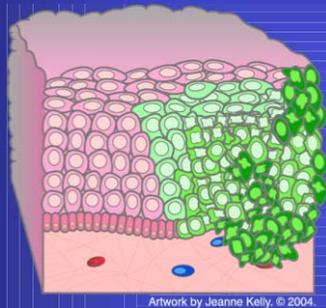


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*Understanding Cancer and Related Topics*  
**Understanding Cancer**

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**Understanding Cancer**

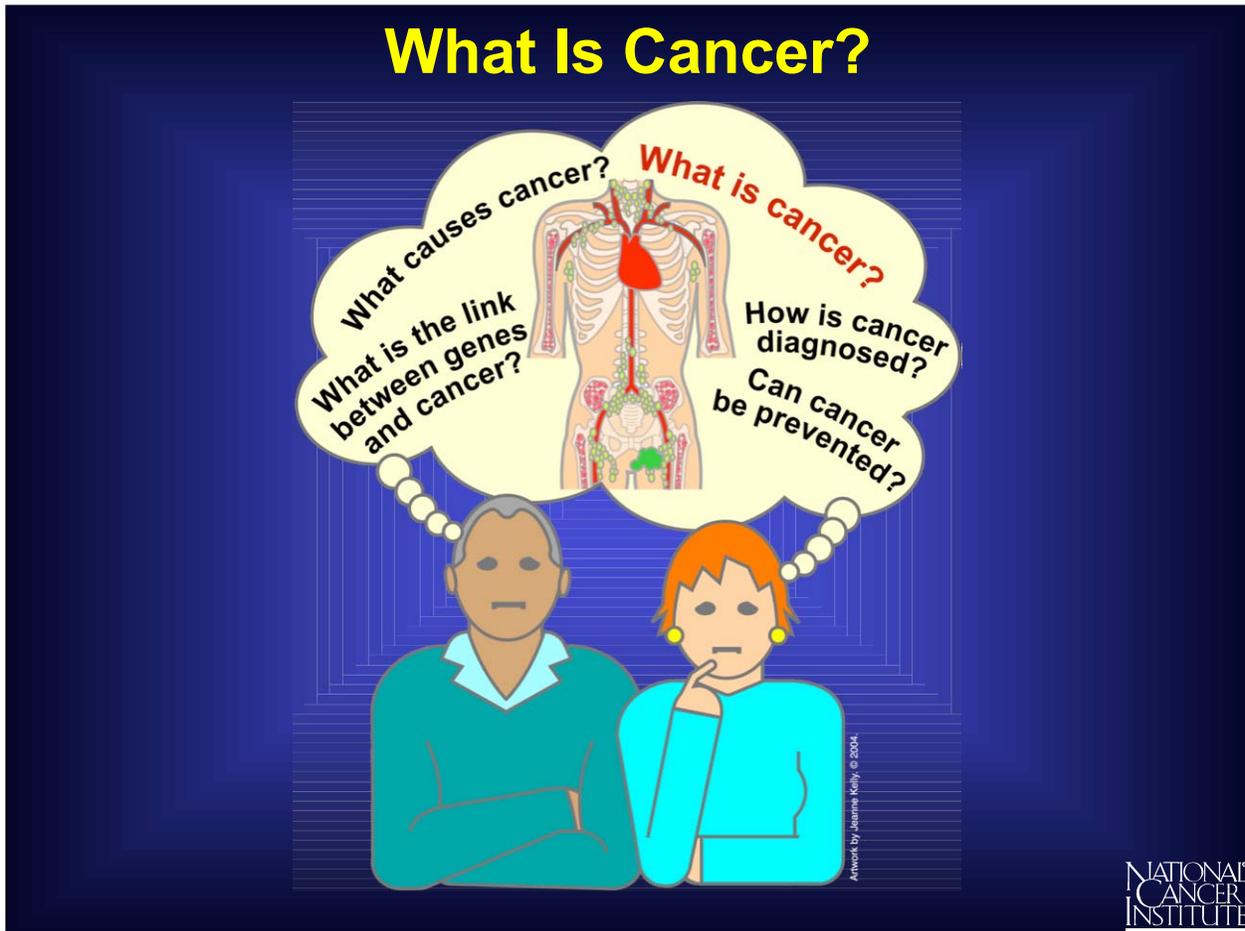


*Developed by:*  
*Lewis J. Kleinsmith, Ph.D.*  
*Donna Kerrigan, M.S.*  
*Jeanne Kelly*  
*Brian Hollen*

Discusses and illustrates what cancer is, explains the link between genes and cancer, and discusses what is known about the causes, detection, and diagnosis of the disease.

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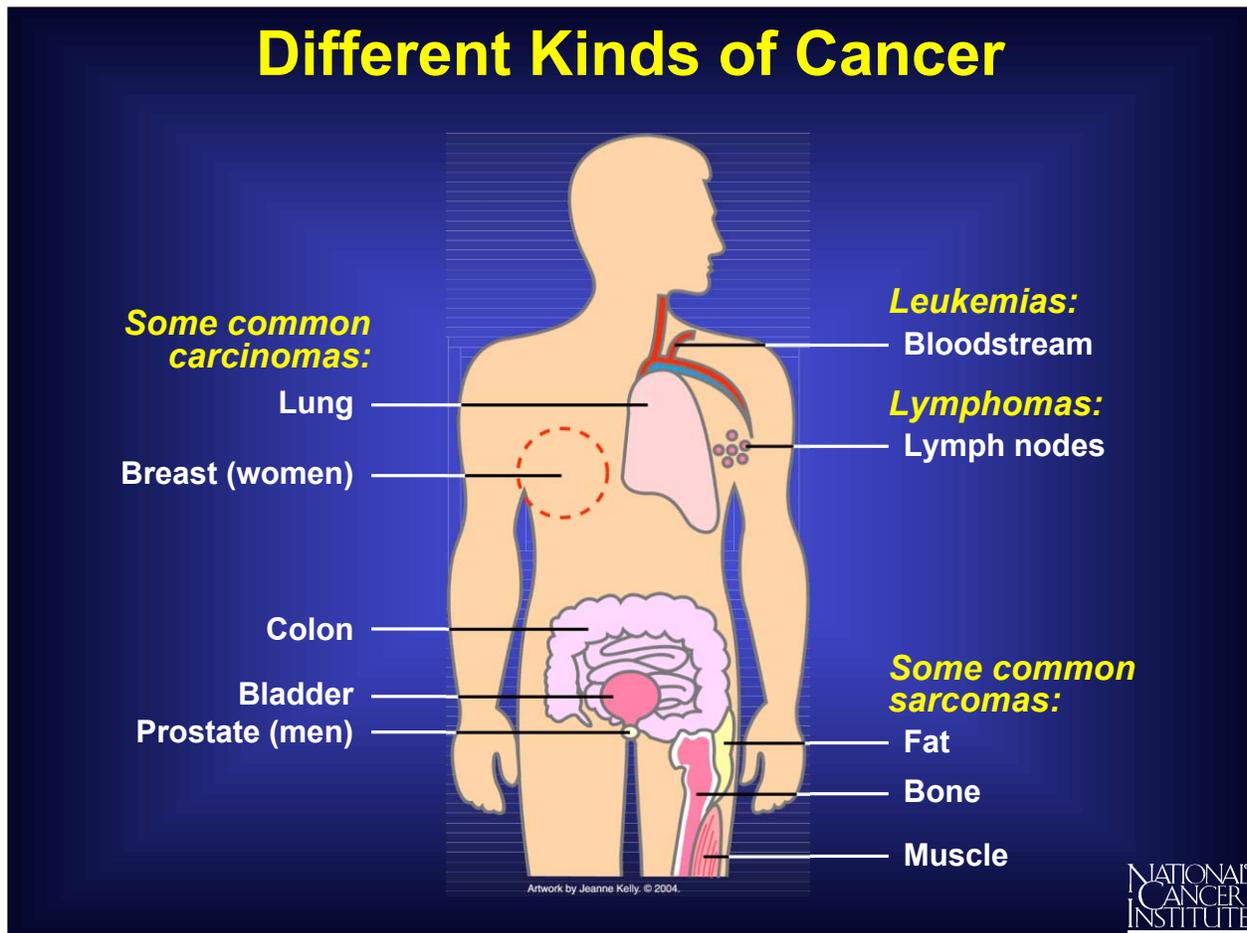


Cancer is a renegade system of growth that originates within a patient's biosystem, more commonly known as the human body. There are many different types of cancers, but all share one hallmark characteristic: unchecked growth that progresses toward limitless expansion.

It is difficult to imagine anyone who has not heard of this illness. Most people have been affected because either they or their loved ones or friends are cancer survivors.

Because cancer is so prevalent, people have many questions about its biology, detection, diagnosis, possible causes, and strategies for prevention.

## Different Kinds of Cancer



Cancer can originate almost anywhere in the body.

**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.

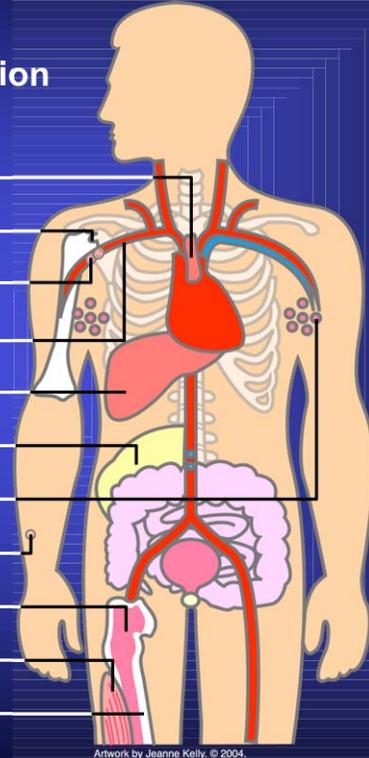
**Lymphomas** are cancers that arise in the lymph nodes and tissues of the body's immune system.

**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

### Cancer Prefixes Point to Location

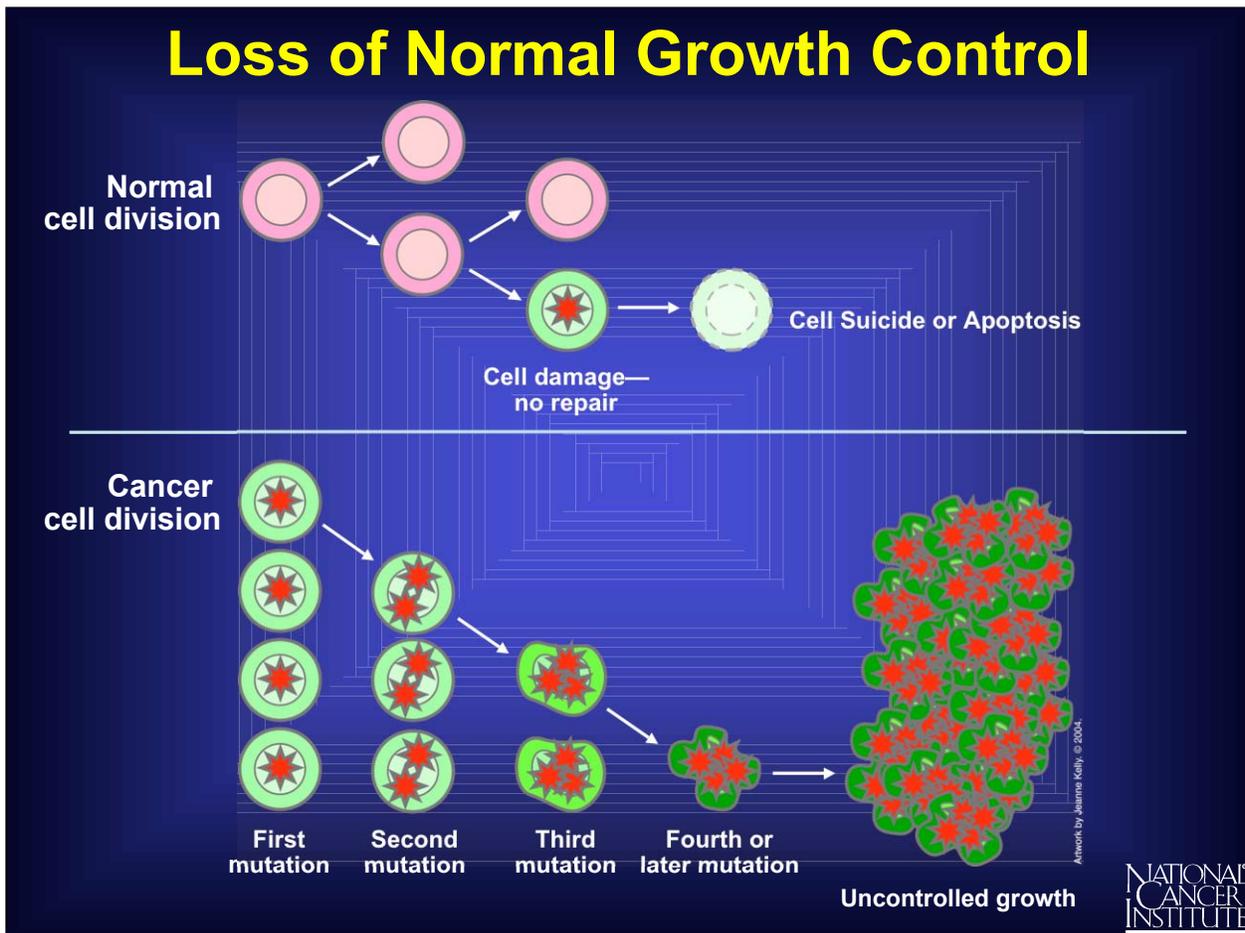
<b>Prefix</b>	<b>Meaning</b>
adeno-	gland
chondro-	cartilage
erythro-	red blood cell
hemangio-	blood vessels
hepato-	liver
lipo-	fat
lympho-	lymphocyte
melano-	pigment cell
myelo-	bone marrow
myo-	muscle
osteo-	bone



Artwork by Jeanno Kelly, © 2004.

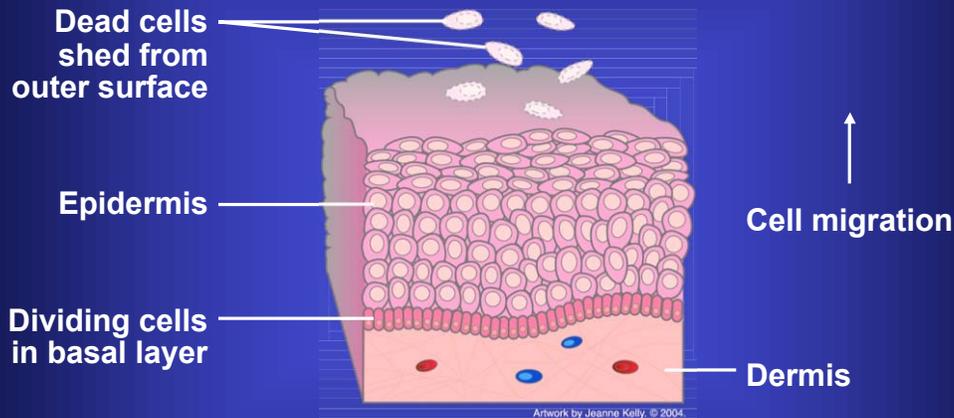
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Scientists use a variety of technical names to distinguish the many different types of carcinomas, sarcomas, lymphomas, and leukemias. In general, these names are created by using different Latin prefixes that stand for the location where the cancer began its unchecked growth. For example, the prefix “osteo” means bone, so a cancer arising in bone is called an osteosarcoma. Similarly, the prefix “adeno” means gland, so a cancer of gland cells is called adenocarcinoma--for example, a breast adenocarcinoma.



Cancer arises from a loss of normal growth control. In normal tissues, the rates of new cell growth and old cell death are kept in balance. In cancer, this balance is disrupted. This disruption can result from uncontrolled cell growth or loss of a cell's ability to undergo cell suicide by a process called "apoptosis." Apoptosis, or "cell suicide," is the mechanism by which old or damaged cells normally self-destruct.

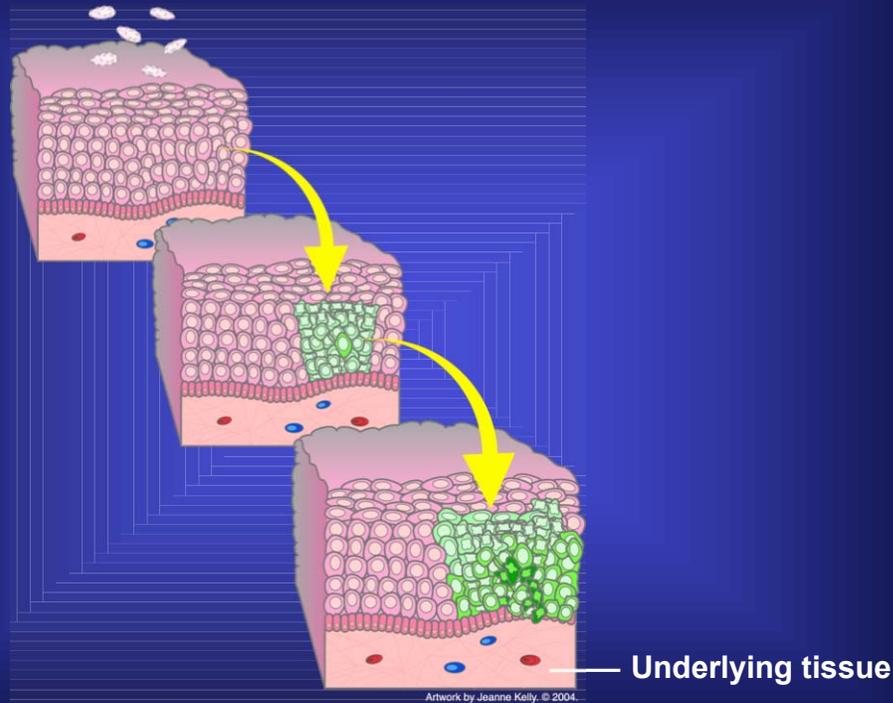
## Example of Normal Growth



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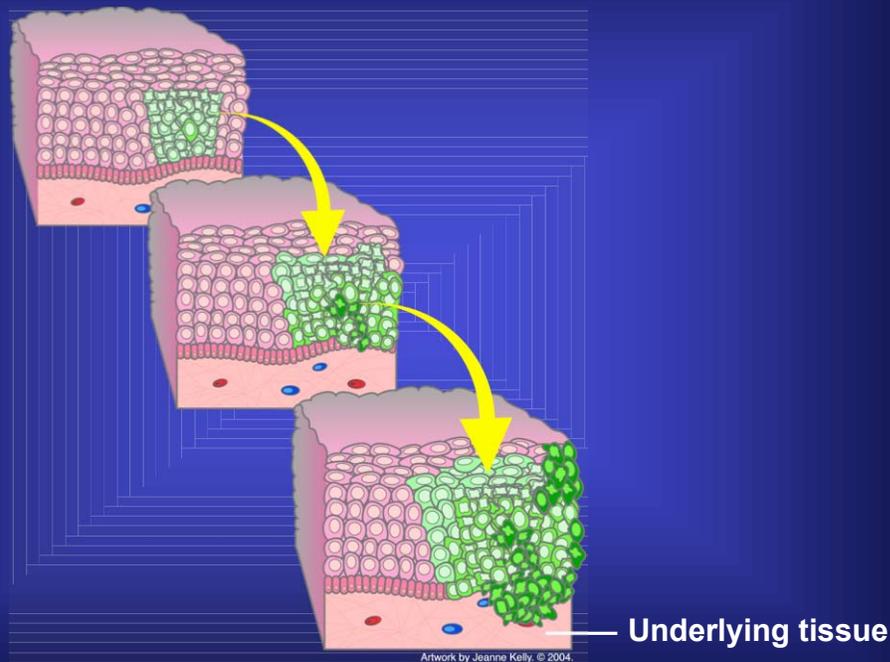
To illustrate what is meant by normal growth control, consider the skin. The thin outermost layer of normal skin, called the epidermis, is roughly a dozen cells thick. Cells in the bottom row of this layer, called the basal layer, divide just fast enough to replenish cells that are continually being shed from the surface of the skin. Each time one of these basal cells 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 Beginning of Cancerous Growth



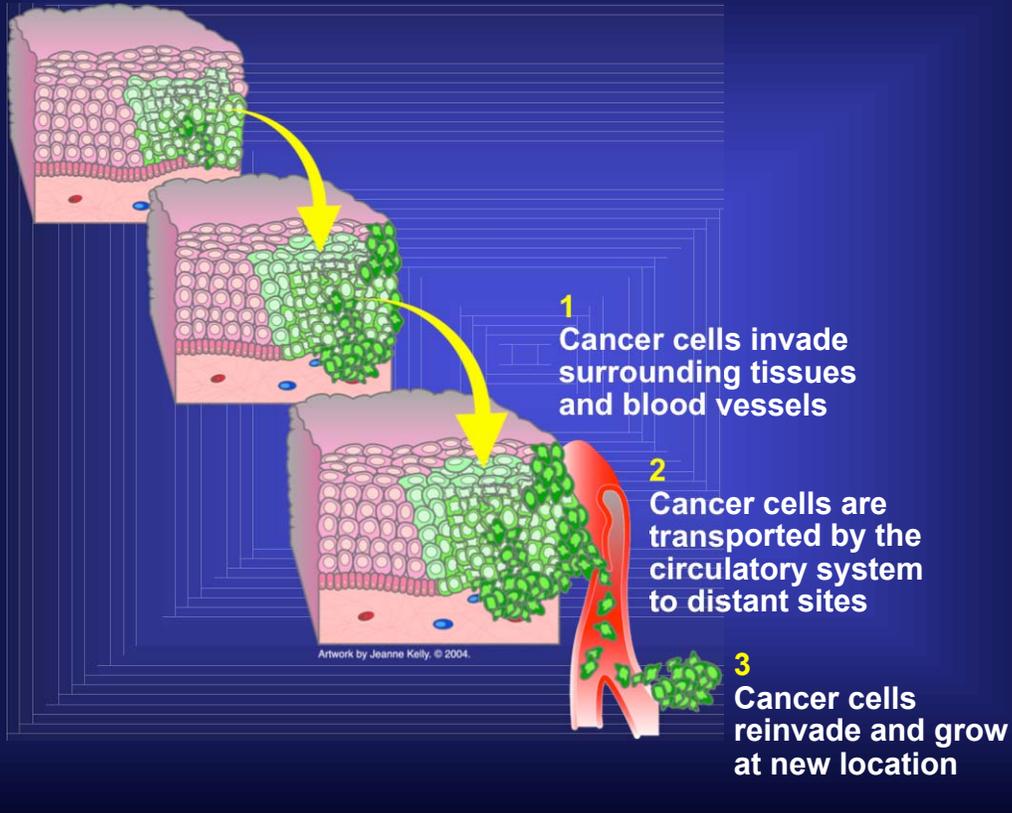
During the development of skin cancer, the normal balance between cell division and cell loss is disrupted. The basal cells now divide faster than is needed to replenish the cells being shed from the surface of the skin. Each time one of these basal cells divides, the two newly formed cells will often retain the capacity to divide, thereby leading to an increase in the total number of dividing cells.

## Tumors (Neoplasms)



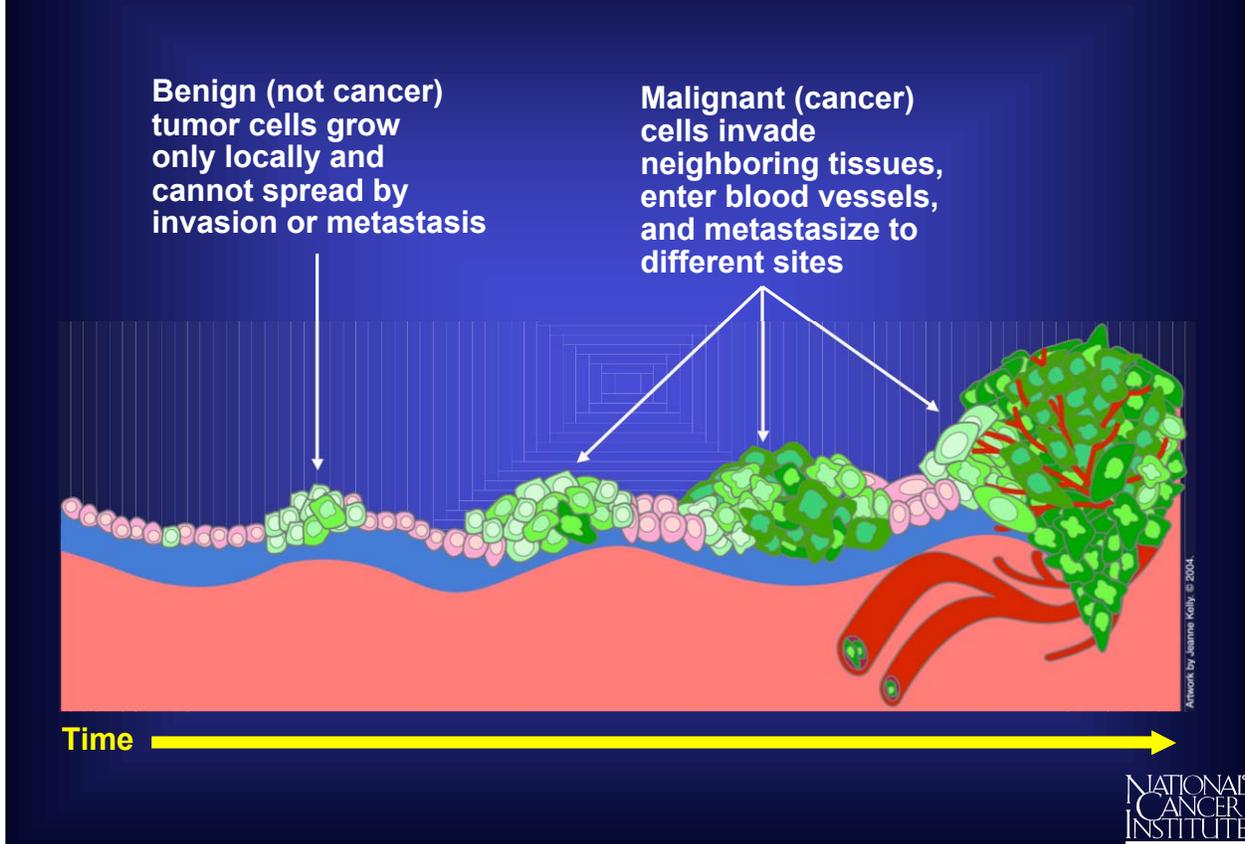
This gradual increase in the number of dividing cells creates a growing mass of tissue called a “tumor” or “neoplasm.” If the rate of cell division is relatively rapid, and no “suicide” signals are in place to trigger cell death, the tumor will grow quickly in size; if the cells divide more slowly, tumor growth will be slower. But regardless of the growth rate, tumors ultimately increase in size because new cells are being produced in greater numbers than needed. As more and more of these dividing cells accumulate, the normal organization of the tissue gradually becomes disrupted.

## Invasion and Metastasis



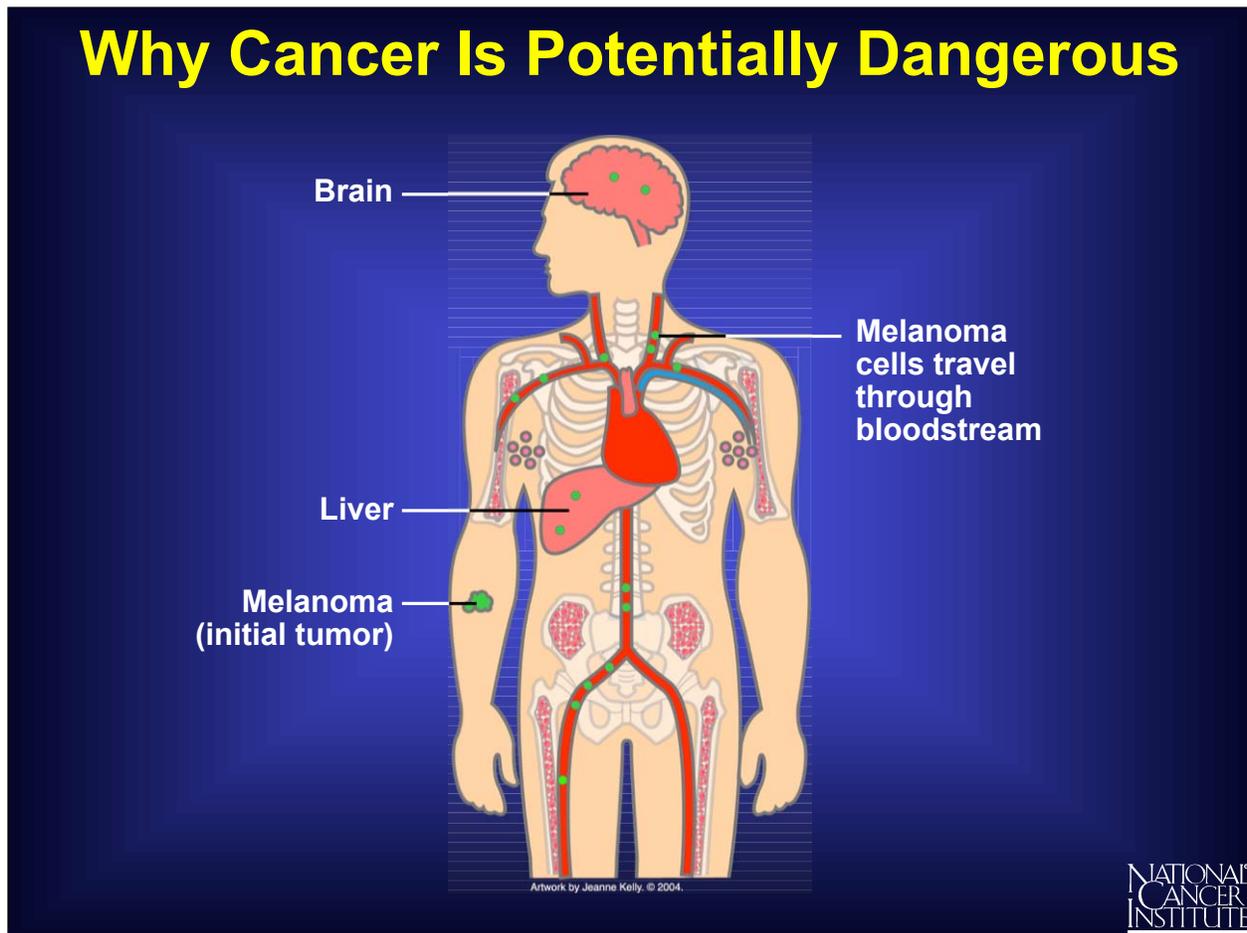
Cancers are capable of spreading throughout the body by two mechanisms: invasion and metastasis. Invasion refers to the direct migration and penetration by cancer cells into neighboring tissues. Metastasis refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade normal tissues elsewhere in the body.

## Malignant versus Benign Tumors



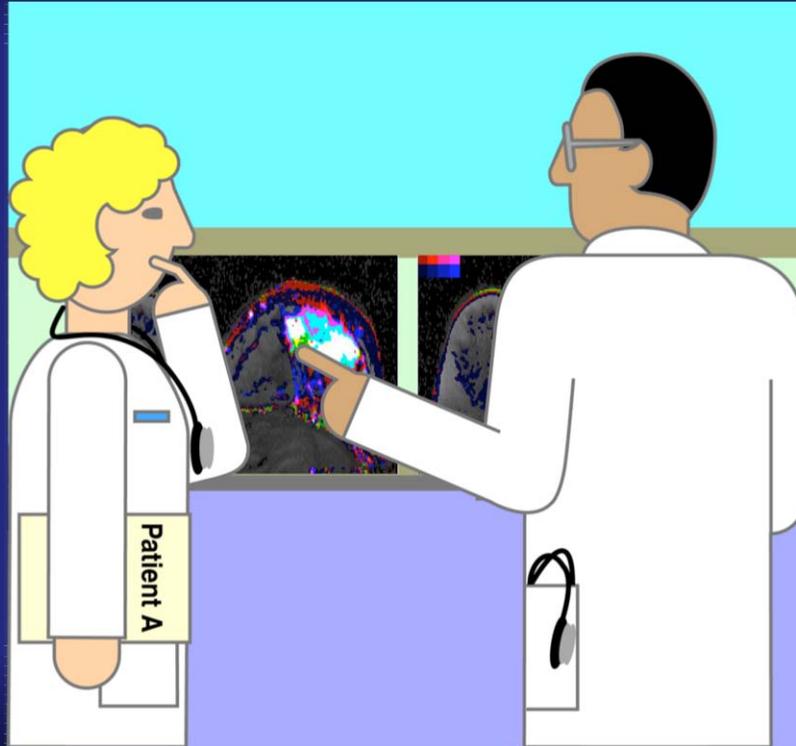
Depending on whether or not they can spread by invasion and metastasis, tumors are classified as being either benign or malignant. Benign tumors are tumors that cannot spread by invasion or metastasis; hence, they only grow locally. Malignant tumors are tumors that are capable of spreading by invasion and metastasis. By definition, the term “cancer” applies only to malignant tumors.

## Why Cancer Is Potentially Dangerous



A malignant tumor, a “cancer,” is a more serious health problem than a benign tumor because cancer cells can spread to distant parts of the body. For example, a melanoma (a cancer of pigmented cells) arising in the skin can have cells that enter the bloodstream and spread to distant organs such as the liver or brain. Cancer cells in the liver would be called metastatic melanoma, not liver cancer. Metastases share the name of the original (“primary”) tumor. Melanoma cells growing in the brain or liver can disrupt the functions of these vital organs and so are potentially life threatening.

## Cancer Detection and Diagnosis



Artwork by Jaume Killy © 2004.

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Detecting cancer early can affect the outcome of the disease for some cancers. When cancer is found, a doctor will determine what type it is and how fast it is growing. He or she will also determine whether cancer cells have invaded nearby healthy tissue or spread (metastasized) to other parts of the body. In some cases, finding cancer early may decrease a person's risk of dying from the cancer. For this reason, improving our methods for early detection is currently a high priority for cancer researchers.

## Early Cancer May Not Have Any Symptoms

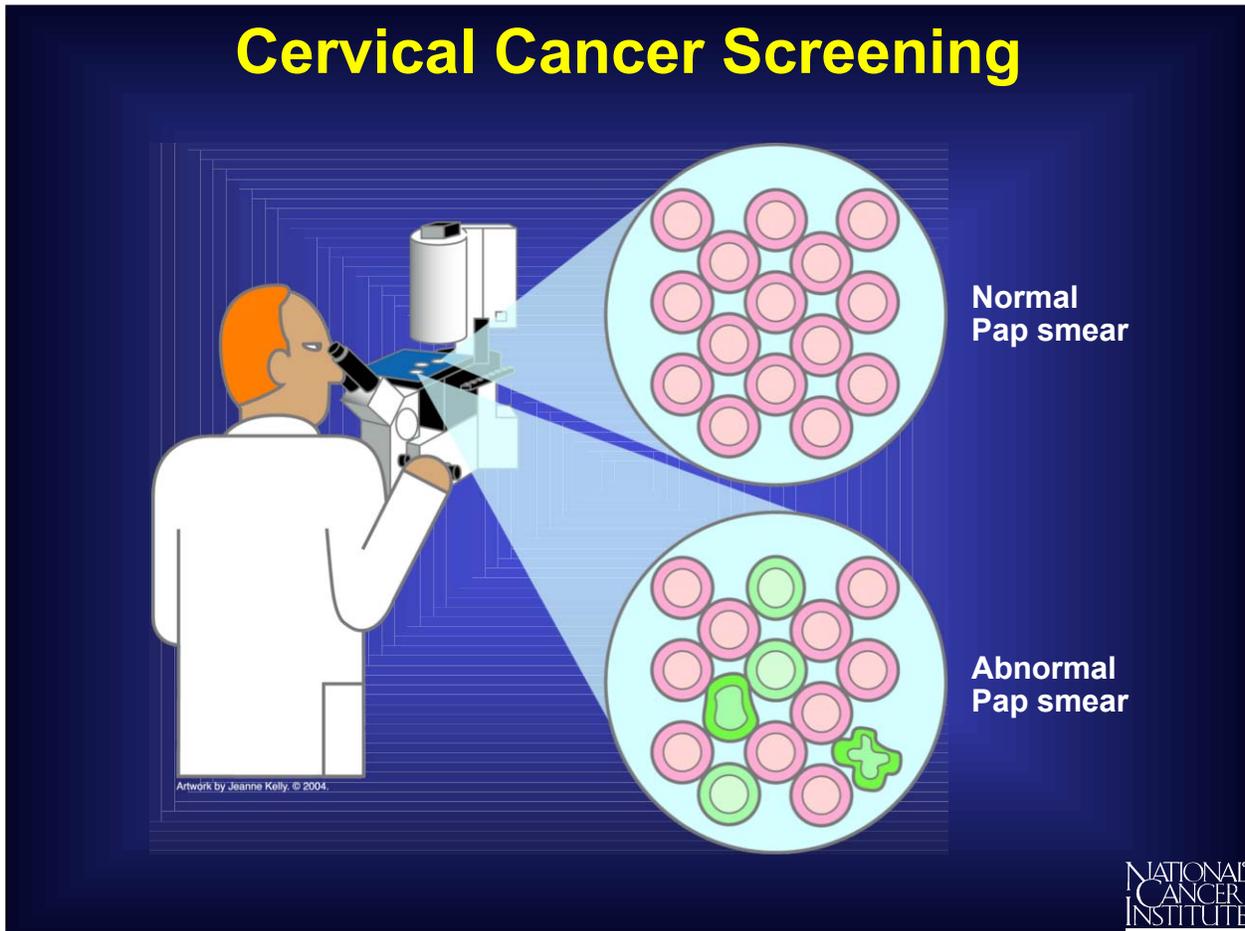


Artwork by Jeanne Kelly, © 2004.

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Some people visit the doctor only when they feel pain or when they notice changes like a lump in the breast or unusual bleeding or discharge. But don't wait until then to be checked because early cancer may not have any symptoms. That is why screening for some cancers is important, particularly as you get older. Screening methods are designed to check for cancer in people with no symptoms.

## Cervical Cancer Screening



A screening technique called the Pap test (or Pap smear) allows early detection of cancer of the cervix, the narrow portion of the uterus that extends down into the upper part of the vagina. In this procedure, a doctor uses a small brush or wooden scraper to remove a sample of cells from the cervix and upper vagina. The cells are placed on a slide and sent to a laboratory, where a microscope is used to check for abnormalities. Since the 1930s, early detection using the Pap test has helped lower the death rate from cervical cancer more than 75 percent.

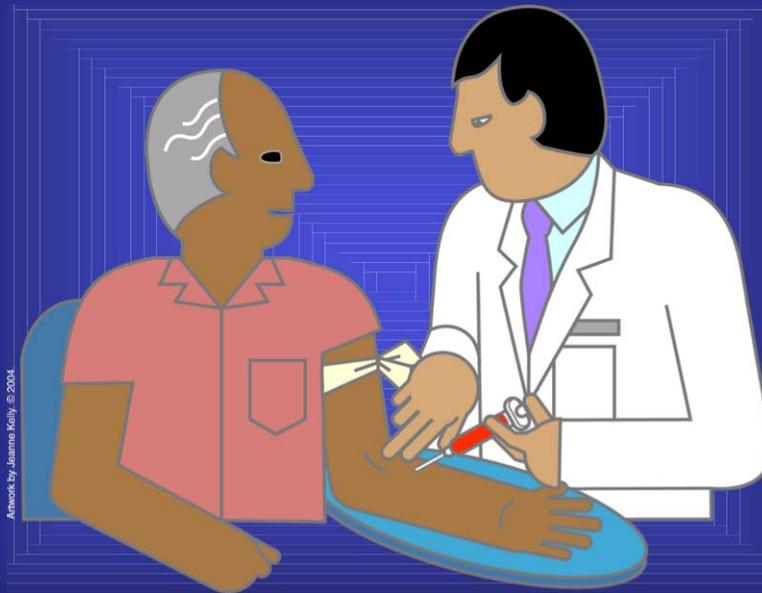
Should abnormalities be found, an additional test may be necessary. There are now 13 high-risk types of human papillomaviruses (HPV) recognized as the major causes of cervical cancer. The U.S. Food and Drug Administration has approved an HPV test that can identify their presence in a tissue sample. This test can detect the viruses even before there are any conclusive visible changes to the cervical cells.

## Breast Cancer Screening



Breast cancer can sometimes be detected in its early stages using a mammogram, an X-ray of the breast. Mammography is most beneficial for women as they age and undergo menopause. Mammography is a screening tool that can detect the possible presence of an abnormal tissue mass. By itself, it is not accurate enough to provide definitive proof of either the presence or the absence of breast cancer. If a mammogram indicates the presence of an abnormality, further tests must be done to determine whether breast cancer actually is present.

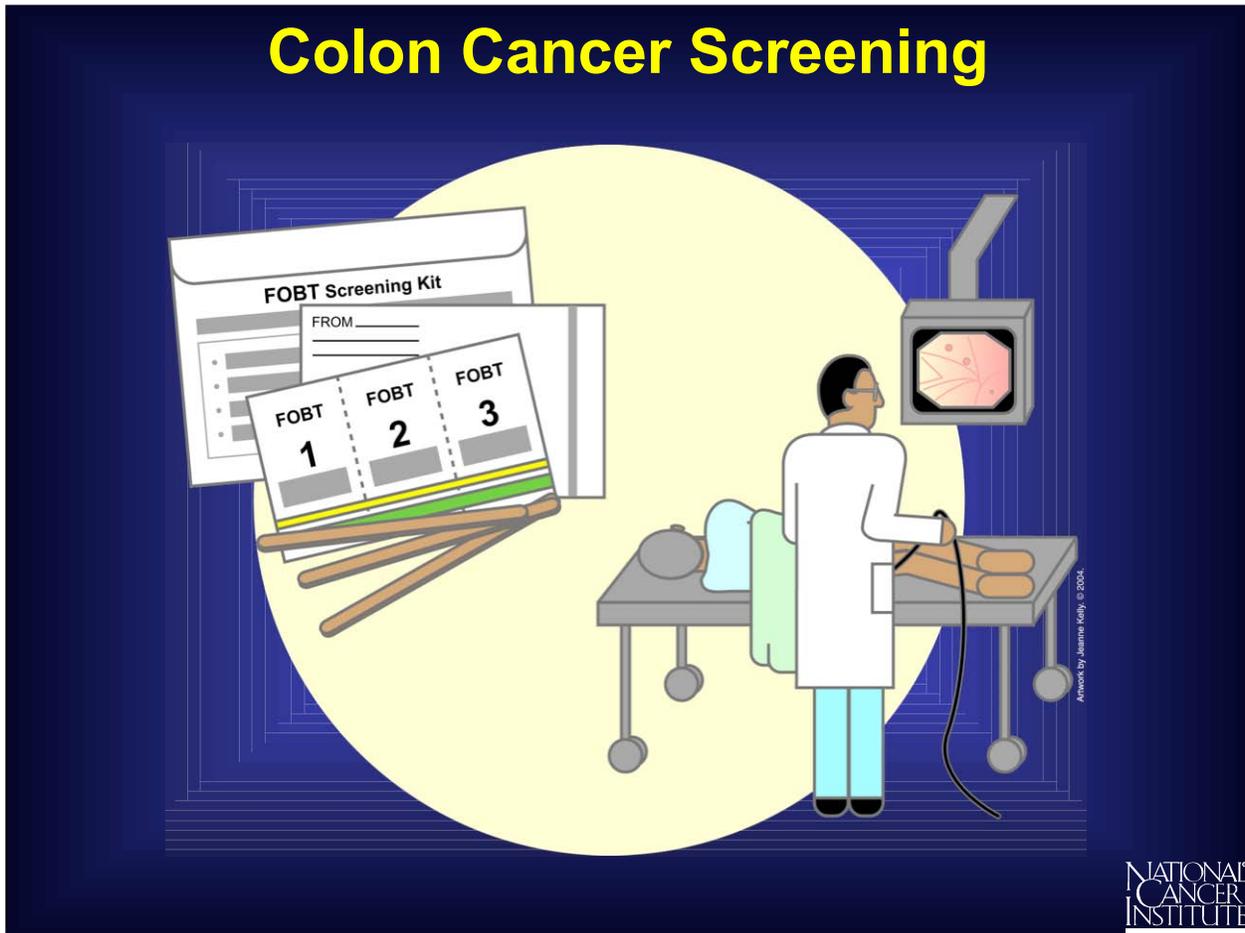
## Prostate and Ovarian Cancer Screening



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The U.S. Food and Drug Administration has approved the PSA test along with a digital rectal exam to help detect prostate cancer in men age 50 and older. Doctors often use the PSA test and DRE as prostate cancer screening tests; together, these tests can help doctors detect prostate cancer in men who have no symptoms of the disease. Most men with an elevated PSA test, though, turn out *not* to have cancer; only 25 to 30 percent of men who have a biopsy due to elevated PSA levels actually have prostate cancer, so researchers are working hard to find new clues. Experts are trying to develop better blood tests that might alert people to malignancies while the cancers are still in their early stages. For example, several new blood tests for ovarian or prostate cancer are under development.

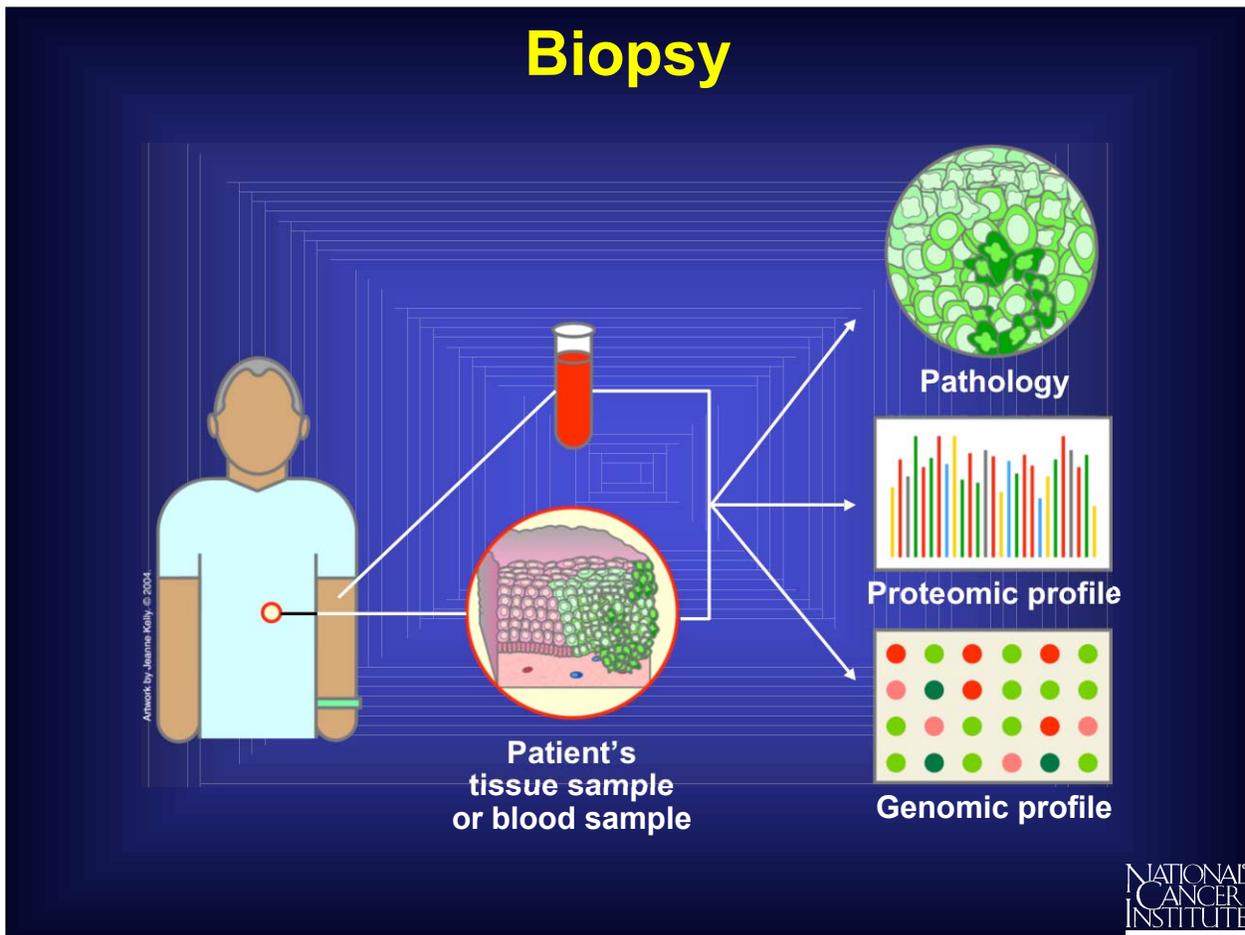
## Colon Cancer Screening



A procedure called a fecal occult blood test (FOBT) detects invisible amounts of blood in the feces, a possible sign of several disorders, including colon cancer. The test is painless and can be done at home or in the doctor's office along with a rectal exam. With an application stick, a dab of a stool specimen is smeared on a chemically treated card, which is tested in a laboratory for evidence of blood. If blood is confirmed in the stool, more elaborate tests may be performed to find the source of the bleeding.

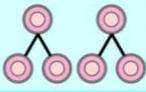
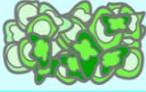
Some other options include sigmoidoscopy and colonoscopy. The former exam uses a lighted instrument called a sigmoidoscope to find precancerous or cancerous growths in the rectum and lower colon. The latter exam uses a lighted instrument called a colonoscope to find precancerous or cancerous growths throughout the colon, including the upper part.

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To diagnose the presence of cancer, a doctor must look at a sample of the affected tissue under the microscope. Hence, when preliminary symptoms, Pap test, mammogram, PSA test, FOBT, or colonoscopy indicate the possible existence of cancer, a doctor must then perform a biopsy, which is the surgical removal of a small piece of tissue for microscopic examination. (For leukemias, a small blood sample serves the same purpose.) This microscopic examination will tell the doctor whether a tumor is actually present and, if so, whether it is malignant (i.e., cancer) or benign. In addition, microarrays may be used to determine which genes are turned on or off in the sample, or proteomic profiles may be collected for an analysis of protein activity. This information will help doctors to make a more accurate diagnosis and may even help to inform treatment planning.

# Microscopic Appearance of Cancer Cells

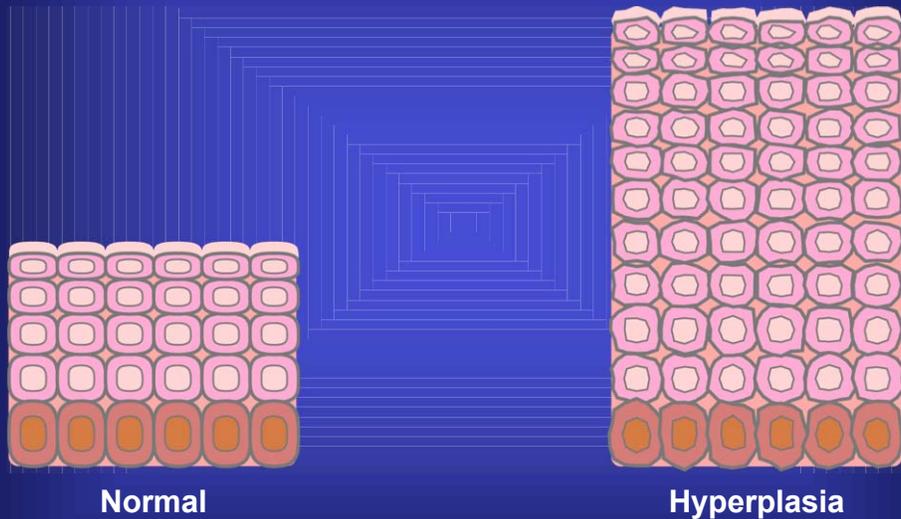
Normal	Cancer	
		Large number of irregularly shaped dividing cells
		Large, variably shaped nuclei
		Small cytoplasmic volume relative to nuclei
		Variation in cell size and shape
		Loss of normal specialized cell features
		Disorganized arrangement of cells
		Poorly defined tumor boundary

Adapted by Christine Kelly, © 2002.



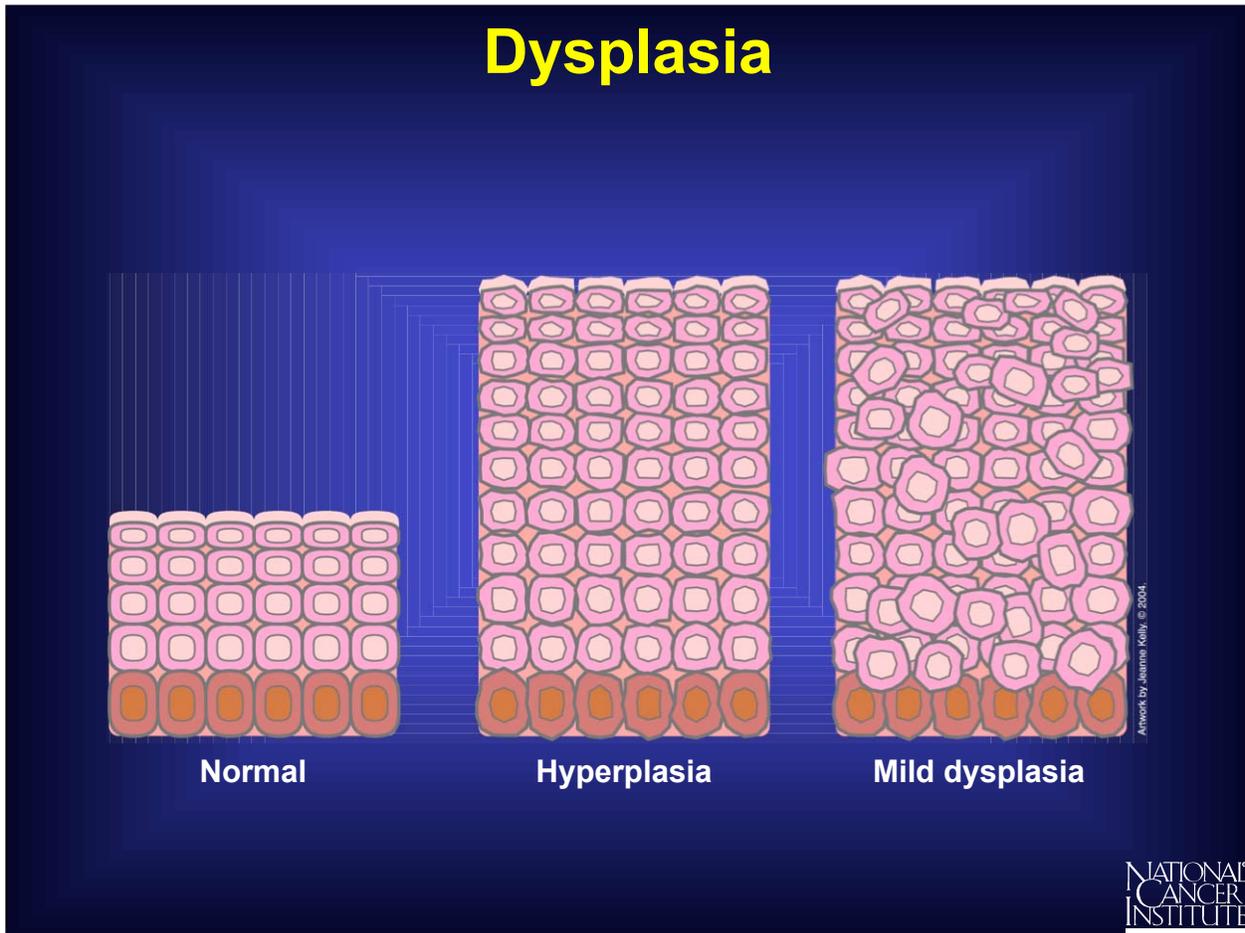
Cancer tissue has a distinctive appearance under the microscope. Among the traits the doctor looks for are a large number of irregularly shaped dividing cells, variation in nuclear size and shape, variation in cell size and shape, loss of specialized cell features, loss of normal tissue organization, and a poorly defined tumor boundary.

## Hyperplasia



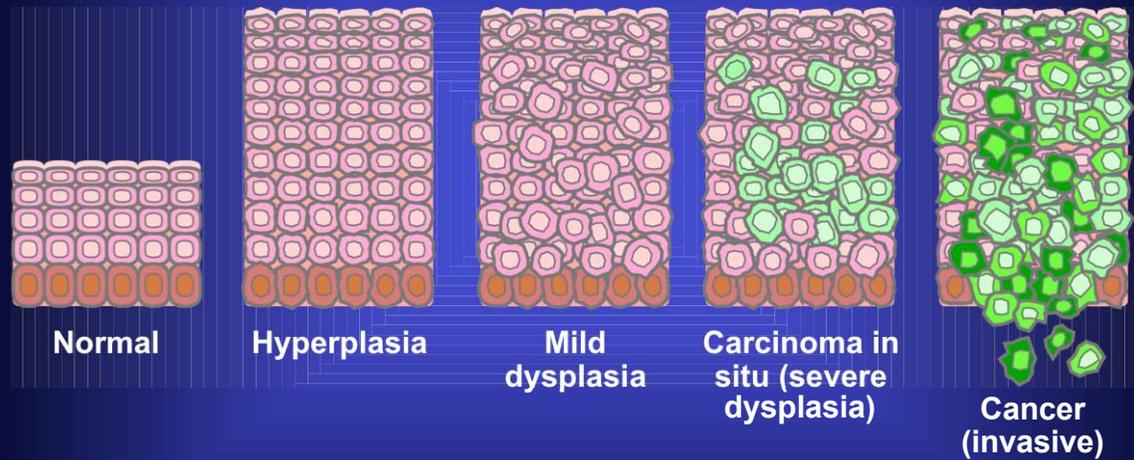
Instead of finding a benign or malignant tumor, microscopic examination of a biopsy specimen will sometimes detect a condition called “hyperplasia.” Hyperplasia refers to tissue growth based on an excessive rate of cell division, leading to a larger than usual number of cells. Nonetheless, cell structure and the orderly arrangement of cells within the tissue remain normal, and the process of hyperplasia is potentially reversible. Hyperplasia can be a normal tissue response to an irritating stimulus. An example of hyperplasia is a callus that may form on your hand when you first learn to swing a tennis racket or a golf club.

## Dysplasia



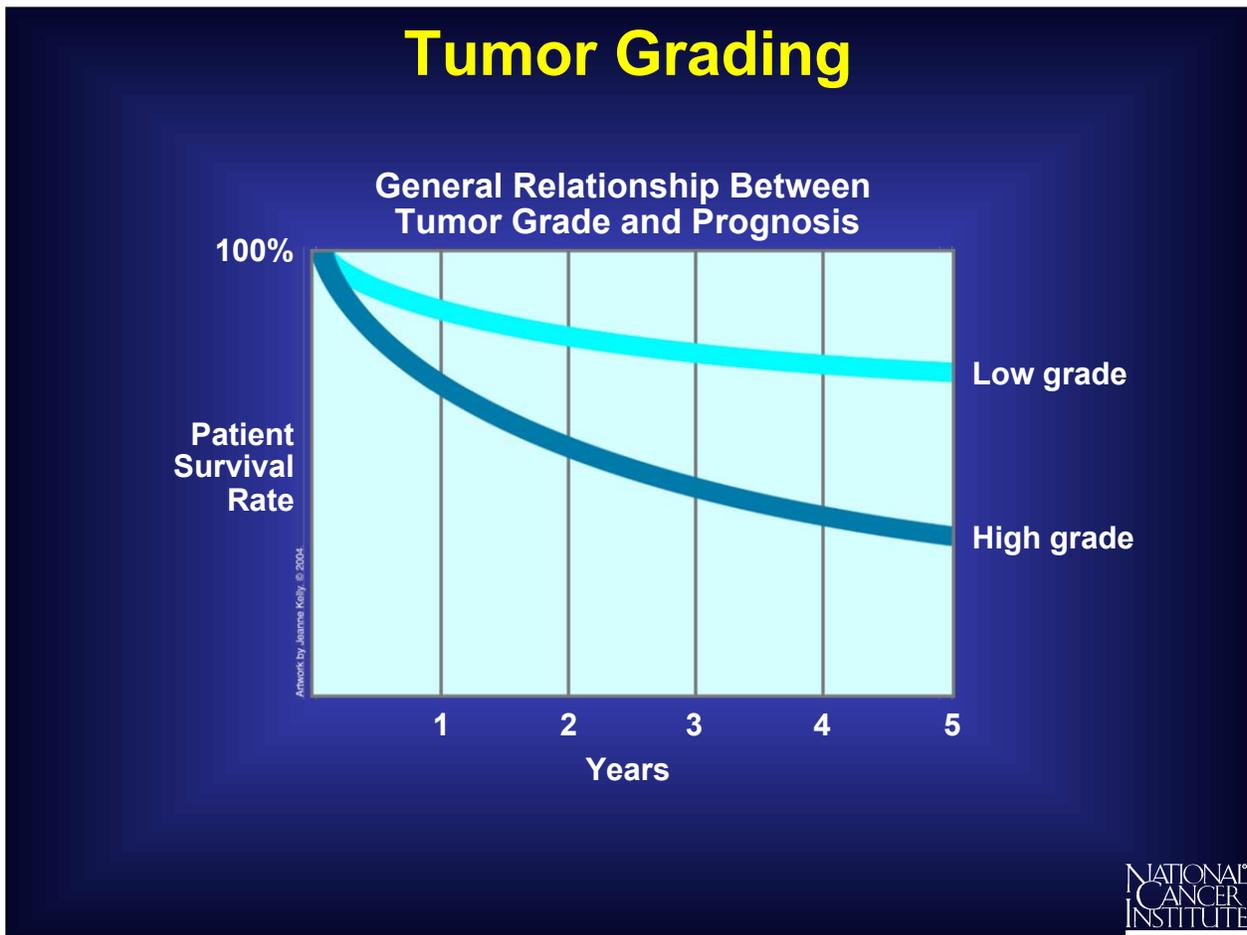
In addition to hyperplasia, microscopic examination of a biopsy specimen can detect another type of noncancerous condition called “dysplasia.” Dysplasia is an abnormal type of excessive cell proliferation characterized by loss of normal tissue arrangement and cell structure. Often such cells revert back to normal behavior, but occasionally they gradually become malignant. Because of their potential for becoming malignant, areas of dysplasia should be closely monitored by a health professional. Sometimes they need treatment.

## Carcinoma in Situ



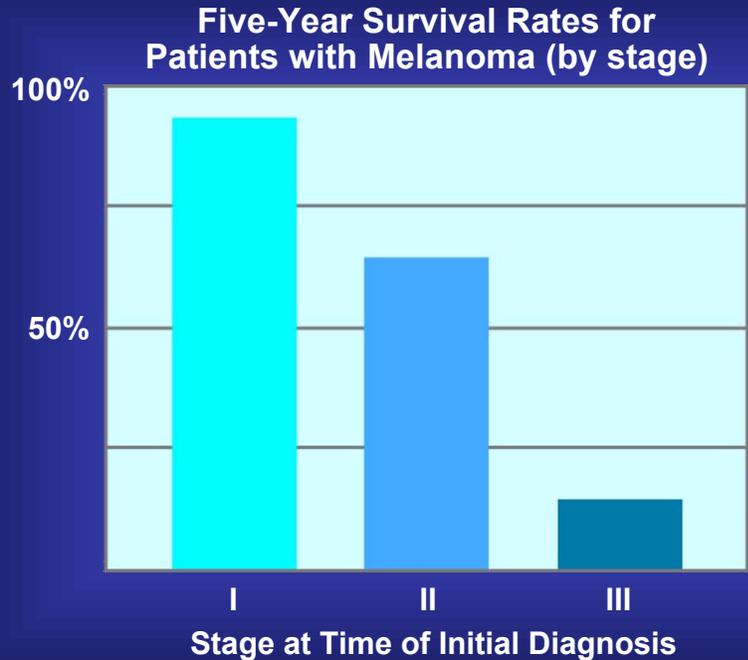
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The most severe cases of dysplasia are sometimes referred to as “carcinoma in situ.” In Latin, the term “in situ” means “in place,” so carcinoma in situ refers to an uncontrolled growth of cells that remains in the original location. However, carcinoma in situ may develop into an invasive, metastatic malignancy and, therefore, is usually removed surgically, if possible.



Microscopic examination also provides information regarding the likely behavior of a tumor and its responsiveness to treatment. Cancers with highly abnormal cell appearance and large numbers of dividing cells 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. In this grading system, a low number grade (grade I or II) refers to cancers with fewer cell abnormalities than those with higher numbers (grade III, IV).

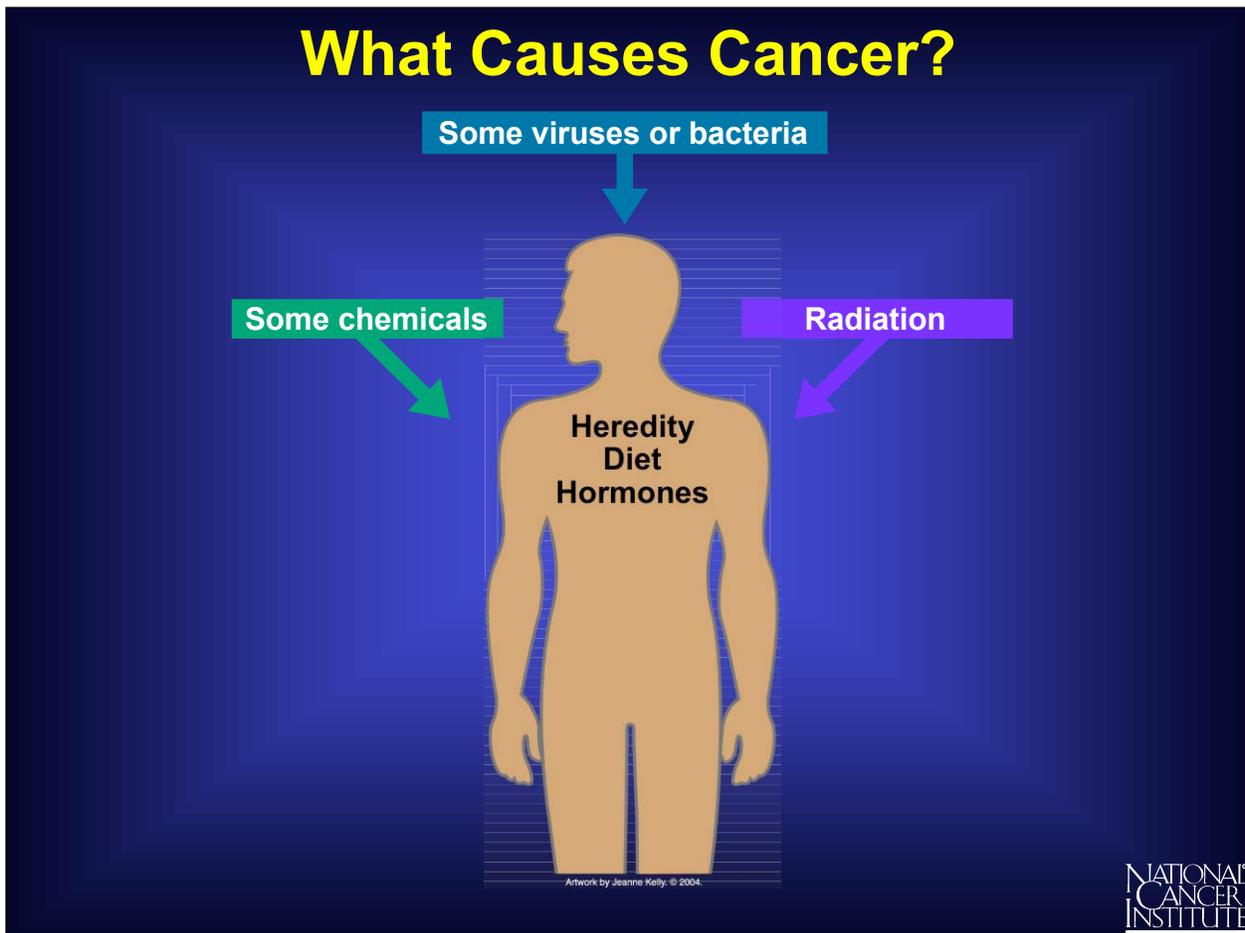
## Tumor Staging



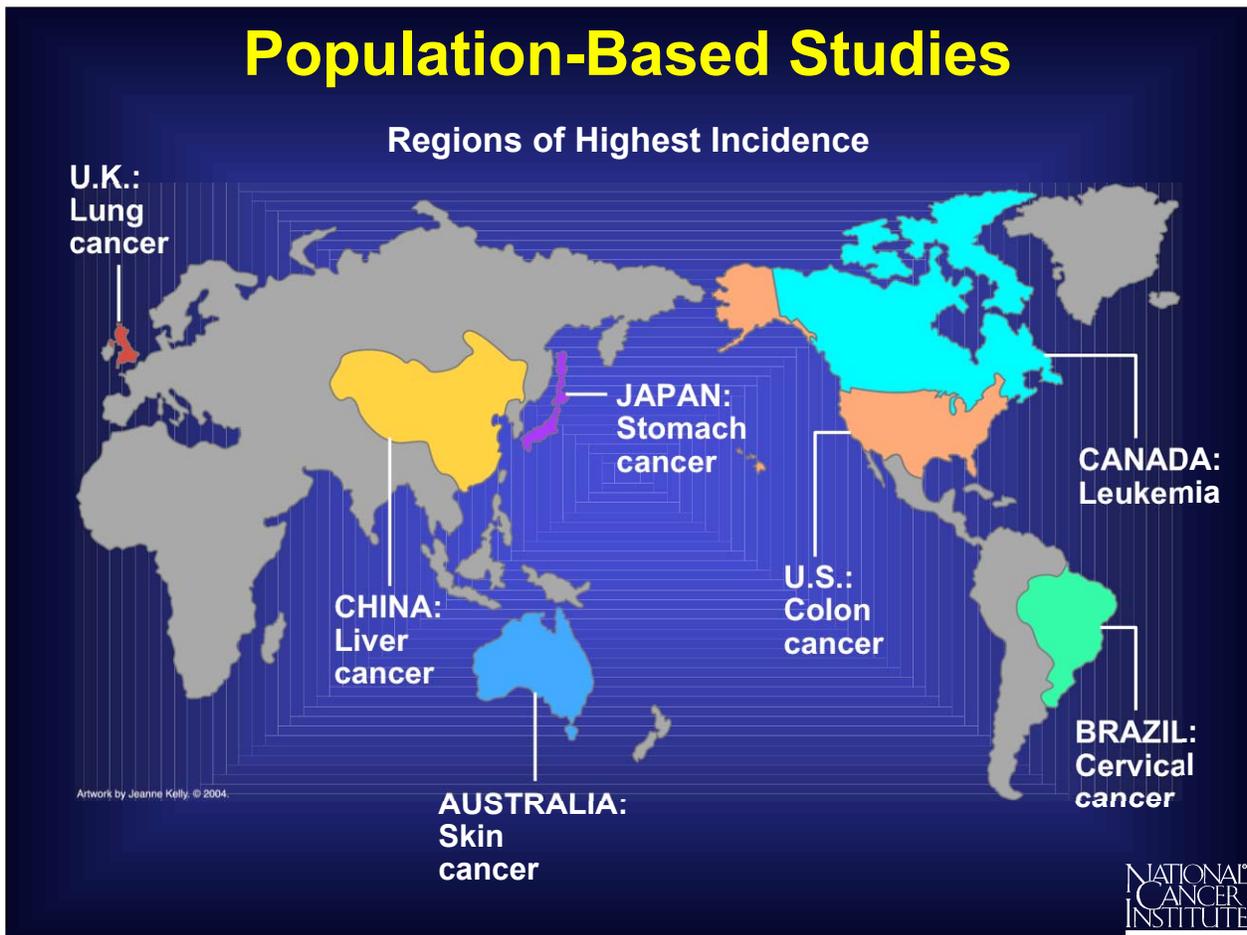
After cancer has been diagnosed, doctors ask the following three questions to determine how far the disease has progressed:

1. How large is the tumor, and how deeply has it invaded surrounding tissues?
2. Have cancer cells spread to regional lymph nodes?
3. Has the cancer spread (metastasized) to other regions of the body?

Based on the answers to these questions, the cancer is assigned a “stage.” A patient’s chances for survival are better when cancer is detected at a lower stage.



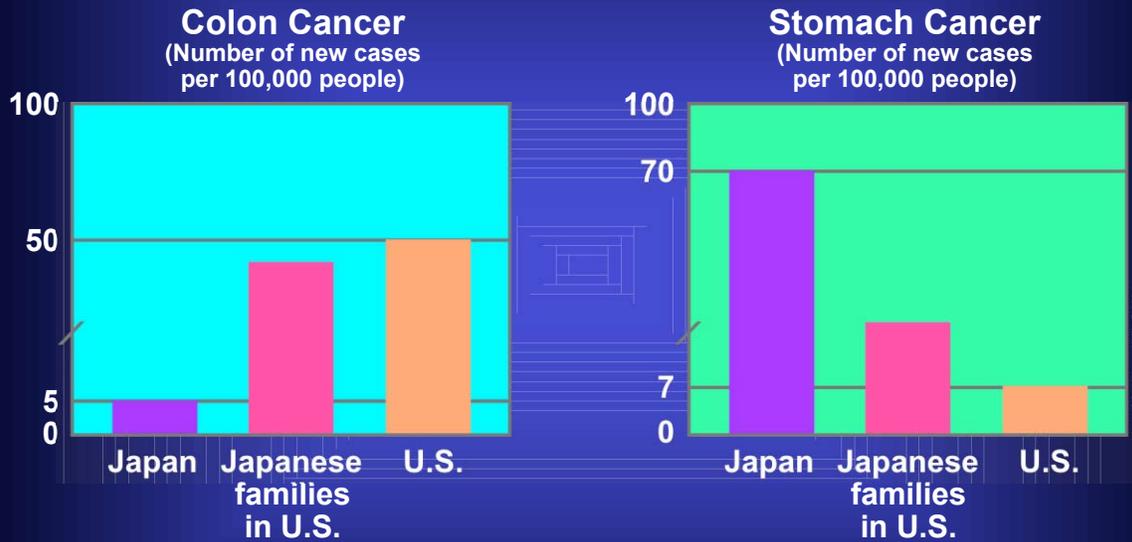
Cancer is often perceived as a disease that strikes for no apparent reason. While scientists don't yet know all the reasons, many of the causes of cancer have already been identified. Besides intrinsic factors such as heredity, diet, and hormones, scientific studies point to key extrinsic factors that contribute to the cancer's development: chemicals (e.g., smoking), radiation, and viruses or bacteria.



One way of identifying the various causes of cancer is by studying populations and behaviors. This approach compares cancer rates among various groups of people exposed to different factors or exhibiting different behaviors. A striking finding to emerge from population studies is that cancers arise with different frequencies in different areas of the world. For example, stomach cancer is especially frequent in Japan, colon cancer is prominent in the United States, and skin cancer is common in Australia. What is the reason for the high rates of specific kinds of cancer in certain countries?

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## Hereditiy? Behaviors? Other Factors?



In theory, differences in heredity or environmental risk factors might be responsible for the different cancer rates observed in different countries. Studies on people who have moved from one country to another suggest that exposure to risk factors for cancer varies by geographic location. For example, in Japan, the rate of colon cancer is lower, and the rate of stomach cancer is higher, than in the United States. But this difference has been found to gradually disappear in Japanese families that have moved to the United States. This suggests that the risk of developing the two kinds of cancer is not determined primarily by heredity. The change in risk for cancer for Japanese families could involve cultural, behavioral, or environmental factors predominant in one location and not in the other.

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## Tobacco Use and Cancer

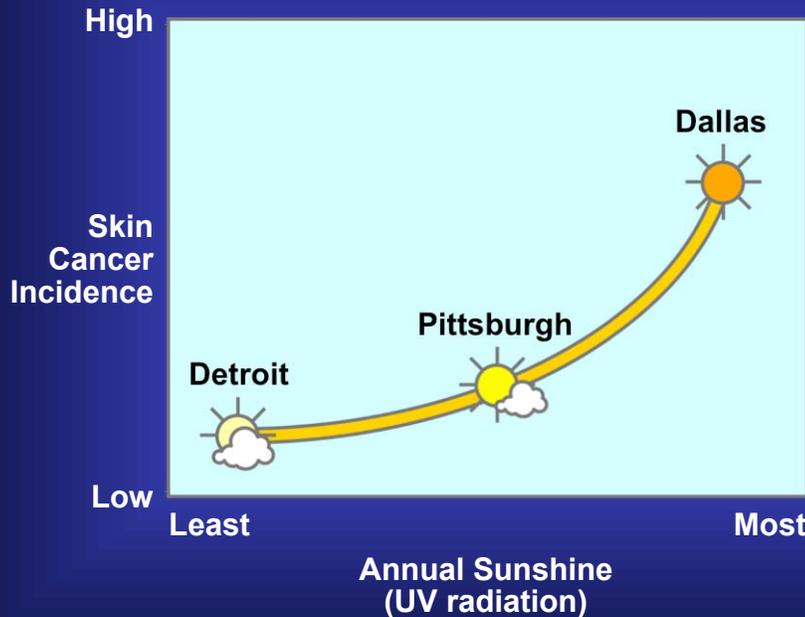
### Some Cancer-Causing Chemicals in Tobacco Smoke

The infographic features a list of 30 cancer-causing chemicals in tobacco smoke, arranged in three columns. A stylized illustration of a person with orange hair and yellow earrings, wearing a blue shirt, is shown smoking a cigarette. A large, light-colored speech bubble-like shape surrounds the list of chemicals. The National Cancer Institute logo is in the bottom right corner.

aminostilbene	indeno[1,2,3-c d]pyrene	N-nitrosomethylethylamine
arsenic	S-methylchrysene	N-nitrosodiethylamine
benz[a]anthracene	S-methylfluoranthene	N-nitrosornicotine
benz[a]pyrene	<i>alpha</i> -naphthylamine	N-nitrosoanabasine
benzene	nickel compounds	N-nitrosopiperidine
benzo[b]fluoranthene	N-nitrosodimethylamine	polonium-210
benzo[c]phenanthrene		
benzo[f]fluoranthene		
cadmium		
chrysene		
dibenz[a c]anthracene		
dibenzo[a e]fluoranthene		
dibenz[a h]acridine		
dibenz[a j]acridine		
dibenzo[c g]carbazone		
N-dibutyl nitrosamine		
2,3-dimethylchrysene		

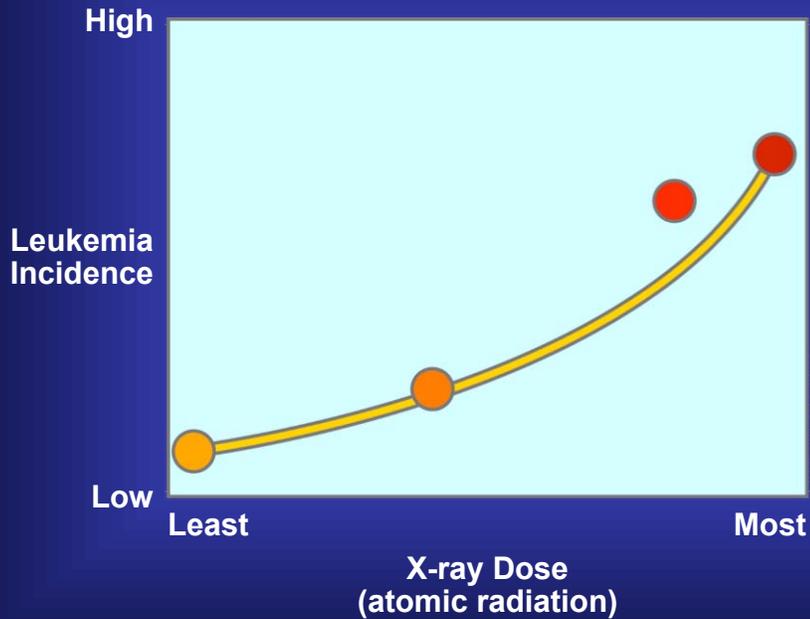
Among the various factors that can cause cancer, tobacco smoking is the greatest public health hazard. Cigarette smoke contains more than two dozen different chemicals capable of causing cancer. Cigarette smoking is the main cause of lung cancer and contributes to many other kinds of cancer as well, including cancer of the 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. Other forms of tobacco use also can cause cancer. For example, cigars, pipe smoke, and smokeless tobacco can cause cancers of the mouth.

## Low-Strength Radiation



Some atoms give off radiation, which is energy that travels through space. Prolonged or repeated exposure to certain types of radiation can cause cancer. Cancer caused by the sun's ultraviolet radiation is most common in people who spend long hours in strong sunlight. Ultraviolet radiation from sunlight is a low-strength type of radiation. Effective ways to protect against ultraviolet radiation and to prevent skin cancer are to avoid going into strong, direct sunlight and to wear protective clothing. Sunscreen lotions reduce the risk of some forms of skin cancers.

## High-Strength Radiation

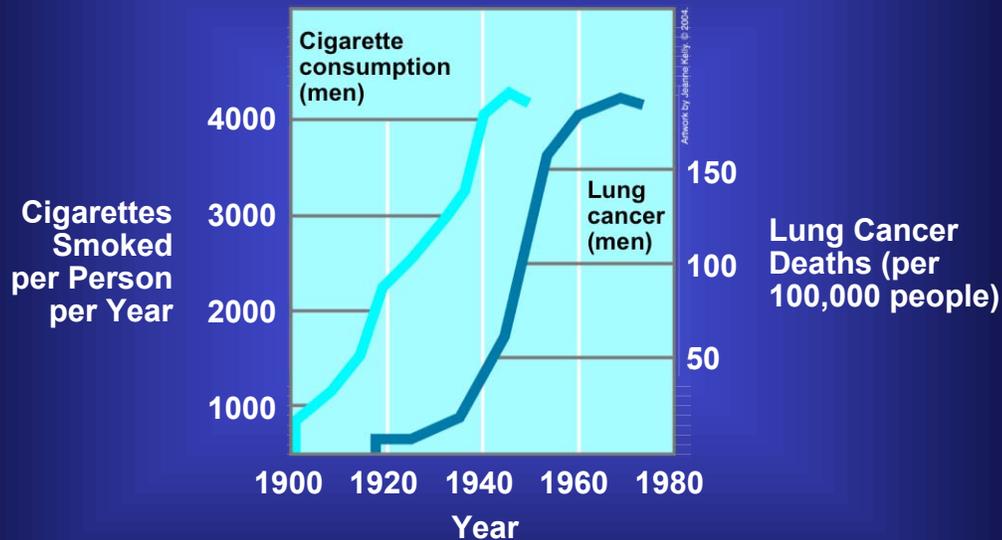


Increased rates of cancer also have been detected in people exposed to high-strength forms of radiation such as X-rays or radiation emitted from unstable atoms called radioisotopes. Because these two types of radiation are stronger than ultraviolet radiation, they can penetrate through clothing and skin into the body. Therefore, high-strength radiation can cause cancers of internal body tissues. Examples include cancer caused by nuclear fallout from atomic explosions and cancers caused by excessive exposure to radioactive chemicals.

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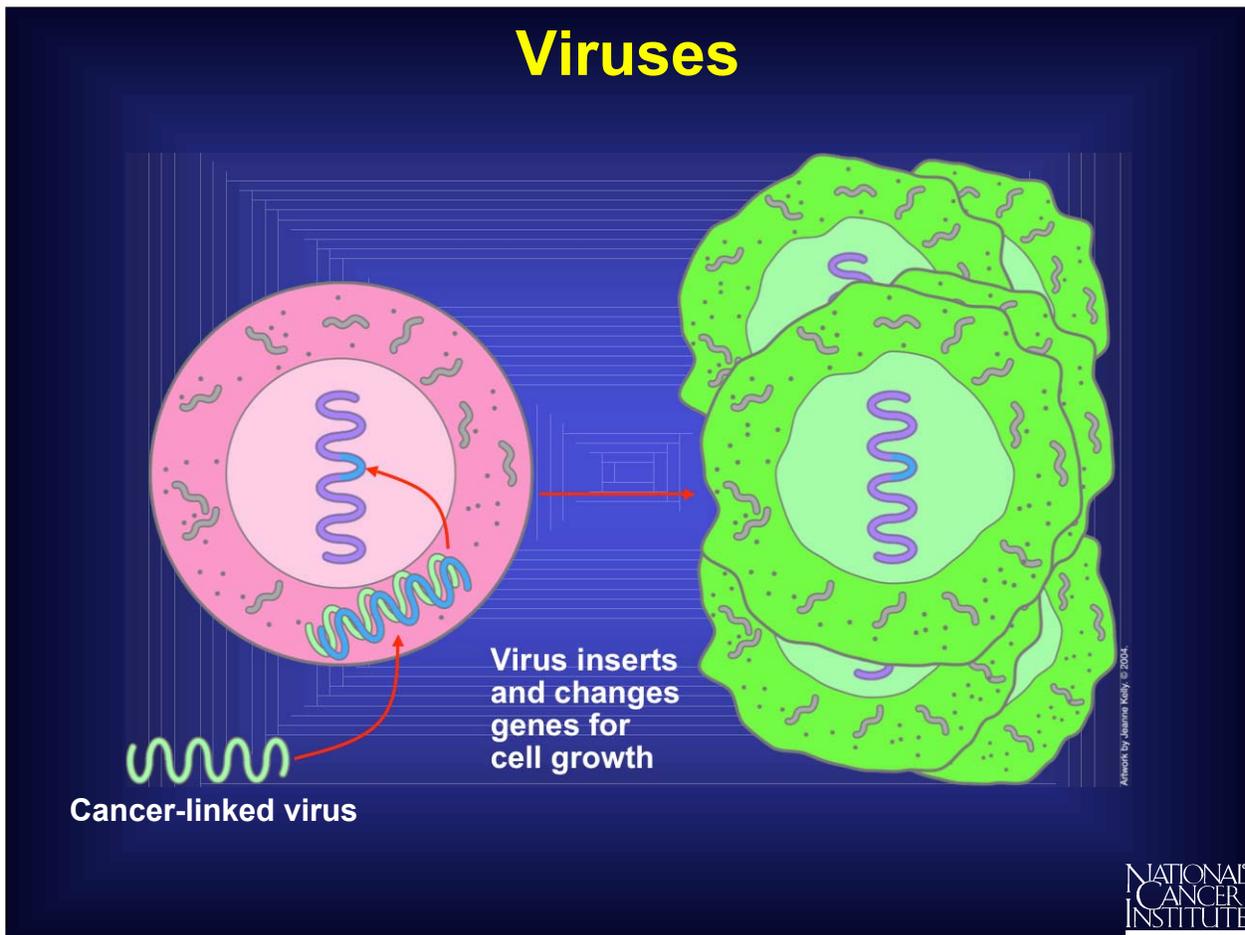
## Lag Time

**20-Year Lag Time Between Smoking and Lung Cancer**



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Chemicals and radiation that are capable of triggering the development of cancer are called “carcinogens.” Carcinogens act through a multistep process that initiates a series of genetic alterations (“mutations”) and stimulates cells to proliferate. A prolonged period of time is usually required for these multiple steps. There can be a delay of several decades between exposure to a carcinogen and the onset of cancer. For example, young people exposed to carcinogens from smoking cigarettes generally do not develop cancer for 20 to 30 years. This period between exposure and onset of disease is the lag time.



In addition to chemicals and radiation, a few viruses also can trigger the development of cancer. In general, viruses are small infectious agents that cannot reproduce on their own, but instead enter into living cells and cause the infected cell to produce more copies of the virus. Like cells, viruses store their genetic instructions in large molecules called nucleic acids. In the case of cancer viruses, some of the viral genetic information carried in these nucleic acids is inserted into the chromosomes of the infected cell, and this causes the cell to become malignant.

## Examples of Human Cancer Viruses

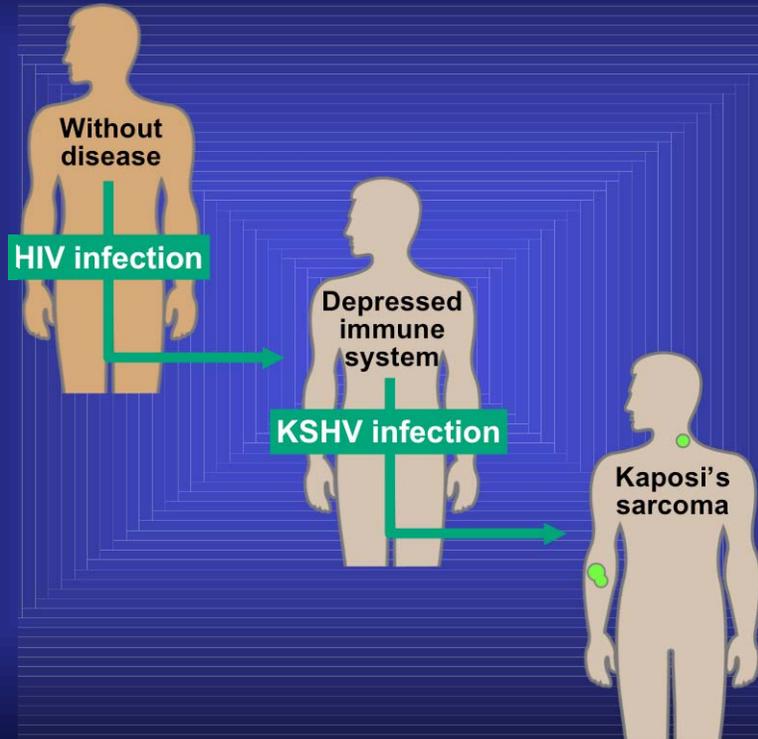
### Some Viruses Associated with Human Cancers

<i>Virus</i>	<i>Type of Cancer</i>
Epstein-Barr virus	Burkitt's lymphoma
Human papillomavirus	Cervical cancer
Hepatitis B virus	Liver cancer
Human T-cell lymphotropic virus	Adult T-cell leukemia
Kaposi's sarcoma-associated herpesvirus	Kaposi's sarcoma

Artwork by Jalaina Koff, © 2004.

Only a few viruses that infect human cells actually cause cancer. Included in this category are viruses implicated in cervical cancer, liver cancer, and certain lymphomas, leukemias, and sarcomas. Susceptibility to these cancers can sometimes be spread from person to person by infectious viruses, although such events account for only a very small fraction of human cancers. For example, the risk of cervical cancer is increased in women with multiple sexual partners and is especially high in women who marry men whose previous wives had this disease. Transmission of the human papillomavirus (HPV) during sexual relations appears to be involved.

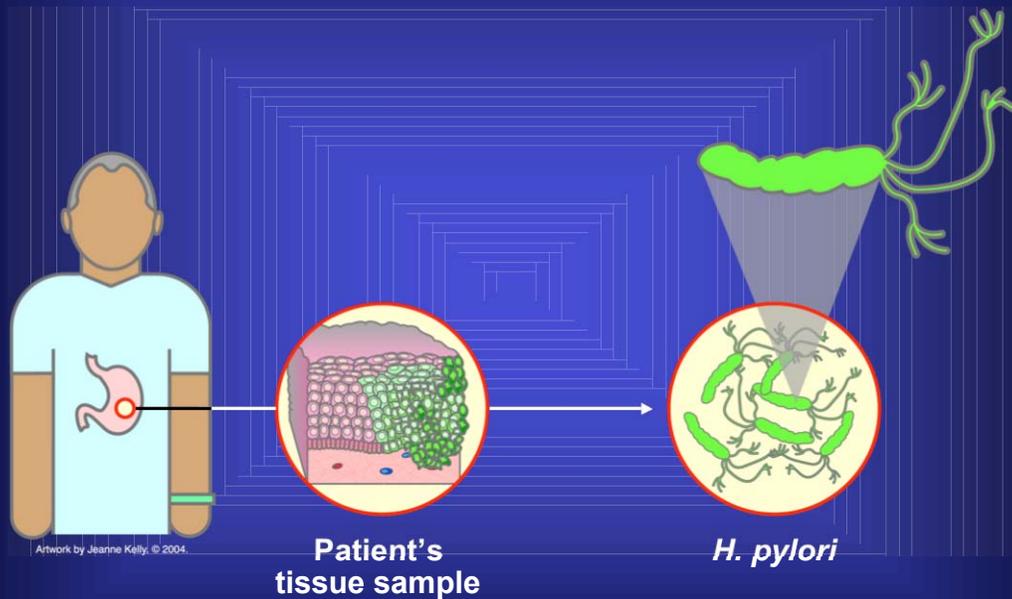
## AIDS and Kaposi's Sarcoma



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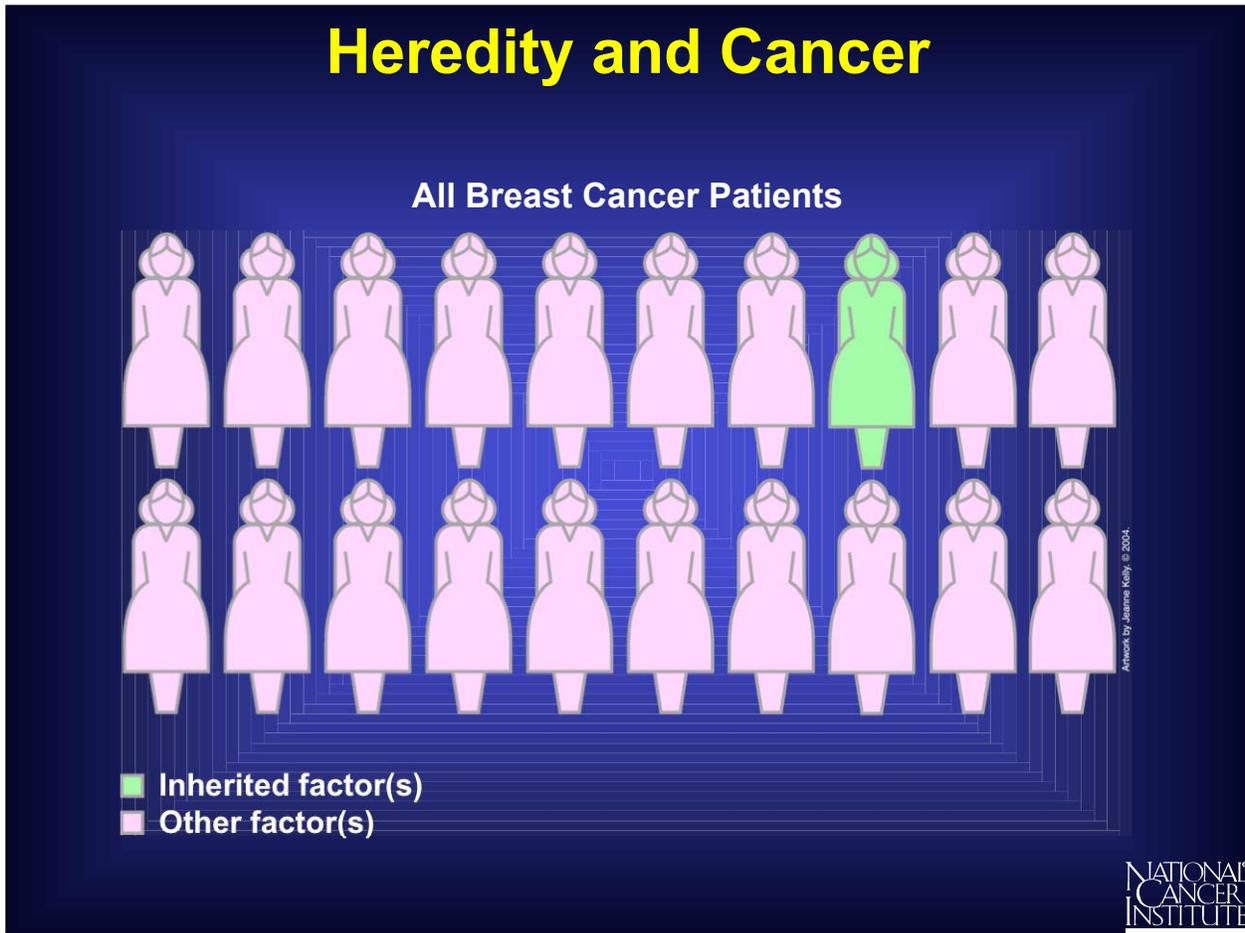
People who develop AIDS after being infected with the human immunodeficiency virus (HIV) are at high risk for developing a specific type of cancer called Kaposi's sarcoma. Kaposi's sarcoma is a malignant tumor of blood vessels located in the skin. This type of cancer is not directly caused by HIV infection. Instead, HIV causes an immune deficiency that makes people more susceptible to viral infection. Infection by a virus called KSHV (Kaposi's sarcoma-associated herpesvirus) then appears to stimulate the development of Kaposi's sarcoma.

## Bacteria and Stomach Cancer



Viruses are not the only infectious agents that have been implicated in human cancer. The bacterium *Helicobacter pylori*, which can cause stomach ulcers, has been associated with the development of cancer, so people infected with *H. pylori* are at increased risk for stomach cancer. Research is under way to define the genetic interactions between this infectious agent and its host tissues that may explain why cancer develops.

## HereditY and Cancer



Cancer is not considered an inherited illness because most cases of cancer, perhaps 80 to 90 percent, occur in people with no family history of the disease. However, a person's chances of developing cancer can be influenced by the inheritance of certain kinds of genetic alterations. These alterations tend to increase an individual's susceptibility to developing cancer in the future. For example, about 5 percent of breast cancers are thought to be due to inheritance of particular form(s) of a "breast cancer susceptibility gene."

## **Heredity Can Affect Many Types of Cancer**

### **Inherited Conditions That Increase Risk for Cancer**

<i>Name of Condition</i>	<i>Type of Cancer</i>
<b>Hereditary retinoblastoma</b>	<b>Retinoblastoma</b>
<b>Xeroderma pigmentosum</b>	<b>Skin</b>
<b>Wilms' tumor</b>	<b>Kidney</b>
<b>Li-Fraumeni syndrome</b>	<b>Sarcomas, brain, breast, leukemia</b>
<b>Familial adenomatous polyposis</b>	<b>Colon, rectum</b>
<b>Paget's disease of bone</b>	<b>Bone</b>
<b>Fanconi's aplastic anemia</b>	<b>Leukemia, liver, skin</b>

Atwork by Jeanne Kelly © 2004.

Inherited mutations can influence a person's risk of developing many types of cancer in addition to breast cancer. For example, certain inherited mutations have been described that increase a person's risk of developing colon, kidney, bone, skin or other specific forms of cancer. But these hereditary conditions are thought to be involved in only 10 percent or fewer of all cancer cases.

## Genetic Testing

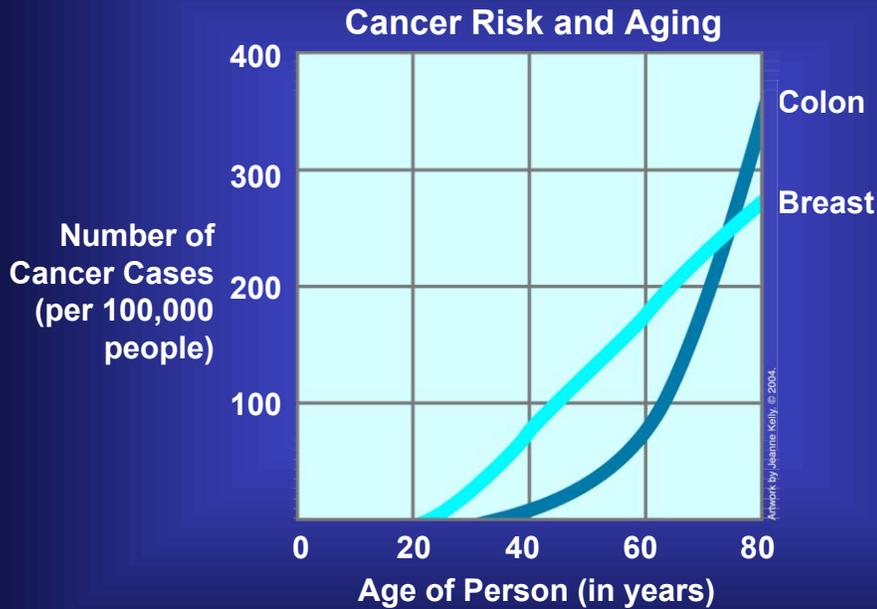


Illustration by Joanna Kelly, © 2004.

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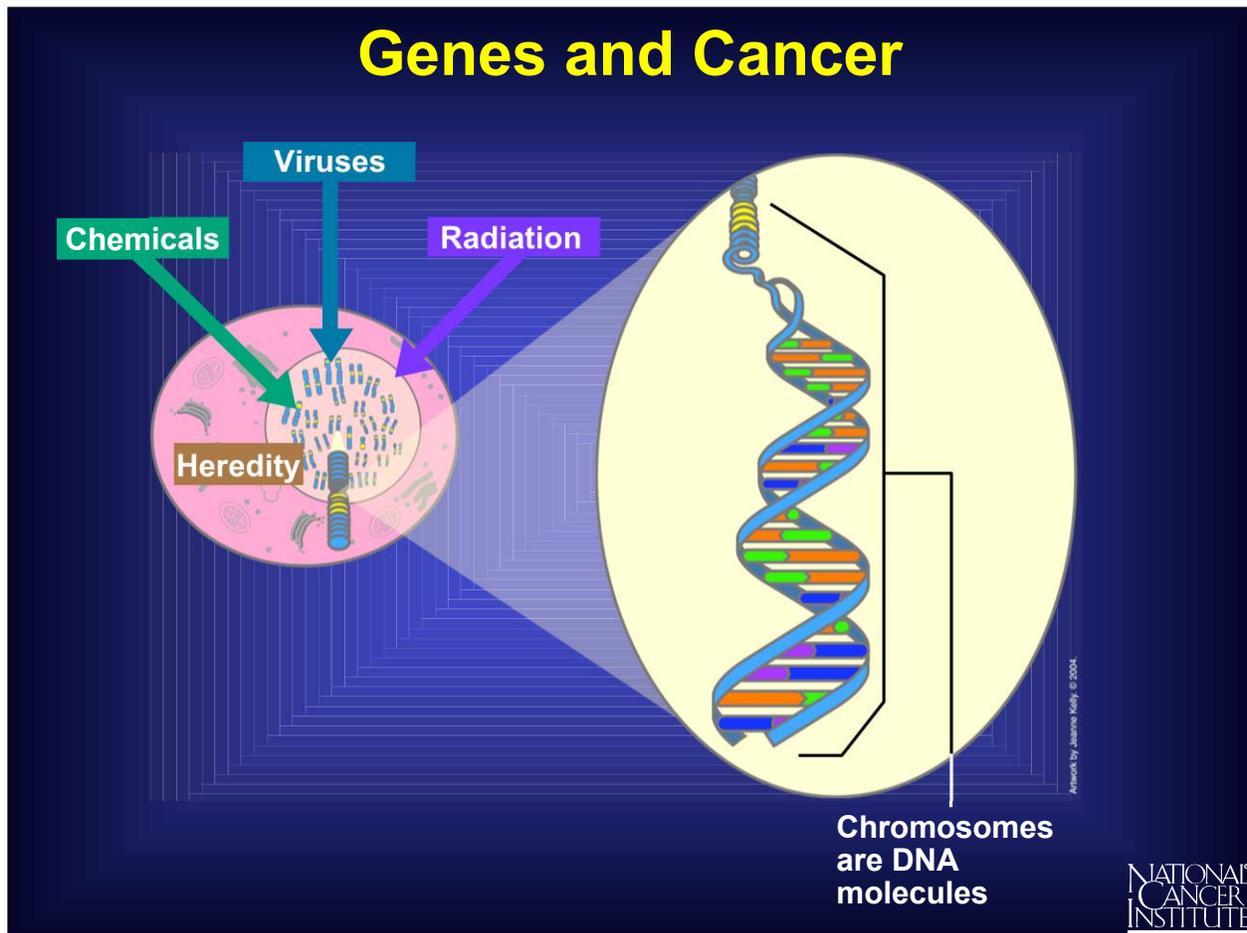
Laboratory tests can determine whether a person carries some of the genetic alterations that can increase the risk of developing certain cancers. For example, women who inherit certain forms of a gene called BRCA1 or BRCA2 have an elevated risk of developing breast cancer. For women with a family history of breast cancer, taking such a test may relieve uncertainty about their future risk. However, the information obtained from genetic tests is often complex and difficult to interpret. The decision to undergo genetic testing should therefore be a personal, voluntary one and should only be made in conjunction with appropriate genetic counseling.

## Cancer Risk and Aging



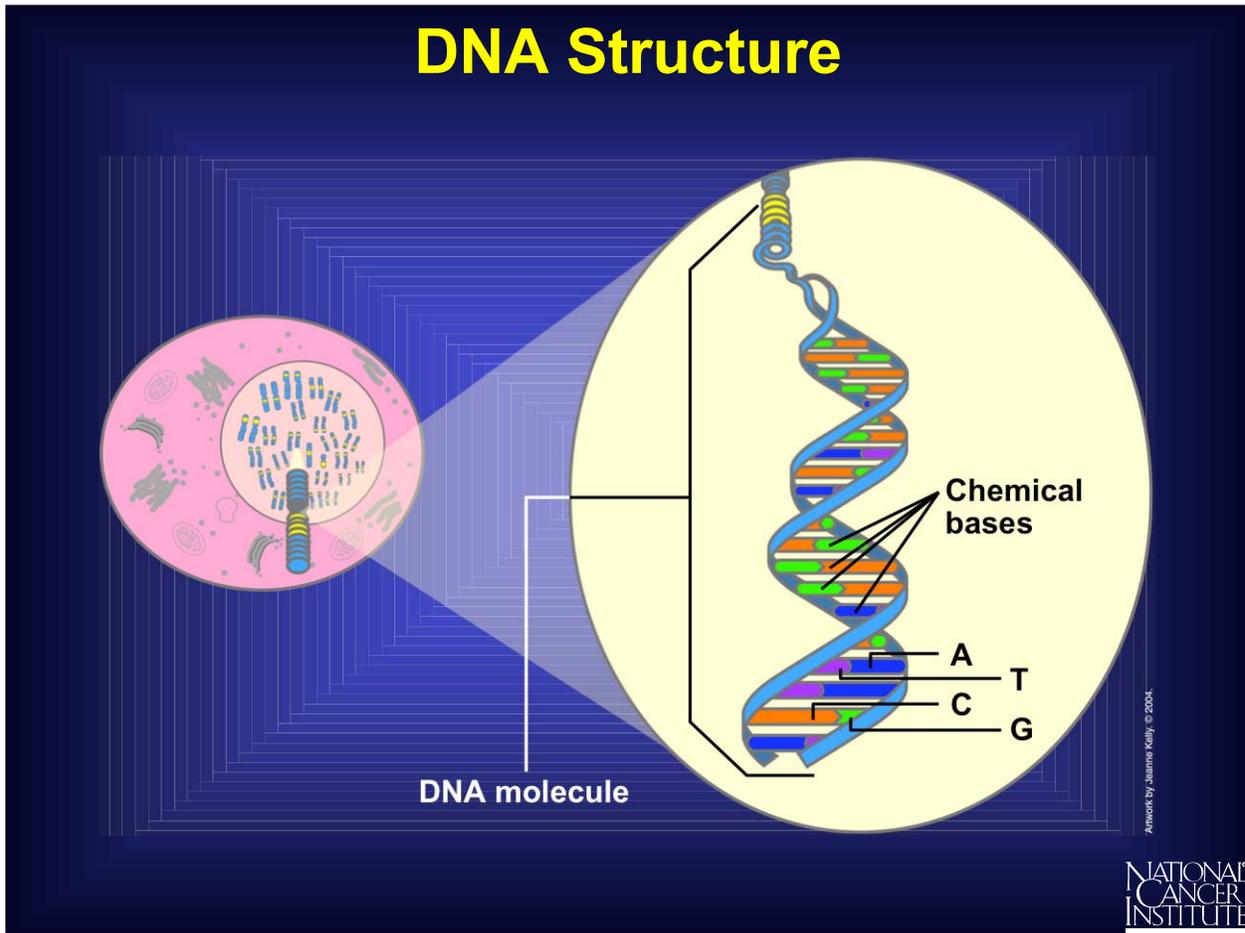
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Because a number of mutations usually must occur for cancer to arise, the chances of developing cancer increase as a person gets older because more time has been available for mutations to accumulate. For example, a 75-year-old person is a hundred times more likely to develop colon cancer than a 25-year-old. Because people are living longer today than they did 50 or 100 years ago, they have a longer exposure time to factors that may promote gene changes linked to cancer.



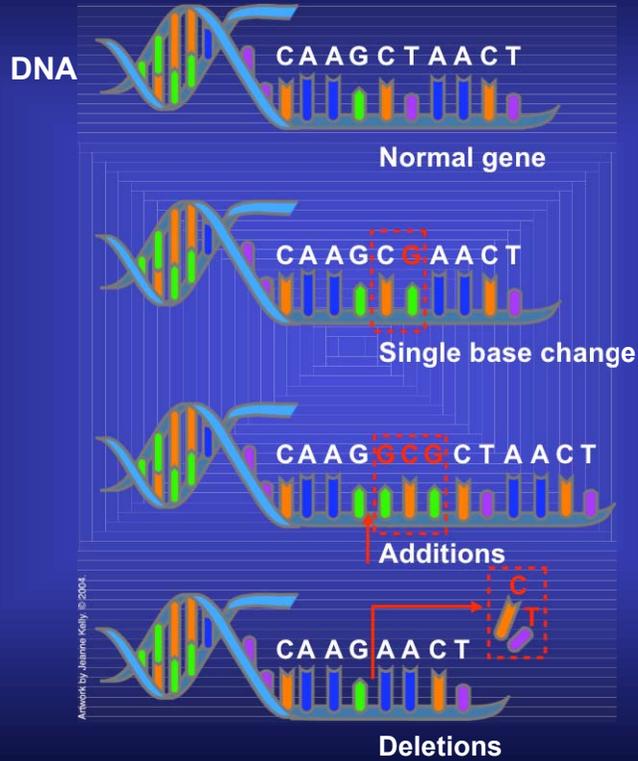
Chemicals (e.g., from smoking), radiation, viruses, and heredity all contribute to the development of cancer by triggering changes in a cell's genes. Chemicals and radiation act by damaging genes, viruses introduce their own genes into cells, and heredity passes on alterations in genes that make a person more susceptible to cancer. Genes are inherited instructions that reside within a person's chromosomes. Each gene instructs a cell how to build a specific product--in most cases, a particular kind of protein. Genes are altered, or "mutated," in various ways as part of the mechanism by which cancer arises.

## DNA Structure

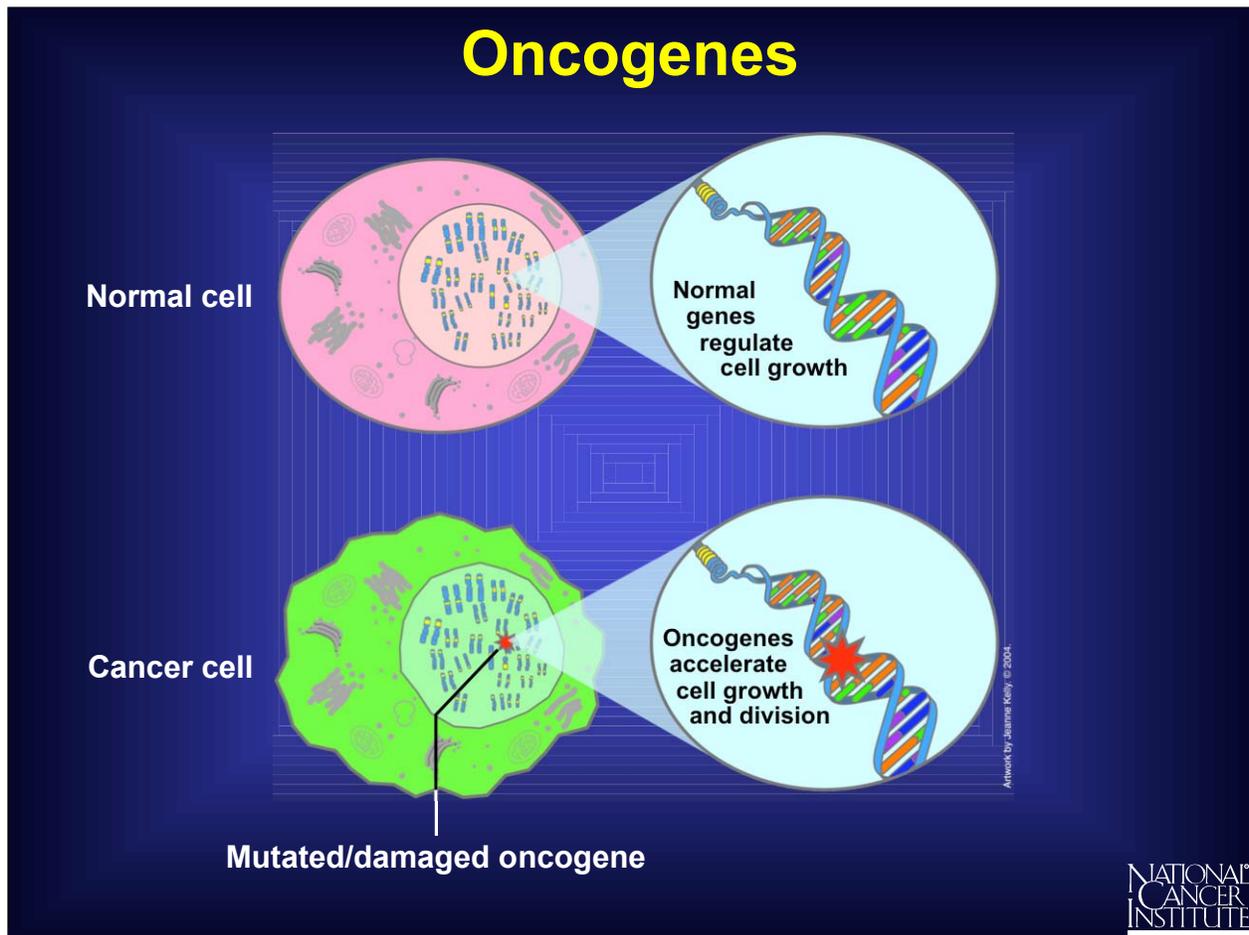


Genes reside within chromosomes, the large DNA molecules, which are composed of two chemical strands twisted around each other to form a “double helix.” Each strand is constructed from millions of chemical building blocks called “bases.” DNA contains only four different bases: adenine, thymine, cytosine, and guanine (abbreviated A, T, G, and C), but they can be arranged in any sequence. The sequential order of the bases in any given gene determines the message the gene contains, just as the letters of the alphabet can be combined in different ways to form distinct words and sentences.

## DNA Mutation

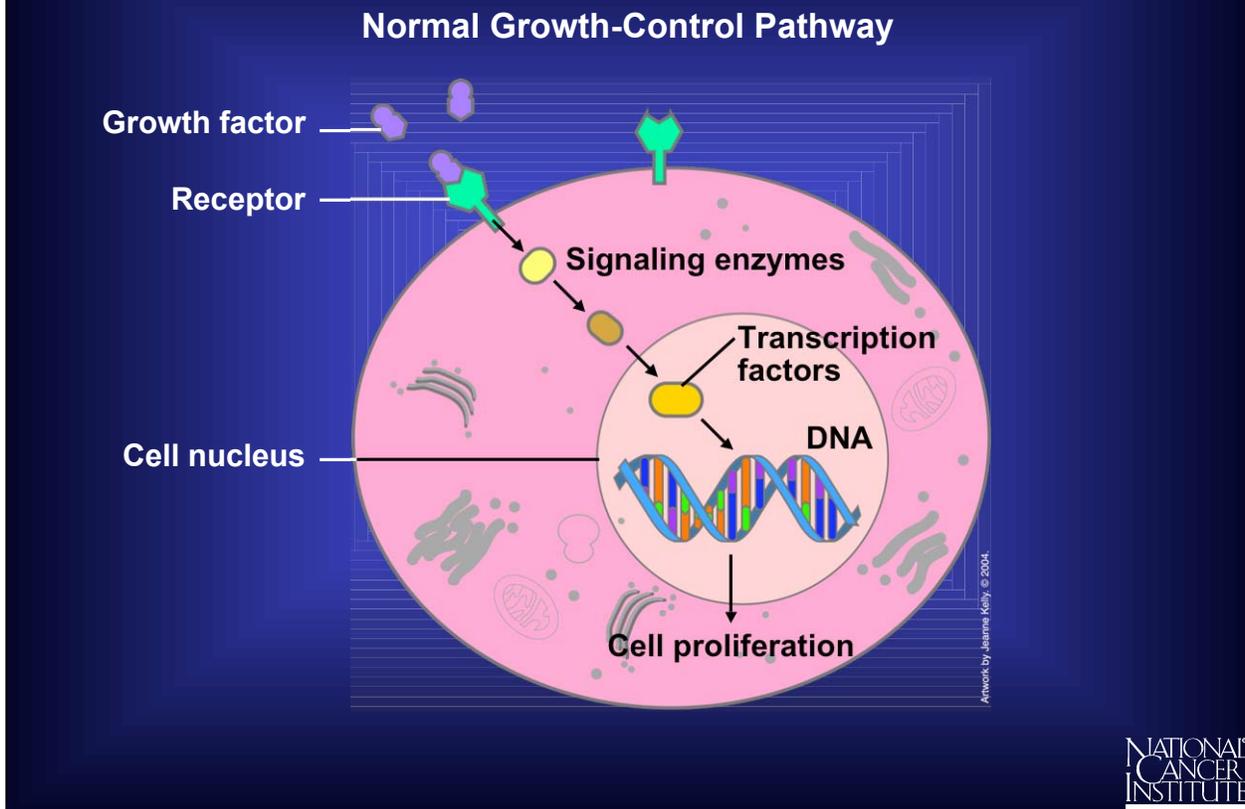


Genes can be mutated in several different ways. The simplest type of mutation involves a change in a single base along the base sequence of a particular gene--much like a typographical error in a word that has been misspelled. In other cases, one or more bases may be added or deleted. And sometimes, large segments of a DNA molecule are accidentally repeated, deleted, or moved.



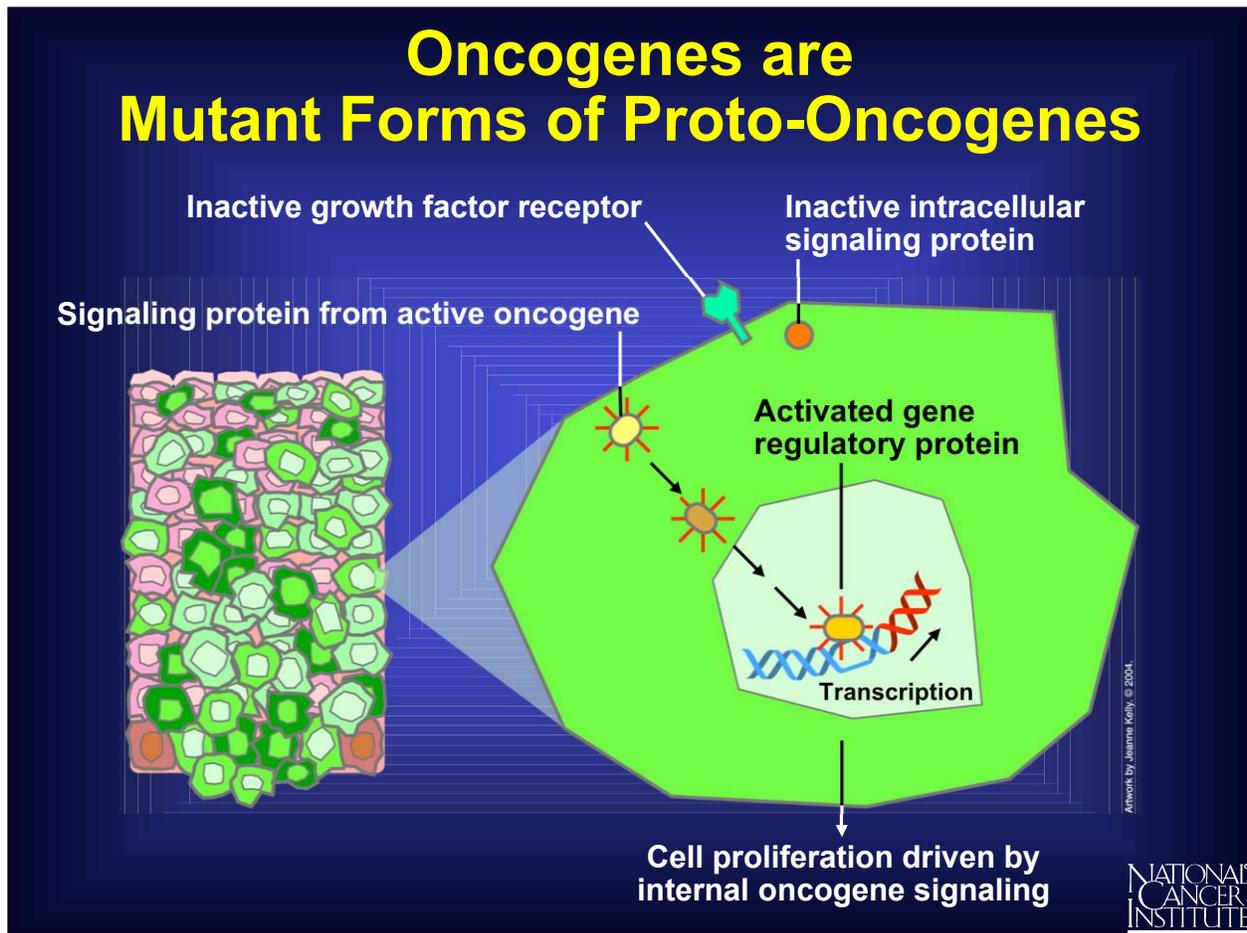
One group of genes implicated in the development of cancer are damaged genes, called “oncogenes.” Oncogenes are genes whose PRESENCE in certain forms and/or overactivity can stimulate the development of cancer. When oncogenes arise in normal cells, they can contribute to the development of cancer by instructing cells to make proteins that stimulate excessive cell growth and division.

## Proto-Oncogenes and Normal Cell Growth



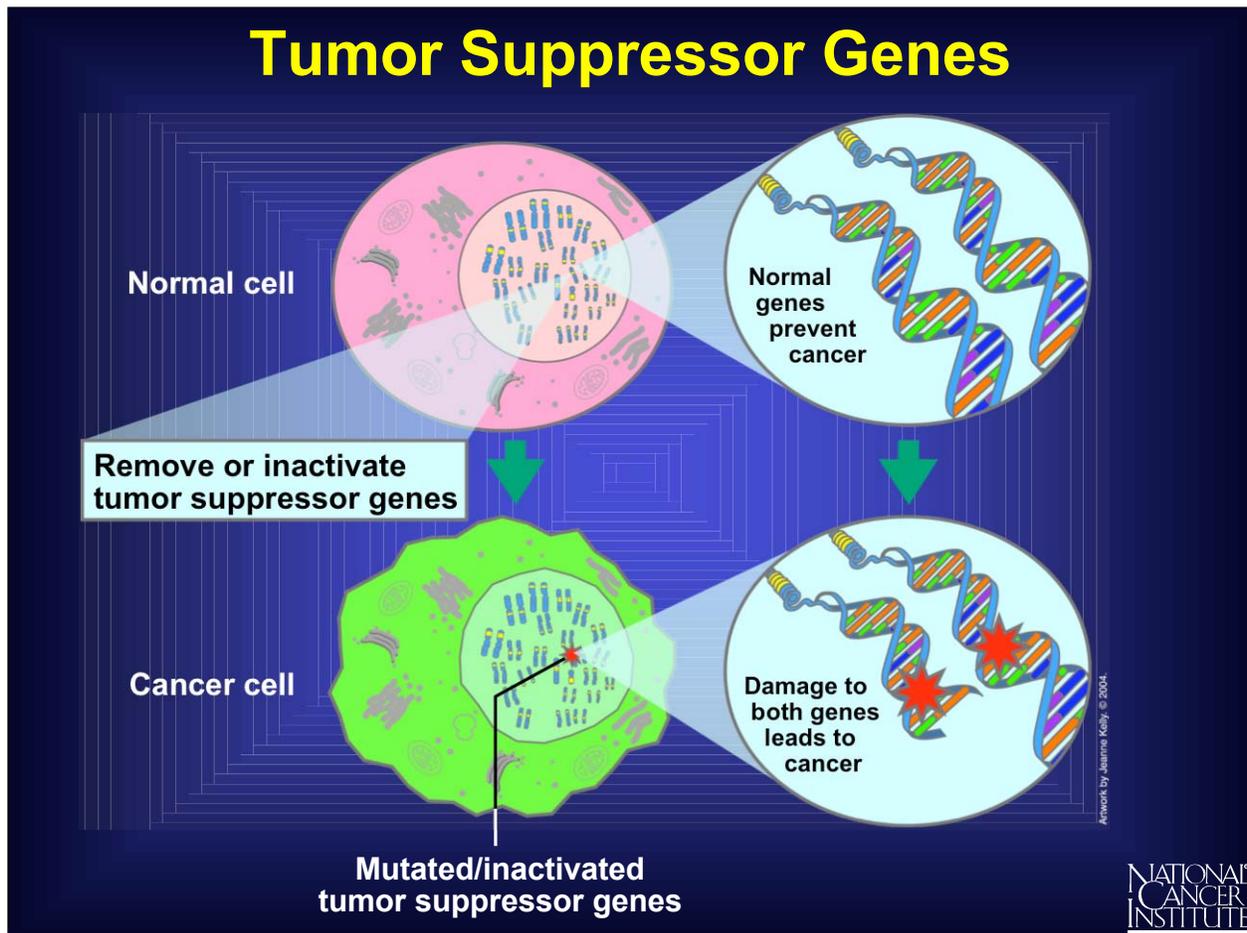
Oncogenes are related to normal genes called proto-oncogenes that encode components of the cell's normal growth-control pathway. Some of these components are growth factors, receptors, signaling enzymes, and transcription factors. Growth factors bind to receptors on the cell surface, which activate signaling enzymes inside the cell that, in turn, activate special proteins called transcription factors inside the cell's nucleus. The activated transcription factors "turn on" the genes required for cell growth and proliferation.

## Oncogenes are Mutant Forms of Proto-Oncogenes



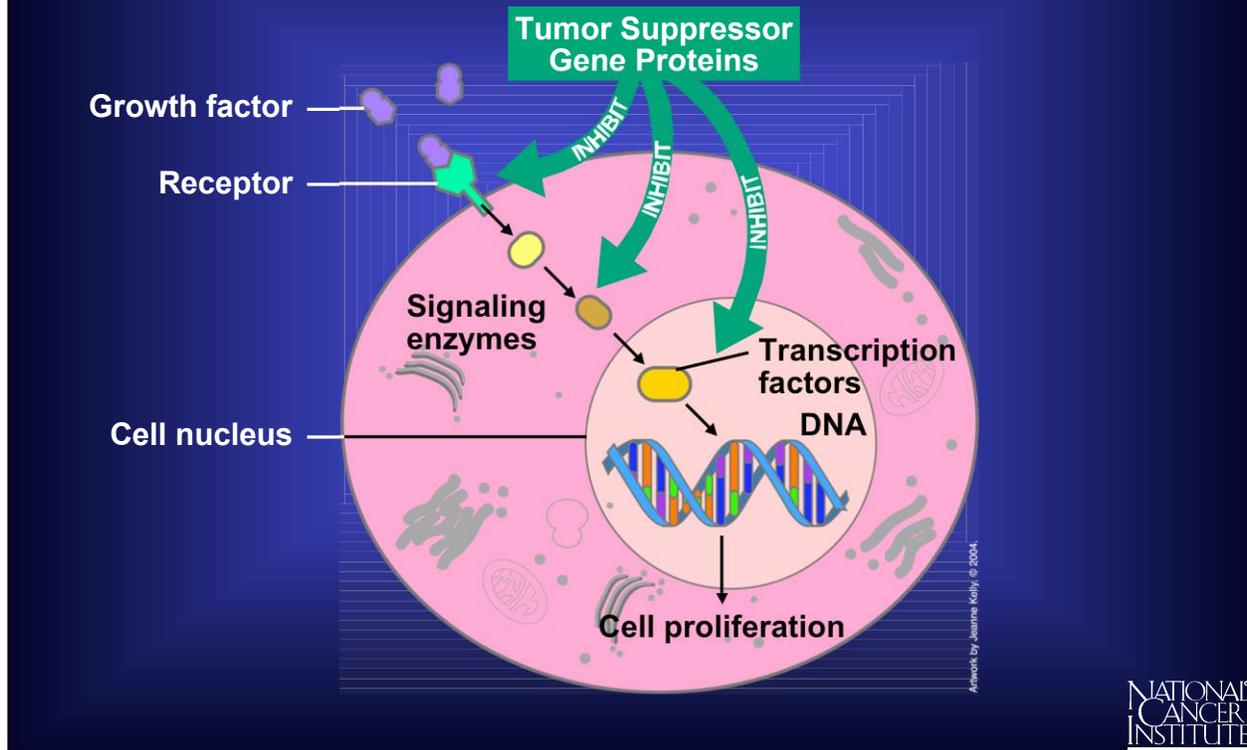
Oncogenes arise from the mutation of proto-oncogenes. They resemble proto-oncogenes in that they code for the production of proteins involved in growth control. However, oncogenes code for an altered version (or excessive quantities) of these growth-control proteins, thereby disrupting a cell's growth-signaling pathway.

By producing abnormal versions or quantities of cellular growth-control proteins, oncogenes cause a cell's growth-signaling pathway to become hyperactive. To use a simple metaphor, the growth-control pathway is like the gas pedal of an automobile. The more active the pathway, the faster cells grow and divide. The presence of an oncogene is like having a gas pedal that is stuck to the floorboard, causing the cell to continually grow and divide. A cancer cell may contain one or more oncogenes, which means that one or more components in this pathway will be abnormal.



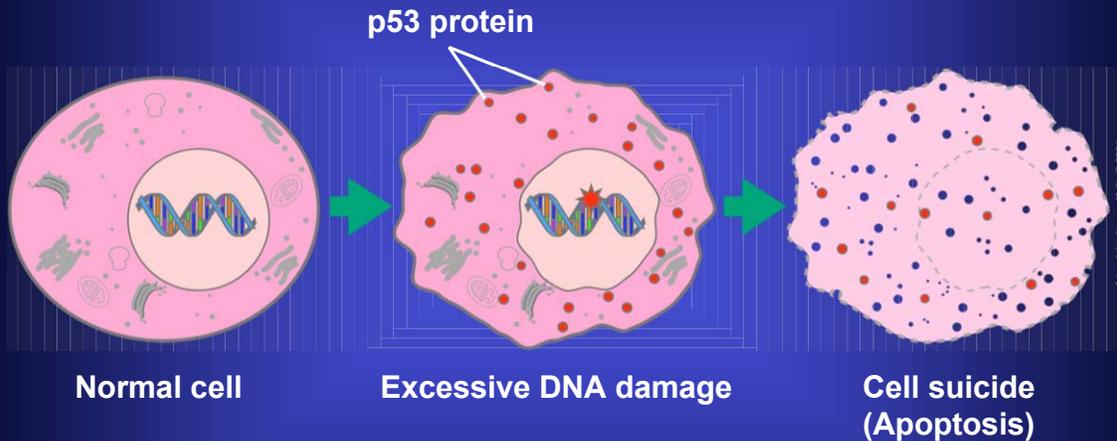
A second group of genes implicated in cancer are the “tumor suppressor genes.” Tumor suppressor genes are normal genes whose ABSENCE can lead to cancer. In other words, if a pair of tumor suppressor genes are either lost from a cell or inactivated by mutation, their functional absence might allow cancer to develop. Individuals who inherit an increased risk of developing cancer often are born with one defective copy of a tumor suppressor gene. Because genes come in pairs (one inherited from each parent), an inherited defect in one copy will not lead to cancer because the other normal copy is still functional. But if the second copy undergoes mutation, the person then may develop cancer because there no longer is any functional copy of the gene.

## Tumor Suppressor Genes Act Like a Brake Pedal



Tumor suppressor genes are a family of normal genes that instruct cells to produce proteins that restrain cell growth and division. Since tumor suppressor genes code for proteins that slow down cell growth and division, the loss of such proteins allows a cell to grow and divide in an uncontrolled fashion. Tumor suppressor genes are like the brake pedal of an automobile. The loss of a tumor suppressor gene function is like having a brake pedal that does not function properly, thereby allowing the cell to grow and divide continually.

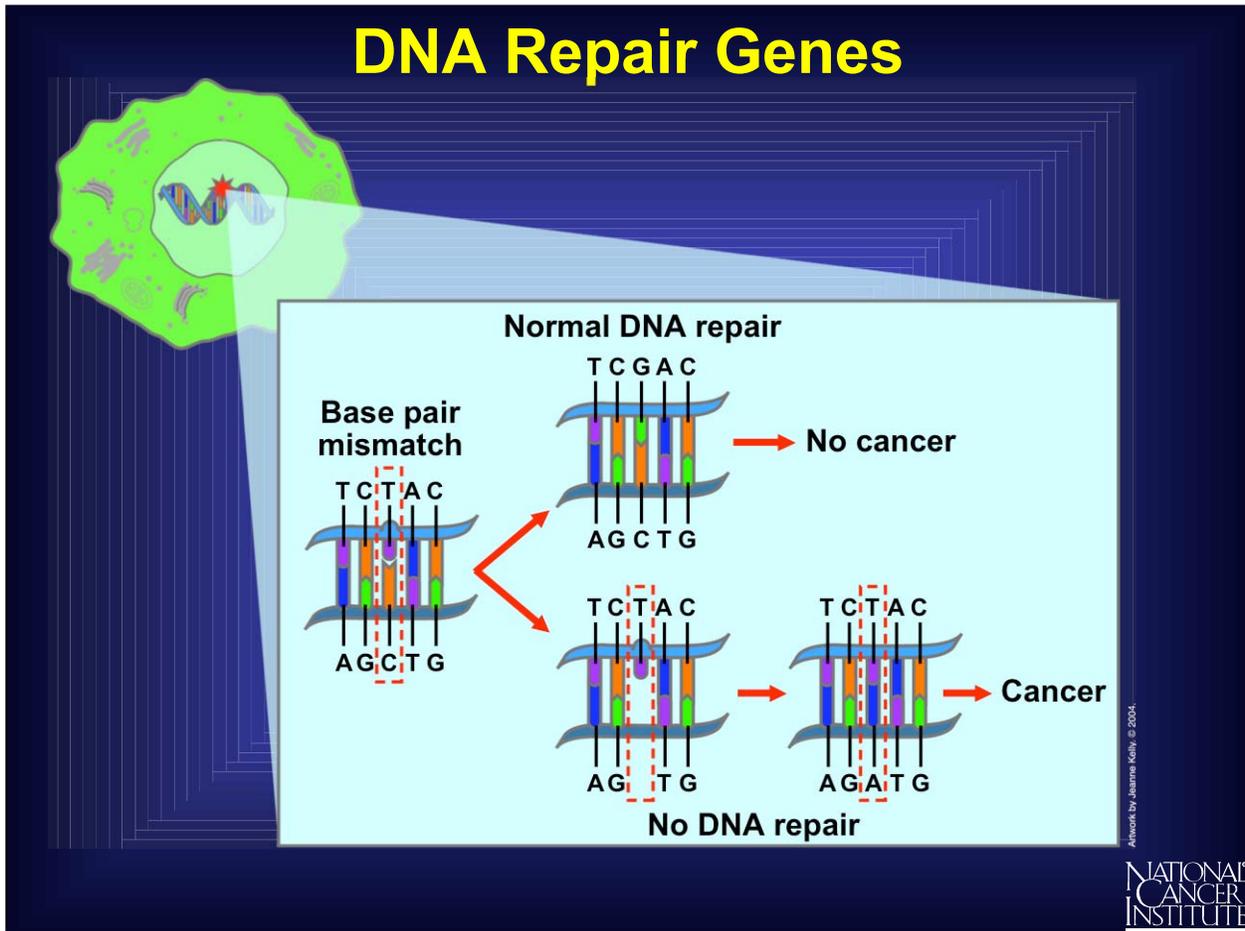
## p53 Tumor Suppressor Protein Triggers Cell Suicide



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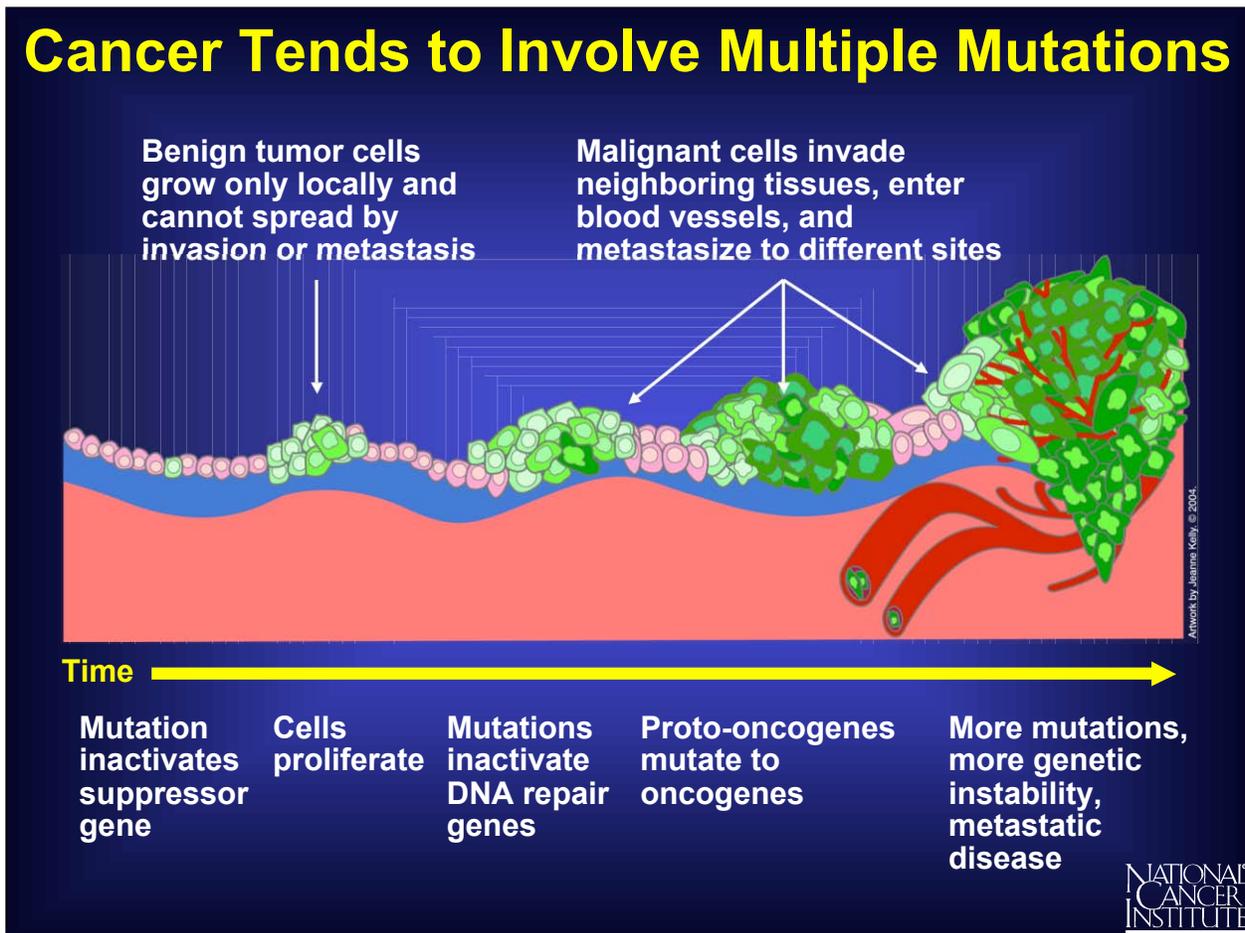
One particular tumor suppressor gene codes for a protein called “p53” that can trigger cell suicide (apoptosis). In cells that have undergone DNA damage, the p53 protein acts like a brake pedal to halt cell growth and division. If the damage cannot be repaired, the p53 protein eventually initiates cell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

## DNA Repair Genes



A third type of genes implicated in cancer are called “DNA repair genes.” DNA repair genes code for proteins whose normal function is to correct errors that arise when cells duplicate their DNA prior to cell division. Mutations in DNA repair genes can lead to a failure in repair, which in turn allows subsequent mutations to accumulate. People with a condition called xeroderma pigmentosum have an inherited defect in a DNA repair gene. As a result, they cannot effectively repair the DNA damage that normally occurs when skin cells are exposed to sunlight, and so they exhibit an abnormally high incidence of skin cancer. Certain forms of hereditary colon cancer also involve defects in DNA repair.

## Cancer Tends to Involve Multiple Mutations



Cancer may begin because of the 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 additional mutations involving DNA repair genes, other tumor suppressor genes, and many other growth-related genes. Over time, the accumulated damage can yield a highly malignant, metastatic tumor. In other words, creating a cancer cell requires that the brakes on cell growth (tumor suppressor genes) be released at the same time that the accelerators for cell growth (oncogenes) are being activated.

# Mutations and Cancer

## Genes Implicated in Cancer

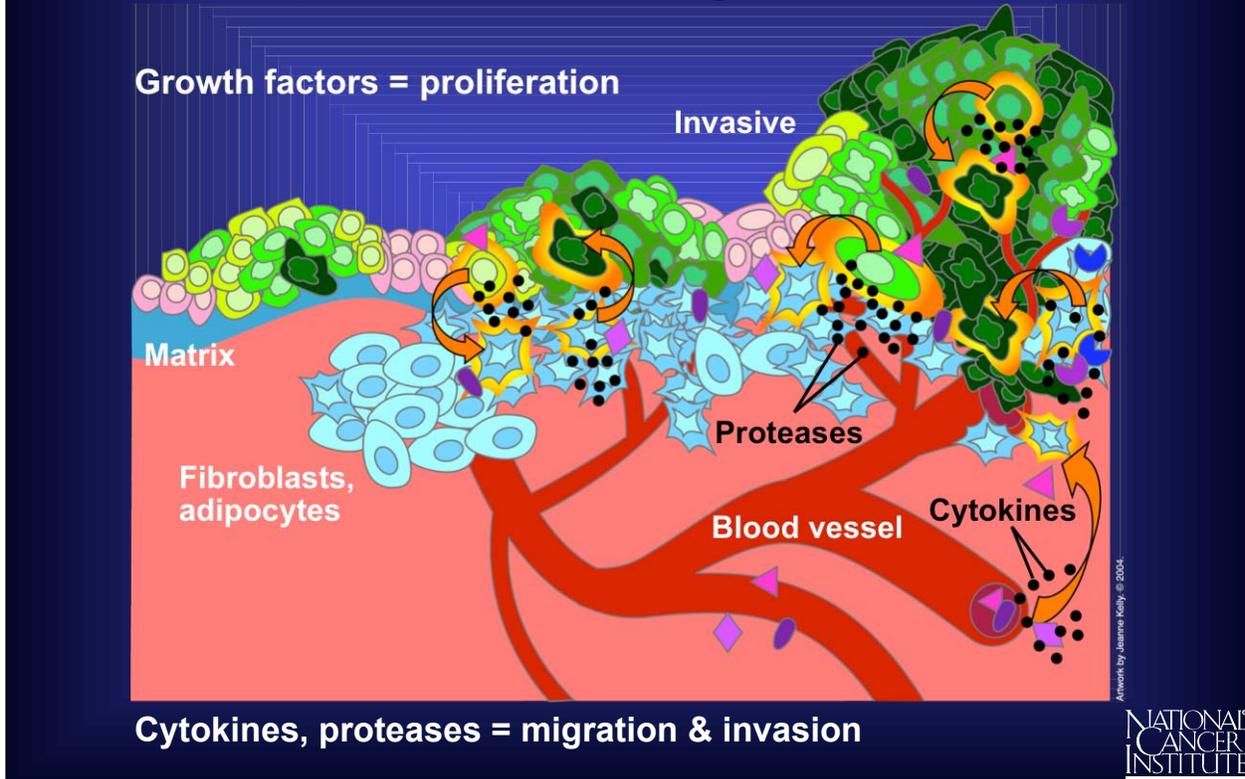
<i>The prime suspects</i>	<i>But</i>
Mutations in:	Other mutations also occur in:
■ Oncogenes	■ Cell death genes
■ Tumor suppressor genes	■ Cell signaling genes
■ DNA repair genes	■ Cell cycle checkpoint genes
	■ Cellular senescence genes
	■ Cellular differentiation genes
	■ Metastasis/invasion genes
	■ Carcinogen –activating genes –deactivating genes

Artwork by Jeannine Kelly, © 2004

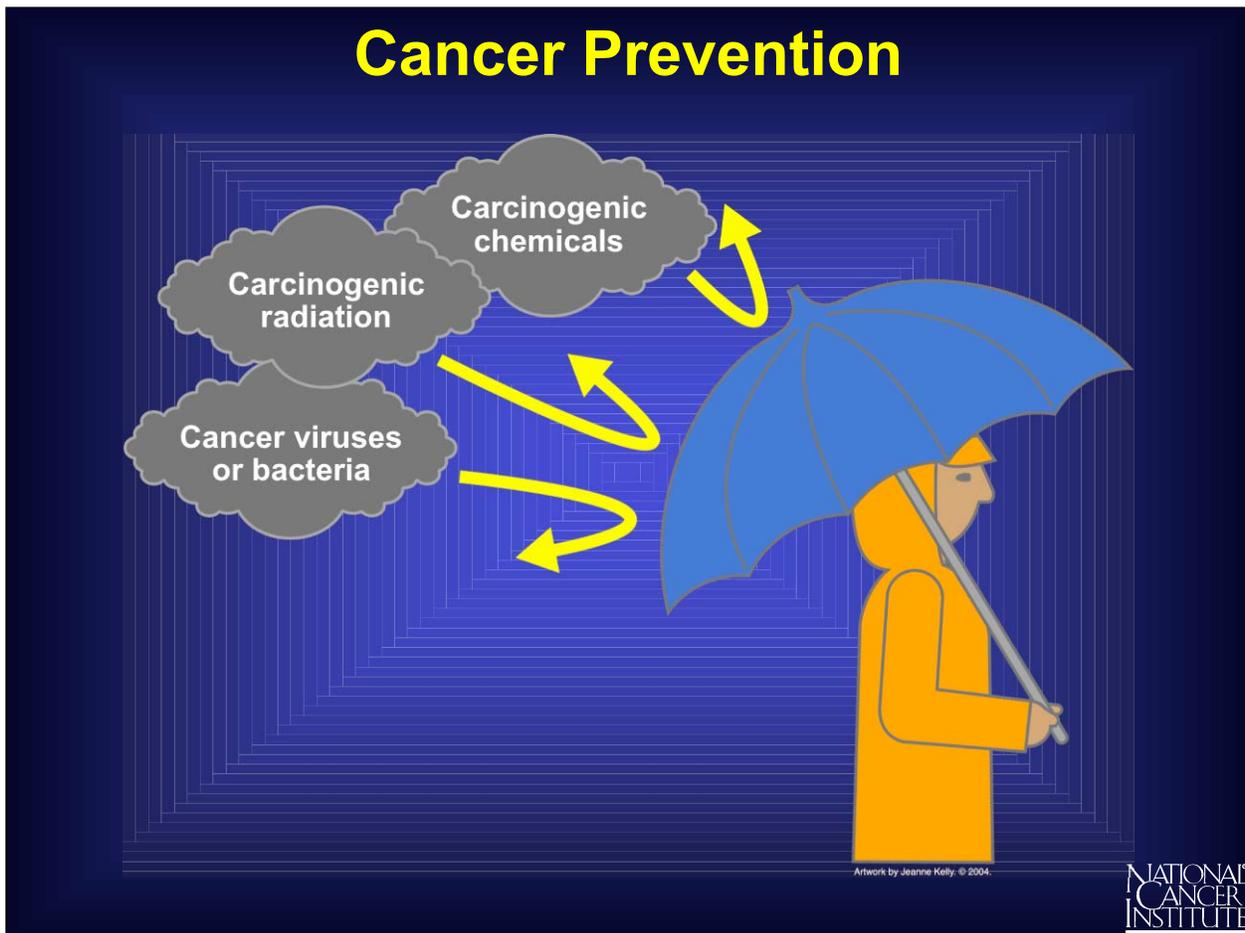


While the prime suspects for cancer-linked mutations are the oncogenes, tumor suppressor genes, and DNA repair genes, cancer conspires even beyond these. Mutations also are seen in the genes that activate and deactivate carcinogens, and in those that govern the cell cycle, cell senescence (or “aging”), cell suicide (apoptosis), cell signaling, and cell differentiation. And still other mutations develop that enable cancer to invade and metastasize to other parts of the body.

## Cancer Tends to Corrupt Surrounding Environment

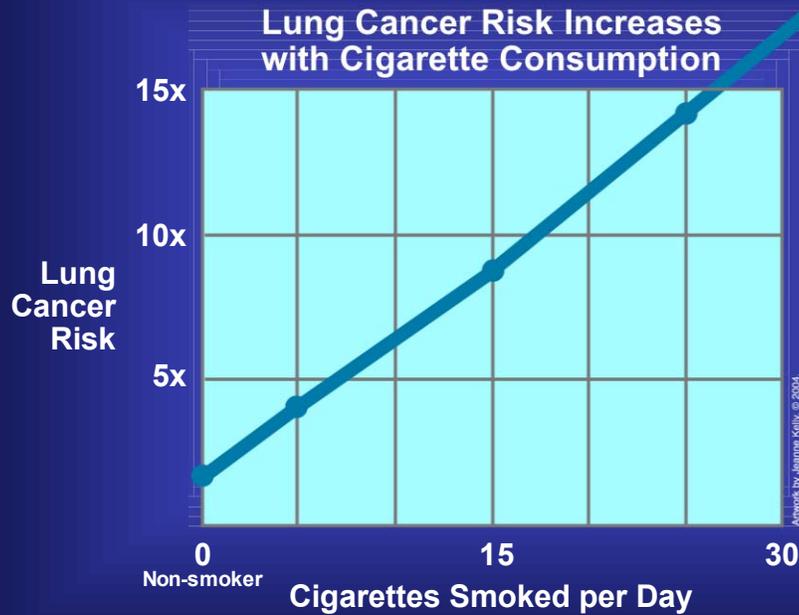


In addition to all the molecular changes that occur within a cancer cell, the environment around the tumor changes dramatically as well. The cancer cell loses receptors that would normally respond to neighboring cells that call for growth to stop. Instead, tumors amplify their own supply of growth signals. They also flood their neighbors with other signals called cytokines and enzymes called proteases. This action destroys both the basement membrane and surrounding matrix, which lies between the tumor and its path to metastasis--a blood vessel or duct of the lymphatic system.



Since exposure to carcinogens (cancer-causing agents) is responsible for triggering most human cancers, people can reduce their cancer risk by taking steps to avoid such agents. Hence the first step in cancer prevention is to identify the behaviors or exposures to particular kinds of carcinogens and viruses that represent the greatest cancer hazards.

## Avoid Tobacco



As the single largest cause of cancer death, the use of tobacco products is implicated in roughly one out of every three cancer deaths. Cigarette smoking is responsible for nearly all cases of lung cancer, and has also been implicated in cancer of the mouth, larynx, esophagus, stomach, pancreas, kidney, and bladder. Pipe smoke, cigars, and smokeless tobacco are risky as well. Avoiding tobacco is therefore the single most effective lifestyle decision any person can make in attempting to prevent cancer.

## Protect Yourself From Excessive Sunlight



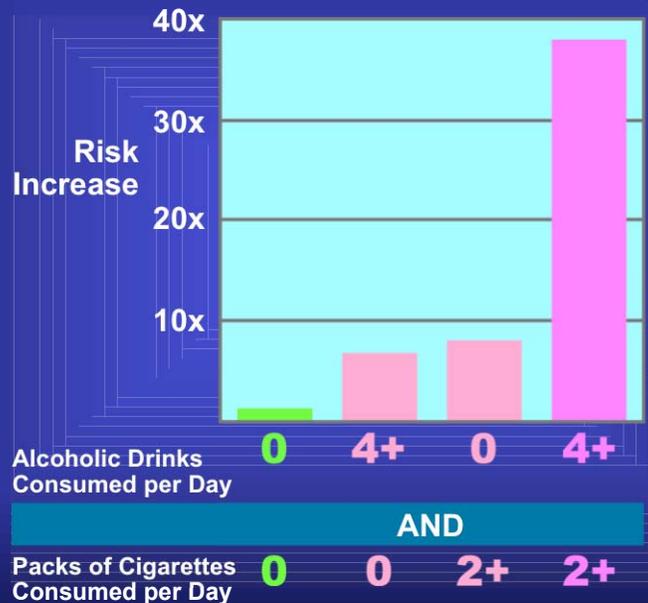
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While some sunlight is good for health, skin cancer caused by excessive exposure to sunlight is not among the sun's benefits. Because some types of skin cancer are easy to cure, the danger posed by too much sunlight is perhaps not taken seriously enough. It is important to remember that a more serious form of skin cancer, called melanoma, is also associated with excessive sun exposure. Melanomas are potentially lethal tumors. Risk of melanoma and other forms of skin cancer can be significantly reduced by avoiding excessive exposure to the sun, using sunscreen lotions, and wearing protective clothing to shield the skin from ultraviolet radiation.

## Limit Alcohol and Tobacco

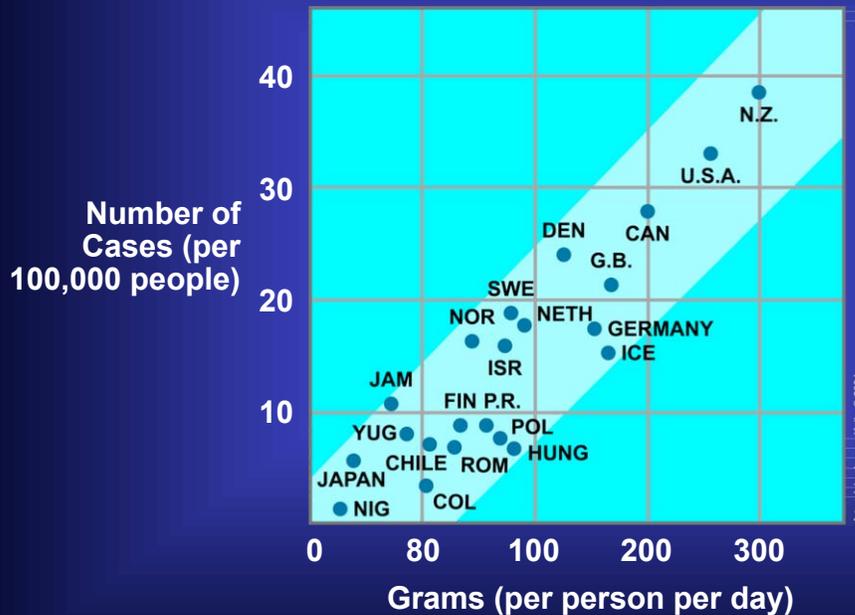
Combination of Alcohol and Cigarettes  
Increases Risk for Cancer of the Esophagus



Drinking excessive amounts of alcohol is linked to an increased risk for several kinds of cancer, especially those of the mouth, throat, and esophagus. The combination of alcohol and tobacco appears to be especially dangerous. For example, in heavy smokers or heavy drinkers, the risk of developing cancer of the esophagus is roughly 6 times greater than that for nonsmokers/nondrinkers. But in people who both smoke and drink, the cancer risk is more than 40 times greater than that for nonsmokers/nondrinkers. Clearly the combination of alcohol and tobacco is riskier than would be expected by just adding the effects of the two together.

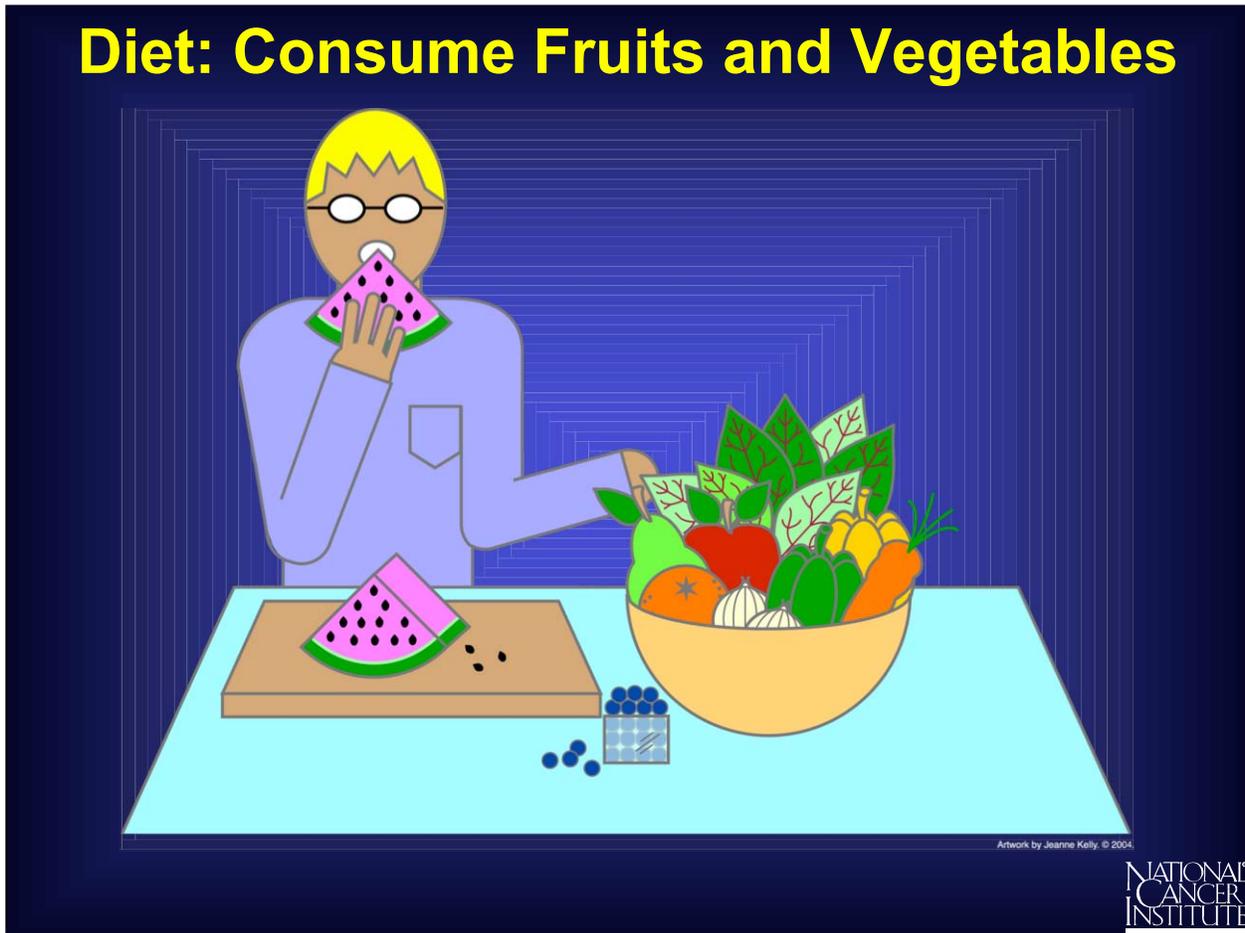
## Diet: Limit Fats and Calories

Correlation Between Meat Consumption and Colon Cancer Rates in Different Countries



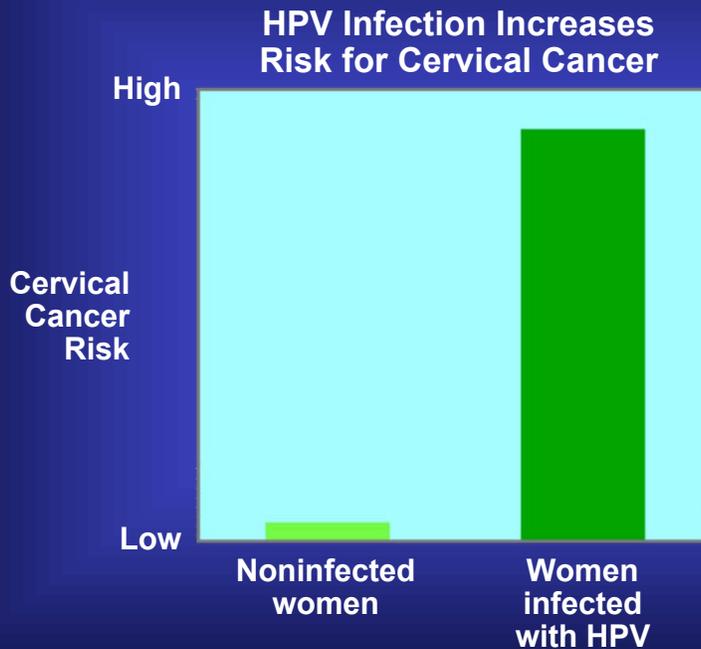
Studies suggest that differences in diet may also play a role in determining cancer risk. Unlike clear-cut cancer risk factors such as tobacco, sunlight, and alcohol, dietary components that influence cancer risk have been difficult to determine. Limiting fat consumption and calorie intake appears to be one possible strategy to decrease risk for some cancers, because people who consume large amounts of meat, which is rich in fat, and large numbers of calories exhibit an increased cancer risk, especially for colon cancer.

## Diet: Consume Fruits and Vegetables



In contrast to factors such as fat and calories, which appear to increase cancer risk, other dietary components may decrease cancer risk. The most compelling evidence has been obtained for fruits and vegetables, whose consumption has been strongly correlated with a reduction in cancer risk. Although the exact chemical components in these foods that are responsible for a protective effect are yet to be identified, eating five to nine servings of fruits and vegetables each day is recommended by many groups.

## Avoid Cancer Viruses



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Actions can also be taken to avoid exposure to the small number of viruses that have been implicated in human cancers. A good example is the human papillomavirus (HPV). Of the more than 100 types of HPVs, over 30 types can be passed from one person to another through sexual contact. Among these, there are 13 high-risk types recognized as the major cause of cervical cancer. Having many sexual partners is a risk factor for infection with these high-risk HPVs, which can, in turn, increase the chance that mild cervical abnormalities will progress to more severe ones or to cervical cancer.

## Avoid Carcinogens at Work

### Some Carcinogens in the Workplace

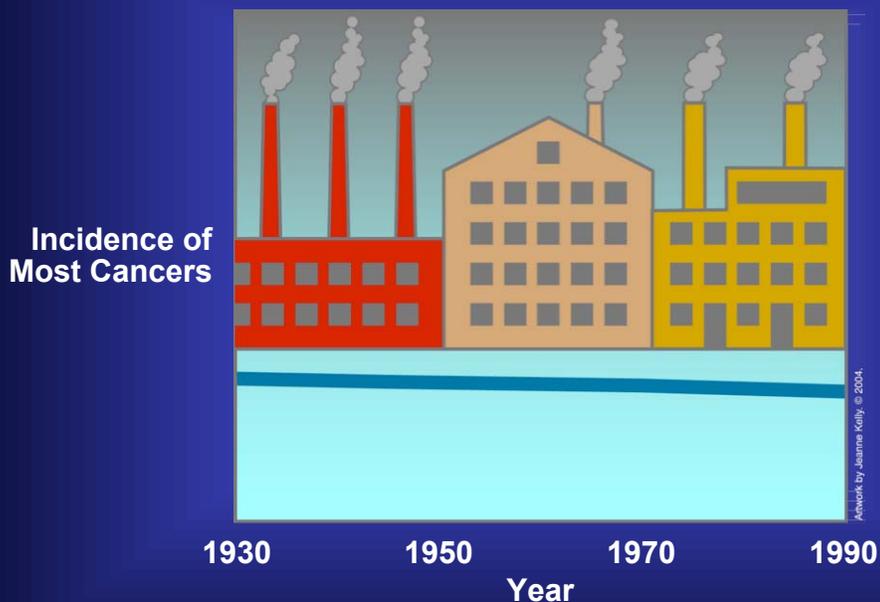
Carcinogen	Occupation	Type of Cancer
Arsenic	Mining, pesticide workers	Lung, skin, liver
Asbestos	Construction workers	Lung, mesothelioma
Benzene	Petroleum, rubber, chemical workers	Leukemia
Chromium	Metal workers, electroplaters	Lung
Leather dust	Shoe manufacturing	Nasal, bladder
Naphthylamine	Chemical, dye, rubber workers	Bladder
Radon	Underground mining	Lung
Soots, tars, oils	Coal, gas, petroleum workers	Lung, skin, liver
Vinyl chloride	Rubber workers, polyvinyl chloride manufacturing	Liver
Wood dust	Furniture manufacturing	Nasal

Artwork by Jeanne Kelly. © 2004.

Because people spend so much time at work, potential carcinogens in the work environment are studied carefully. Some occupational carcinogens have been identified because coworkers exposed to the same substances have developed a particular kind of cancer at increased frequency. For example, cancer rates in construction workers who handle asbestos have been found to be 10 times higher than normal.

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## Industrial Pollution



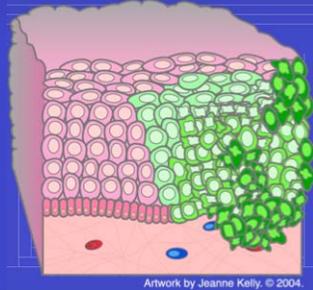
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The fact that several environmental chemicals can cause cancer has fostered the idea that industrial pollution is a frequent cause of cancer. However, the frequency of most human cancers (adjusted for age) has remained relatively constant over the past half-century, in spite of increasing industrial pollution.

So, 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.



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