seminal fluid.
- Symptoms: nonspecific, weak or interrupted urine flow, difficulty starting or stopping urination
- Risk factors: age, race, nationality, family history, diet, lifestyle, and vasectomy
- Prevention: diet high in lycopenes, vitamin E

Skin Cancer

- Long term effects of sun exposure can result in skin cancer
- Malignant melanoma, deadliest form of skin cancer
- Sun give off 3 types of harmful rays:
 - UVA
 - UVB
 - UVC
- Prevention: limit exposure to harmful UV rays, drink more fluids than usual, apply cool compresses to skin, moisturize skin

Skin Cancer – cont.

- What to look for – The *ABCD* rule
 - Asymmetry – half of mole does not look like the other half
 - Border irregularity – the edges are uneven
 - Color – pigmentation is not uniform
 - Diameter – greater than 6mm



The sun gives off three types of harmful ultraviolet rays:

- *UVA (ultraviolet A)*. These longer wavelengths penetrate deeply into the skin, damaging the skin's collagen. They result in premature aging and help prime the skin for cancers.
- *UVB (ultraviolet B)*. These are short wavelengths and are believed to be the primary rays causing sunburn and ultimately resulting in cancers.
- *UVC (ultraviolet C)*. These very short rays are deadly to plants and animals. Normally, the atmospheric ozone layer protects us by absorbing UVC rays. Interestingly, as the global ozone layer has become progressively depleted over the last decade, the incidence of skin cancer has risen dramatically, as have cases of sun-related eye damage.

Testicular Cancer

- Affects nearly 8,250 young men in 2006
- Men between the ages 15-35 are at the greatest risk
- Important to practice regular testicular self exams
- Lance Armstrong Foundation “LiveStrong” campaign to raise awareness

Ovarian Cancer

- Fifth leading cause of cancer death for women, 20,180 new cases diagnosed reported in 2006
- Most common symptom is enlargement of the abdomen
- Risk factors include: family history, age, childbearing, cancer history, fertility drugs, talc use in genital area, genetic predisposition
- Prevention: diet high in vegetables and low in fat, exercise, sleep, stress management, and weight control

Cervical and Endometrial (Uterine) Cancer

- 9,710 new cases of cervical cancer, 41,200 cases of endometrial cancer in U.S. in 2006
- Pap test – cells are taken from the cervical region
- Risk factors:
 - Cervical cancer: early age at first intercourse, multiple sex partners, cigarette smoking, and certain STIs
 - Endometrial cancer: age, endometrial hyperplasia, overweight, diabetes, and high blood pressure

Other Cancers

- Pancreatic cancer – “silent” 4% 5-year survival rate
- Leukemia – cancer of blood forming tissues

Detecting Cancer

- The earlier the diagnosis the better the prospect for survival
- Magnetic resonance imaging (MRI)
- Computerized axial tomography scan (CAT scan)
- Prostatic ultrasound
- Regular self-exams, and check ups

New Hope In Cancer Treatments

- Remove less surrounding tissue during surgery
- Combine surgery with radiation or chemotherapy
- Immunotherapy
- Cancer-fighting vaccines
- Gene therapy
- Stem cell research

