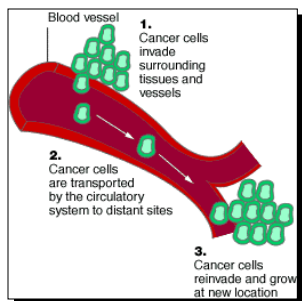


## Biochemistry of Cancer



## Biochemistry of Cancer

### Diseases and popular conceptions

- **Cancer, Coronary Disease and Cancer-**

- Is there a competition between diseases and how they are funded? studied and prevented? - your decision

- 9.7 Billion in federal money for aids

- People with Aids/HIV 297,137 1999

- 1.9 billion (19.5%) for research

- The rest is Care / Assistance 71.1%

- Prevention 8%

- International 1.5%

- 1.4 Billion in federal money for Cancer

- 1,784,900 persons with or died with Cancer 1999

- 0.6% for prevention and education

**So... How are we doing?**  
**8 to 1 dollars for research**  
**41 to 1 dollars overall**

## Cancer

- Knowledge of tumors date from antiquity.
  - Egyptians and Greeks
- Streaks of hard gray tissue that extended from tumors reminded the Greeks of a crab.
  - Named the condition cancer from the Latin word for crab.
- Today, Cancer is a generic term for a malignant tumor.
- Essentially, cancer is a good cell gone bad

### Leading causes of death 1995

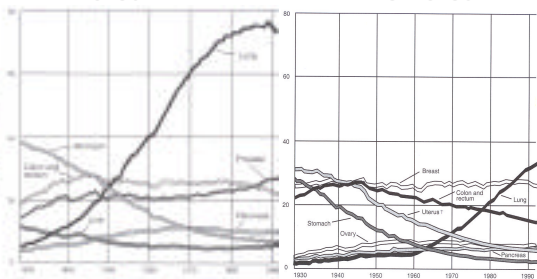
	All Ages		25 - 44	
	%	Rank	%	Rank
Diseases of the heart	31.9	1	11.4	4
Cancer	23.3	2	14.7	3
Stroke	6.8	3	2.3	8
Lung Disease	4.4	4	-	-
Accidents	4.0	5	18.2	2
Pneumonia and influenza	3.7	6	1.4	10
Diabetes mellitus	2.5	7	1.6	9
HIV	1.9	8	20.5	1
Suicide	1.4	9	8.5	5
Liver disease	1.1	10	2.9	7
Homicide	-	-	6.8	6

- Source: US National center for health statistic

## Changing Rates of Cancer

Males

Females

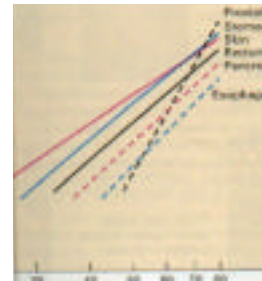


## Growing old-

563,100 people died from cancer in 1999 an increase from 331,000 in 1970

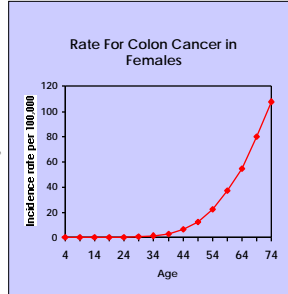
40% of Americans will be stricken with the disease and 1 in 5 will die from it - 1,221,800 person incidence rate in 1999

For the most part cancer is obviously a disease of age - of individual and DNA



## A Disease of Age

- Most cancers develop late in life.
- Cancer did not become a major societal challenge until the middle 19<sup>th</sup> century.



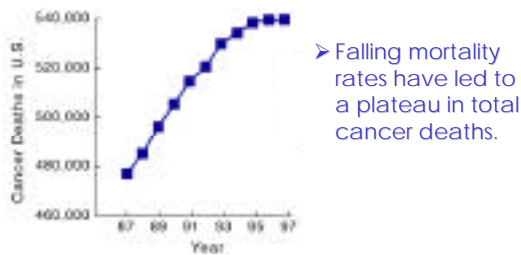
## Cancer in the United States

In 1999 - 563,100 people died from cancer.

- Increase from 331,000 in 1970
- In 1999, 1,221,800 new cases of cancer were reported.
- At least one in three people will develop cancer in their lifetime.
  - 1 in 4 men will die of cancer.
  - 1 in 5 women will die cancer.

## Cancer in the United States

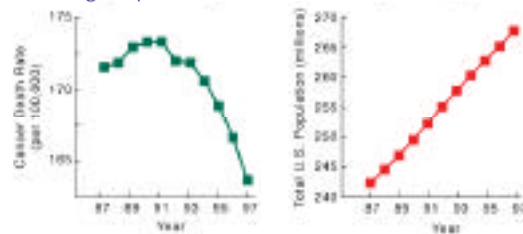
The actual number of people dying from cancer each year has leveled off.



- Falling mortality rates have led to a plateau in total cancer deaths.

## Cancer Death Rates Continue to Fall

- Cancer mortality rates fell in the 1990's
  - expressed per 100,000 individuals in the population
- The population of the U.S. has continued to increase during this period.



## The Process of Carcinogenesis

- **Steps of tumor development**
  - **Initiation:** essential step that is latent until next step. Often occurs as DNA damage in stem cells
  - **Promoting Agent:** Typically not a carcinogen but a chemical that can induce cells to grow.
  - **Growth Inhibition:** Normal control of cell growth can influence tumor growth .

### Initiating Agent

- Chemical-Carcinogens
- Viruses
- Radiation
- UV Light
- Replication Errors

### Promoting Agent

- Specific Promoters
- Inflammation
- Hormones
- Normal growth promoters

### Growth Inhibitors

- Hormones - therapeutic or physiological
- Normal Growth Inhibitors - age, surgery, radiation

## Causes of cancer

- 80% of human cancers are estimated to be caused by environmental factors - such as diet, lifestyle and occupation
- biggest two causes are tobacco and diet (60 % of total cancer mortalities)
- heredity is a major factor in some cancers (breast and colon)
- Cancer are cells out of control - signal transduction without the regulation
- loss of normally controlled cell growth
- final result usually from loss of both an on and an off signal
- Signals controlling growth clock - cell cycle - are mutated

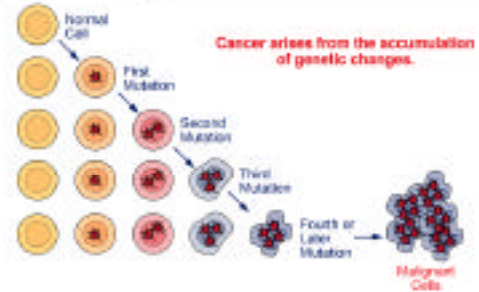
**Stimulatory pathways** - this pathway will become hyperactive if a mutation causes any component, such as growth factor receptors to issue stimulatory messages autonomously, without waiting for commands from upstream.

- growth factor receptors mutated so the intracellular kinase domain is "on"
- cytosolic signaling molecules improperly activated
- nuclear DNA binding proteins turned on
- Growth factors or hormones over-produced without control

**Inhibitory pathways** - conversely inhibitory pathways will shut down when some constituent, such as a cytosolic protein is eliminated and thus breaks down the off signaling path

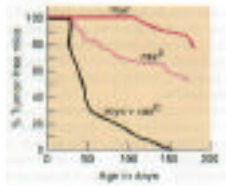
- specific tumor suppresser genes exist
- some are involved in normal cell cycle regulation
- some are inhibitory for specific stimulatory proteins (EGFR and Ras)

### Understanding the Molecular Basis of Cancer



### The Process of Carcinogenesis

- **Carcinogenesis is a multistage event**
  - Application of a single cancer-producing agent (carcinogen) does not lead to tumor development
  - Most cancers are collaborative events



### Forces That Influence Cancer

There is no single cause of cancer.

- **Genetics** – Breast and ovarian cancer (BRCA gene), Li-Fraumeni Syndrome, colorectal cancers
- **Environment** – smoking contributes to nearly 1/3 of all cancer deaths. Smoking increases risk 1,200 fold for women and 2,000 fold for men.



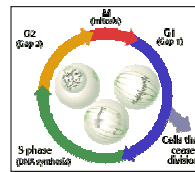
### Forces That Influence Cancer

- **Diet** – Contribution can vary. High fiber, fruit and vitamins can decrease risk and high fat increases
- **Virus** – Limited to a few types of cancer – stomach, cervical and Kaposi's sarcoma (AIDS-related)

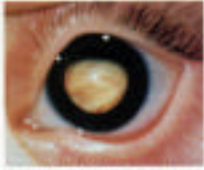
Factor	%
Tobacco	33
Diet	30
Infection	9
Hormones	7
Radiation	6
Occupation	3
Alcohol	3
UV light	1

### Progression of Cancer Control of the Cell Cycle

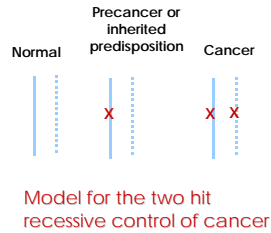
**Oncogene**: "gene capable of causing cancer"



## Multiple Hit Theory of Tumor Suppressor Cancer



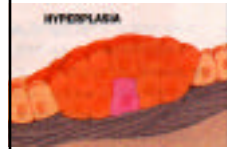
- 5/100,000 children get retinoblastoma
- 40% of cases are familial remainder result from both genes being mutated



## Tumor development occurs in stages



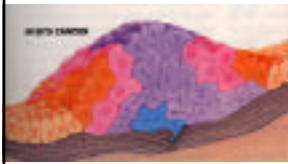
1) **Genetically altered cell** - tumor development begins when a single cell within a normal population sustains a genetic mutation that increases when it would normally rest



2) **Hyperplasia**  
The altered cell continues to grow and the daughter cells continue to look normal but they produce too much - after years some of these cells suffer another mutation that further loosens controls on cell growth



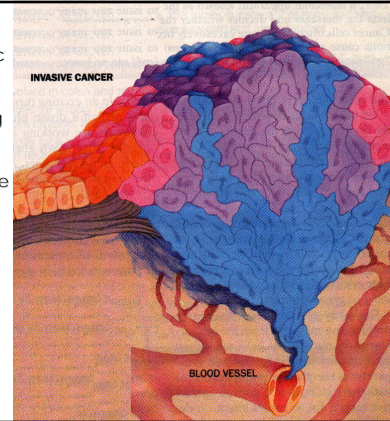
3) **Dysplasia**  
In addition to proliferation excessively, the mutated cells begin to appear abnormal in shape and orientation - morphology changes; After time an additional mutation occurs



4) **In situ cancer**  
The effected cells become still more abnormal in growth and may or may not have begun to lose containment in the original tissue. Additional cells gain another mutation

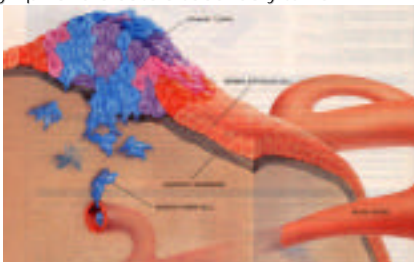
## 5) Invasive cancer

if the genetic changes allow the tumor to begin invading underlying tissue and to shed cells into the blood stream or lymph, the mass is considered to have become malignant. The renegade cells are likely to establish themselves throughout the body; these may become lethal by disrupting a vital organ



**Invasion and Metastasis** - the method which spreads cancer through out the body. First cancer cells detach from the primary tumor and breach the basal membrane surrounding a blood vessel and are free to circulate via the blood stream. Eventually a cancer cell may lodge in a capillary or lymph and create a secondary tumor.

- Less than one in 10,000 cancer cells that escape the primary tumor survives to colonize another tissue



## Tumors Grades

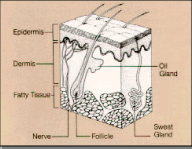
A malignant tumor can be removed and classified for tumor grade and the degree of cell differentiation.

The term "differentiated" describes the extent to which cancer cells are similar in appearance and function to healthy cells of the same tissue type. The degree of differentiation often relates to the clinical behavior of the particular tumor.



The cells of Grade 1 tumors are often well-differentiated or low-grade tumors, and are generally considered the least aggressive in behavior. Conversely, the cells of Grade 3 or Grade 4 tumors are usually poorly differentiated or undifferentiated high-grade tumors, and are generally the most aggressive in behavior.

## Melanoma

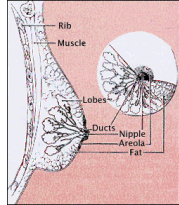


The most serious cancer of the skin. In Western countries, the number of people who develop melanoma is increasing faster than any other cancer. In the United States, for example, the number of new cases of melanoma has more than doubled in the past 20 years.

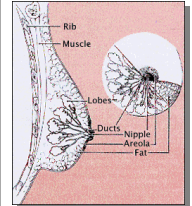
Melanoma occurs when melanocytes (pigment cells) become malignant.

- Melanoma can occur on any skin surface. In men, it is often found on the trunk or the head and neck. In women, melanoma often develops on the lower legs. Melanoma is rare in black people and others with dark skin.
- Melanoma is one of the most common cancers in young adults.

## Breast Cancer



- Other than skin cancer, breast cancer is the most common type of cancer among women in the United States. More than 180,000 women are diagnosed with breast cancer each year.
- The exact causes of breast cancer are not known. However, studies show that the risk of breast cancer very increases as a woman gets older. This disease is very uncommon in women under the age of 35. Most breast cancers occur in women over the age of 50, and the risk is especially high for women over age 60. Also, breast cancer occurs more often in white women than African American or Asian women.

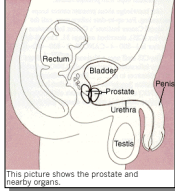


A report from the National Cancer Institute (NCI) estimates that about 1 in 8 women in the United States (approximately 12.8 %) will develop breast cancer during her lifetime.

from age 30 to age 40	.....	1 out of 257
from age 40 to age 50	.....	1 out of 67
from age 50 to age 60	.....	1 out of 36
from age 60 to age 70	.....	1 out of 28
from age 70 to age 80	.....	1 out of 24
Ever	.....	1 out of 8

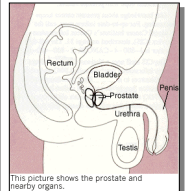
- 1 in 8 means that, if current rates stay constant, a female born today has a 1 in 8 chance of developing breast cancer sometime during her life.
- Considering time and race - age 50, a cancer-free black woman has about a 2.5-percent chance of developing breast cancer by age 60, and a cancer-free white woman has about a 2.8-percent chance

## Prostate Cancer



This picture shows the prostate and nearby organs.

- Prostate cancer is the most common type of cancer in men in the United States (other than skin cancer). Of all the men who are diagnosed with cancer each year, more than one-fourth have prostate cancer.
- The causes of prostate cancer are not well understood. Doctors cannot explain why one man gets prostate cancer and another does not.



This picture shows the prostate and nearby organs.

## Risk Factors

- **Age.** In the United States, prostate cancer is found mainly in men over age 55. The average age of patients at the time of diagnosis is 70.
- **Family history.** A man's risk for developing prostate cancer is higher if his father or brother has had the disease.
- **Race.** This disease is much more common in African American men than in white men. It is less common in Asian and American Indian men.
- **Diet and dietary factors.** Some evidence suggests that a diet high in animal fat may increase the risk of prostate cancer and a diet high in fruits and vegetables may decrease the risk.

## So what good new is there?

- **Microarrays (Chip technology)**- The National Cancer Institute (NCI) will spend \$4.1 million to help 24 cancer research centers DNA microarray facilities. DNA microarray technology is a powerful, but technically challenging, new research tool that allows scientists to assess the level of expression of a large subset of the 100,000 human genes in a cell or tissue.



### **So what good new is there?**

- This technology can quickly produce a snapshot of the genes that are active in a tumor cell, critical information in narrowing down the precise molecular causes of a cancer.
- The microarray centers also will support the work of scientists involved in a new NCI initiative entitled, "The NCI's Director's Challenge: Toward a Molecular Classification of Tumors."
- The five-year initiative aims for the first time to define tumor cells based on their unique molecular changes, information that promises to improve the diagnosis and treatment of cancer.