Environment and Gene Interactions Cancer Module

- ■ **Introduction**
- ■ **Basics of Toxicology (The Science of Poisons)**
- ■ **DNA and the origins of Cancer**
- ■ **Defining Cancer Risk**
- ■ **Tobacco and Alcohol**
- ■ **Sunlight and Skin Cancer**
- ■ **Diet and Nutrition**
- ■ **Hormones and Cancer**
- ■ **Viruses and Cancer**

The Dose Makes the Poison

- ■ **all chemicals are toxic**
- ■ **toxicity can be modified radically with minor chemical modifications**

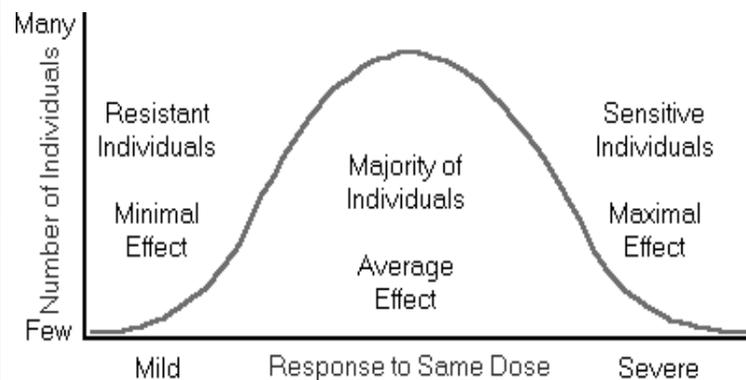**Benzene**
Carcinogenic

Toluene
Non-Carcinogenic

Definitions

- **Potency is inversely related to the amount of a chemical that causes toxicity**
- **Risk is proportional to the amount of a chemical to which one is likely to be exposed, and the duration of the exposure**
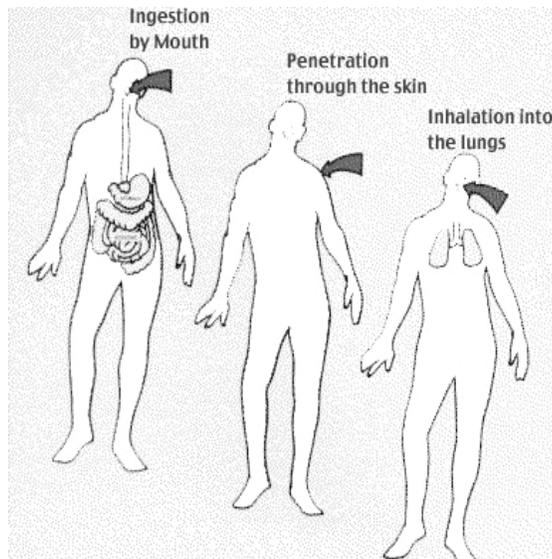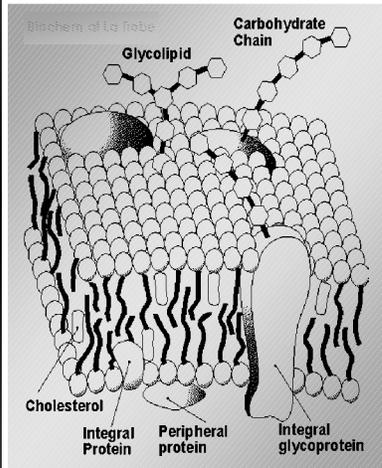- **Potency is just one factor in risk**

Dose-Response Relationship

Dose versus Time

■ **A low dose for a long time may be more hazardous than a higher dose for a shorter time**
  ◆ **Factors:**
    – **Mechanism of action**
    – **Accumulation**
    – **Reactivity**

Routes of Toxin Exposure
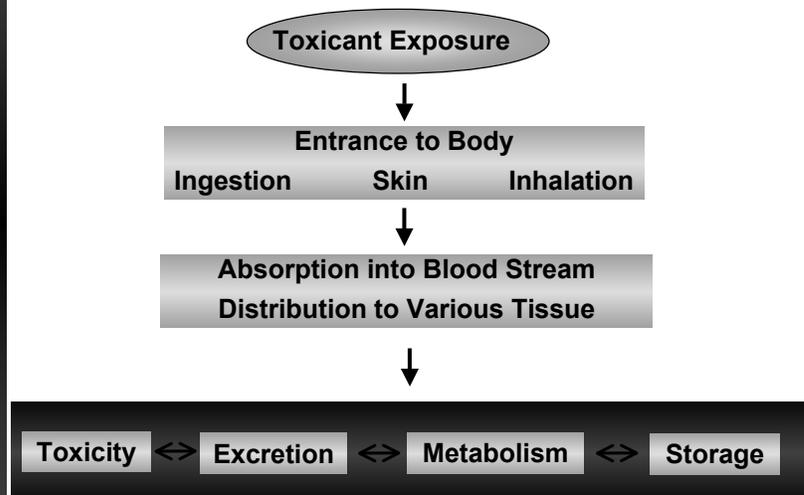
Cell Membrane

- ■ **Lipid barrier**
  - ◆ **Fat soluble substances penetrate better**
- ■ **Dynamic**
- ■ **Can itself be a target**

Entry and Fate of Toxicants

Computers Use a Binary (Two-Digit) Language

1011001101101011011010001010101110101110101101001011
0101101010101010101110101010101000010101010101111010101011
0110011011010110110100010101011101011101011010010110100101
0101101010101010101110101010101000010101010101111010101011
10110011011010110110100010101010 100101
0101101010101010101110101010100 0101
10110011011010110110100010101010 101
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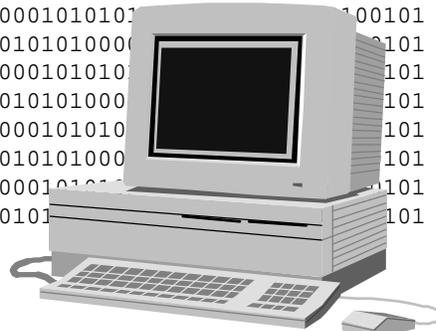
Cells Use a Four Letter Language- the "Genetic Code"

CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT
CCCGGATTAAACCGGAAATTTCGATTTACCGGAATTCTTATTCTTAGATTACG
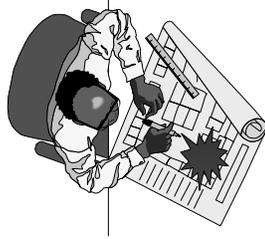ATTACAGGTTACCGCCAATAACAAGAATTCTTGGAGGCTAACGACCCACACTT

DNA

Long Strands of DNA Make up Our Chromosomes, the Functional Units of Chromosomes are Genes
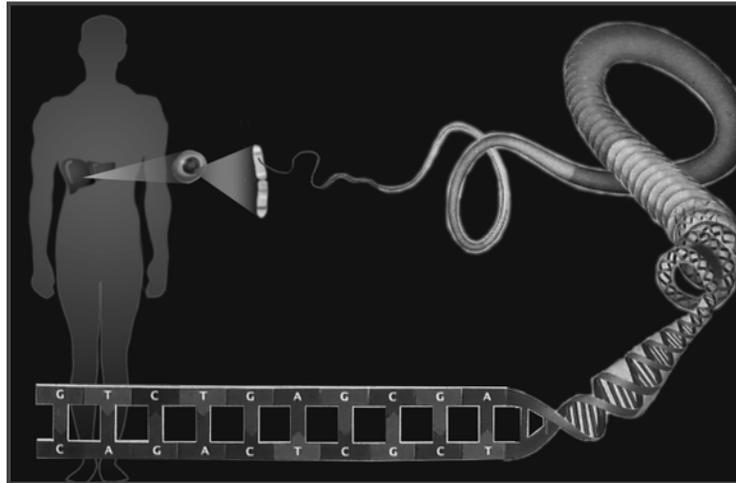
Our Genes Are the Blueprints for Making a Person
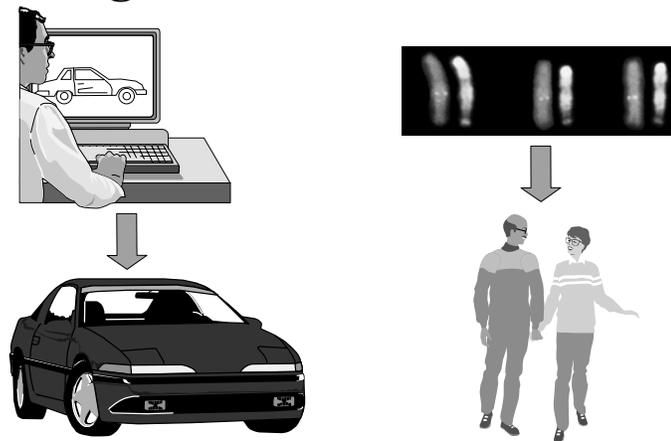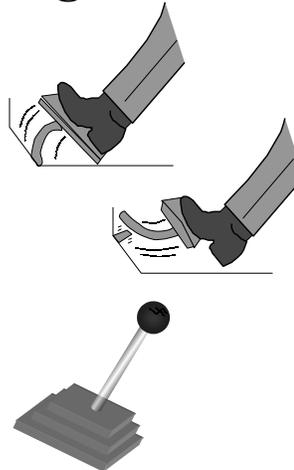
## Damage to Blueprints Leads to a Faulty Car

Three Main Classes of Genes are Important in Carcinogenesis

- **Oncogenes:** speed up cell growth
  - ◆ (like a car's accelerator)

- **Tumor Suppressors:** slow down cell growth
  - ◆ (like a car's brakes)

- **Modifiers of Carcinogenesis:** alter the effects of carcinogen exposure
  - ◆ (like a car's transmission)

Alterations in Tumor Suppressor Genes, Due to Carcinogen Exposure or Heredity, Can Increase Your Likelihood of Getting Cancer

Male without cancer   Female without cancer

Male with cancer   Female with cancer
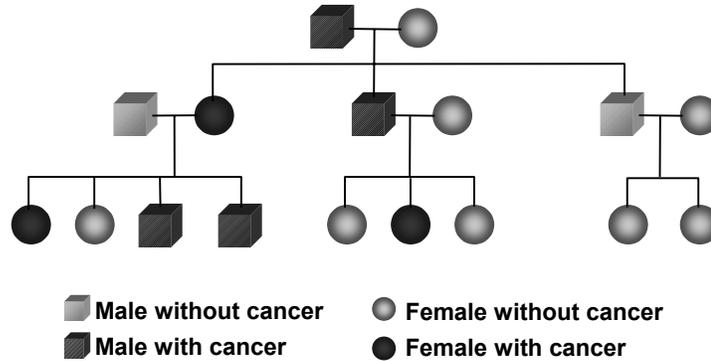
An Inactive Tumor Suppressor Gene Fails to Put the Brakes on Growth
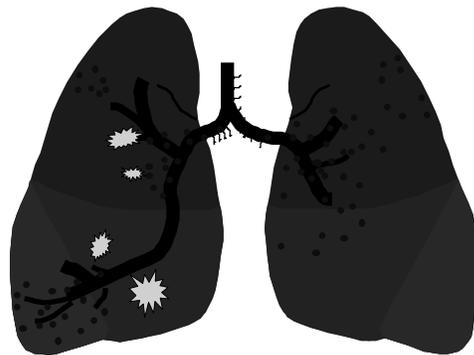
Lung cancer often results from damage to the p53 tumor suppressor gene

Cancer is a Multi-step Process & Genetic Changes Can Occur at Various Stages of Tumorigenesis

Initiation   **Promotion**   **Progression**

| Genetically altered cell | Hyperplasia (cell division) | Dysplasia (pre-malignant lesion) | Carcinoma *in situ* | Invasive carcinoma |

Hepatitis, Sunlight
Known   Unknown
Environmental Exposure

Individual Susceptibility
Known   Unknown
BRCA1,2
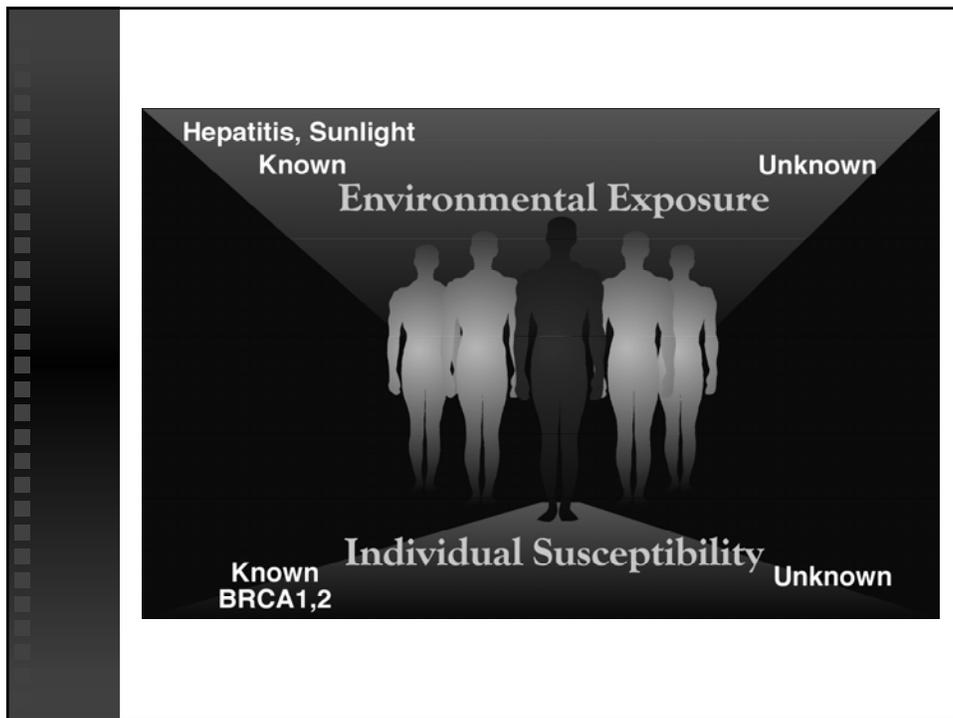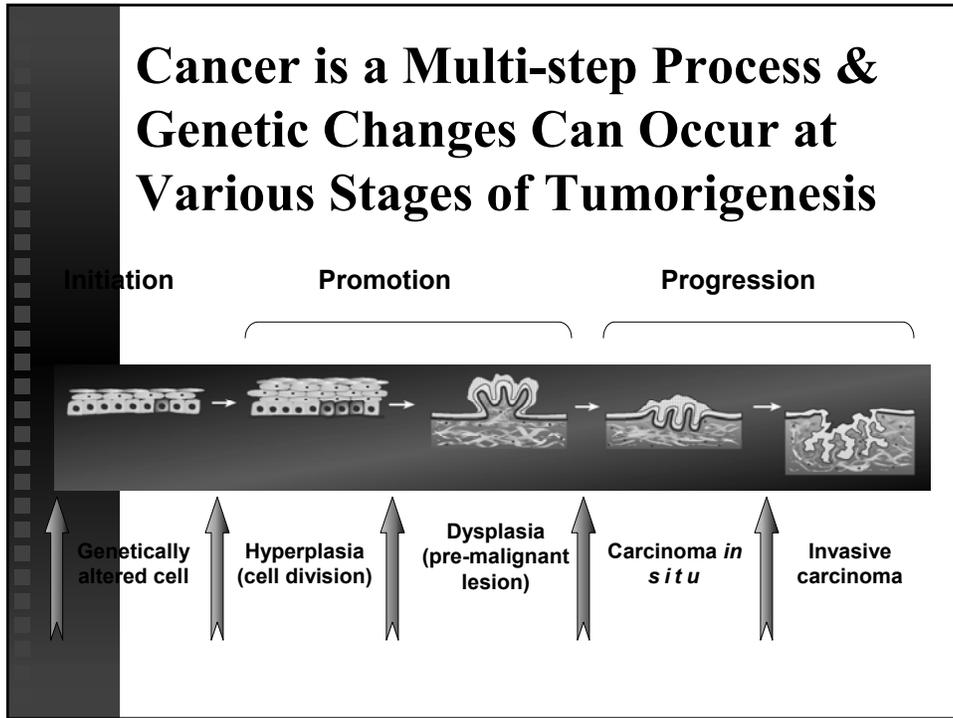
Definition of "Risk"

■ The chance of injury, damage or loss; dangerous chance; hazard

■ To expose to hazard, as to "risk" one's life

Absolute Risk

The rate of occurrence or death

from cancer within the general

population.

Relative Risk

The occurrence or death from cancer among those with a risk factor(s) relative to those without the risk factor(s).

Attributable Risk

Amount of disease within a population that could be prevented by alteration of risk factors.

Risk Factors

Inherited characteristics or

exposure to substances, that

create or increase the potential

of developing cancer

Traditional Epidemiology

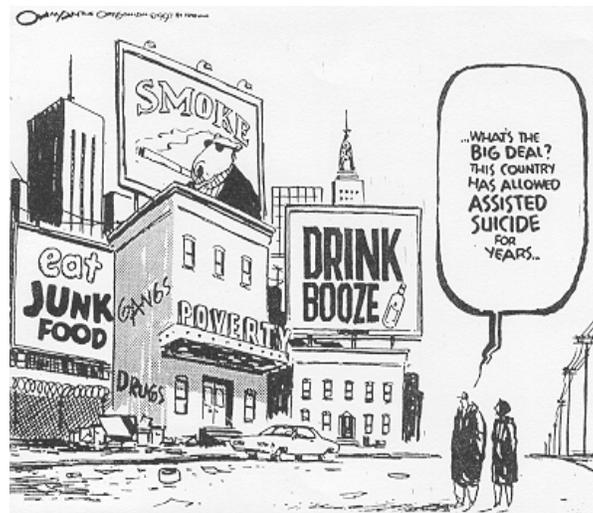**Exposure** → **Cancer**

One-in-a-Million Risk of Dying from Accidents

Activity

- **3 hrs in coal mine**
- **Traveling 6 minutes by canoe**
- **Traveling 10 miles by bicycle**
- **Traveling 300 miles by car**
- **Flying 1,000 miles by jet**

Source: J NCI Res, 1991

## One-in-a-Million Risk of Dying from Cancer

Activity

- Smoking 1.4 cigarettes
- Flying 6,000 miles by jet
- Living in Denver for 2 months
- Living in stone or /brick building for 2 months
- 1 chest x-ray in good hospital
- Living with cigarette smoker for 2 months
- Drinking Miami drinking water for 1 year
- Drinking 30 - 12 oz cans of diet soda
- Living 5 years at site boundary of a typical nuclear power plant
- Drinking 1,000 24 oz soft drinks from plastic bottles
- Living 20 years near polyvinyl chloride plant
- Living 150 years within 5 miles of a nuclear power plant
- Eating 100 charcoal broiled steaks

Source: J NCI Res, 1991

Perception of Risk

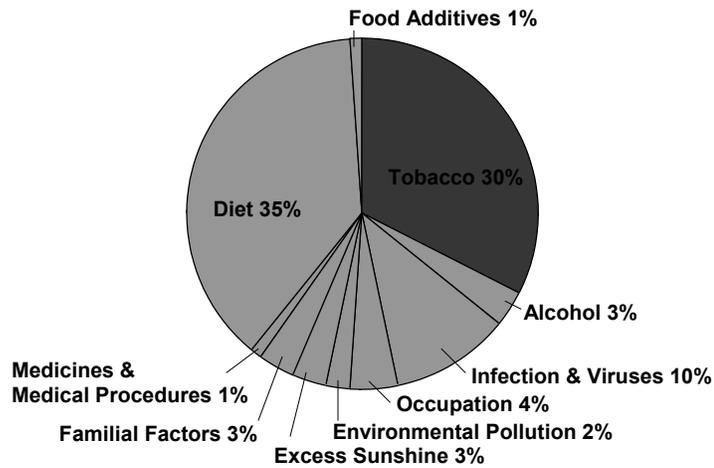| League of Women Voters	College Students	Business Club Members	Actual Rank/Risk
Nuclear power	Nuclear power	Handguns	Smoking
Motor vehicles	Handguns	Motorcycles	Alcohol
Handguns	Smoking	Motor vehicles	Motor vehicles
Smoking	Pesticides	Smoking	Handguns
Motorcycles	Motor vehicles	Alcohol	Electric power

Source: Upton, AC
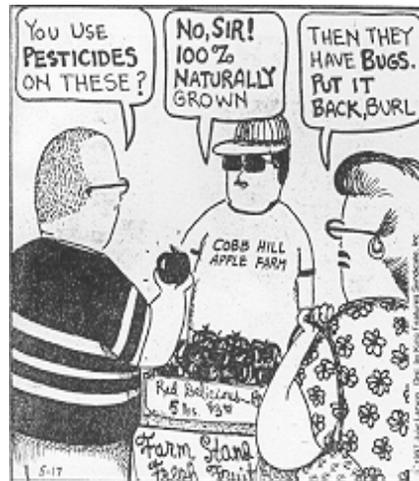
. . . but remember no cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one, would affect all . . .

Galen, 200 A.D.

Cancer Risk Factors

Food Additives 1%

Tobacco 30%

Diet 35%

Alcohol 3%

Medicines &
Medical Procedures 1%

Infection & Viruses 10%

Occupation 4%

Familial Factors 3%

Environmental Pollution 2%

Excess Sunshine 3%

Tobacco in Any Form Kills

Nicotine Addicts CHEW

CIGARETTES

SNUFF
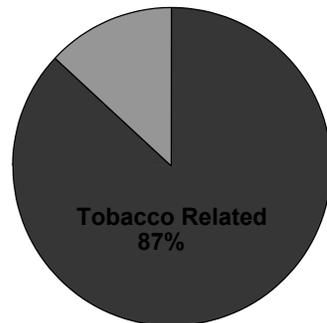
Cancer Risks Associated with Specific Tobacco Products

- **Pipe and Cigar Smoking (alkaline smoke)**
  - ◆ Mouth
  - ◆ Esophagus
  - ◆ Larynx

- **Chewing Tobacco and Snuff**
  - ◆ Mouth (leukoplakia)
  - ◆ Larynx

- **Cigarettes (acidic smoke)**
  - ◆ Lung   ◆ Bladder
  - ◆ Esophagus ◆ Kidney
  - ◆ Larynx   ◆ Pancreas
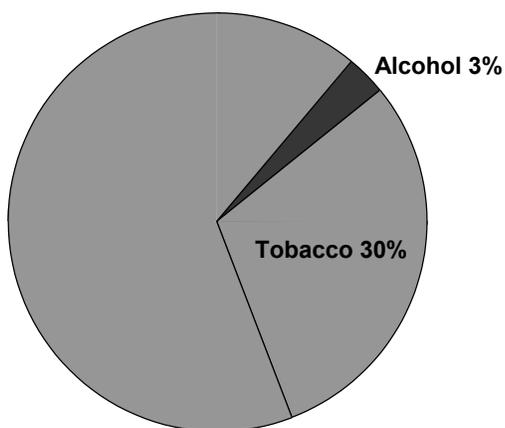 - ◆ Pharynx   ◆ Cervix

Lung Cancer

Tobacco Related
87%

- **More pack-years increases risk**
- **Passive smoking increases risk**
- **Low tar/nicotine cigarettes don't decrease risk**
- **Quitting lowers risk**

Passive Smoking Leads to Increased Risk of Lung Cancer

- **Spouses of smokers have an approximately 30% increased risk of lung cancer**

Cancer Risk Factors

Alcohol 3%

Tobacco 30%

Cancer Sites Linked to Alcohol

- **Mouth**

- **Esophagus**

- **Larynx**

- **Pharynx**

- **Liver**

CIGARETTES

+ = **Risk**

Esophagus
Mouth
Pharynx
Larynx

600,000 New Cases per Year

Skin Cancer

High Energy Particles   UVC   UVB   UVA
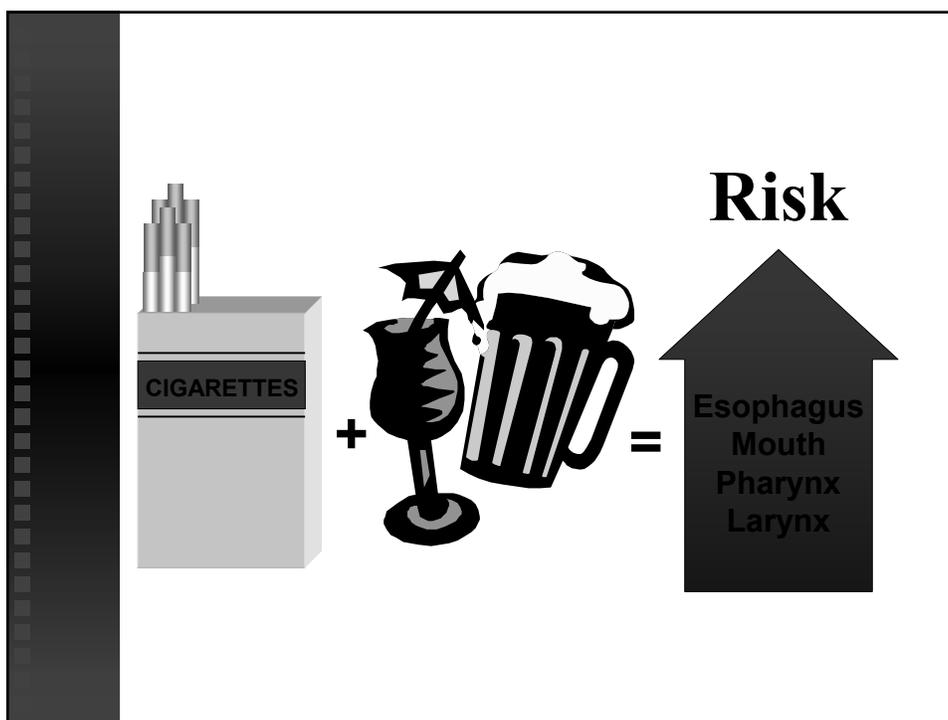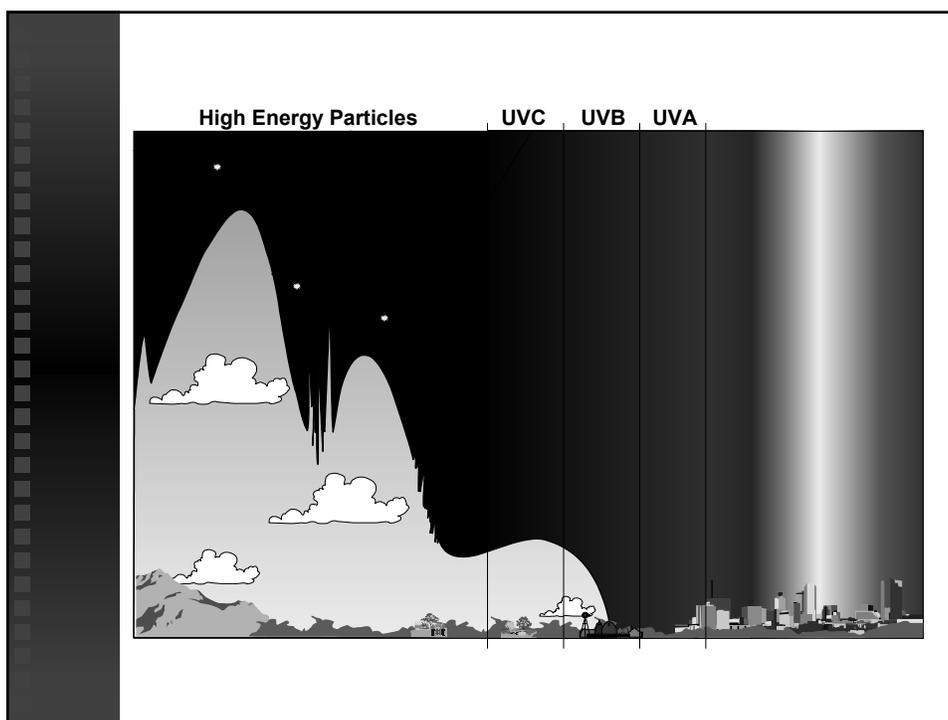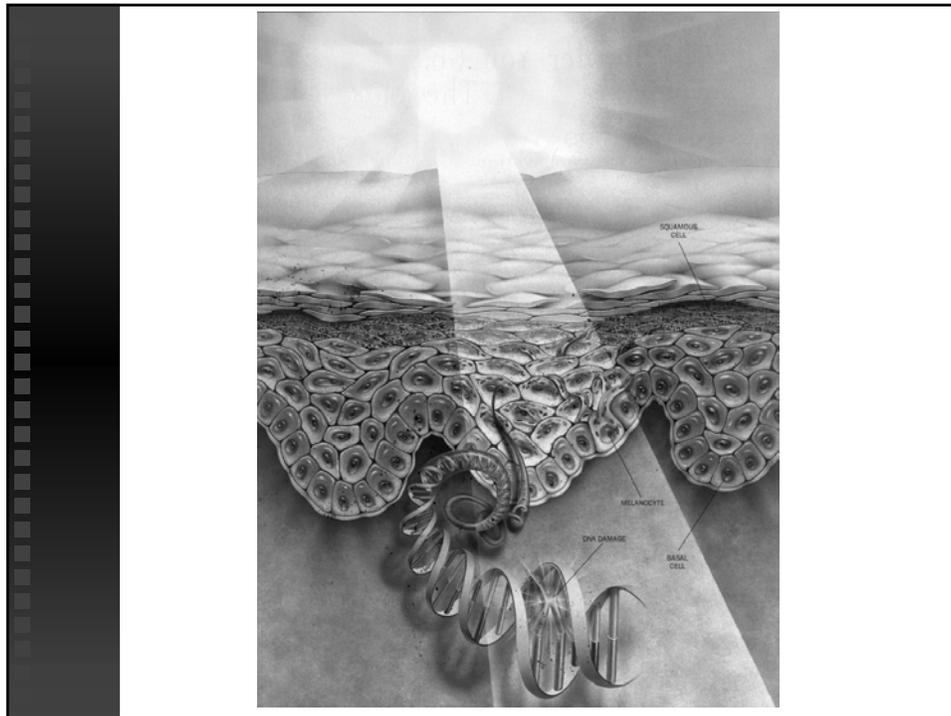
Nonmelanoma

- Basal cell carcinoma

- Squamous cell carcinoma

Nonmelanoma
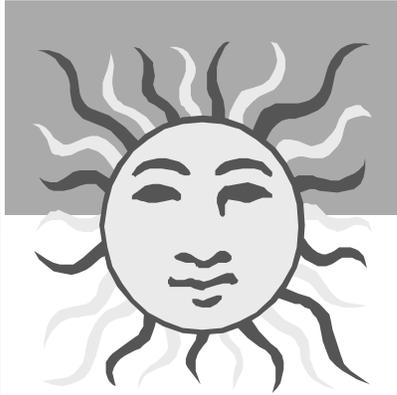
- **Most Common**

- **90% caused by overexposure to excessive radiation**

- **95% curable when found and treated early**

Melanoma

- **Life threatening**

- **Spreads rapidly**

- **Linked to moles**

- **Incidence rapidly increasing**

Skin Self-Exam

Look for:
- **Moles**
- **Birthmarks**
- **Blemishes**
- **New marks**
- **Sores**

Note changes in:
- **Color**
- **Shape**
- **Size**

Use Sunscreen of SPF 15 or Greater

Factors Contributing to Cancer Risk in the United States

- **Diet: ~35%**
- **Tobacco: ~30%**
- **Occupational and Pollution: ~5%**
- **Infection: ~10%**
- **Other: ~20%**
  - ◆ **Genetic susceptibility**
  - ◆ **Sunlight / radiation**
  - ◆ **Alcohol**
  - ◆ **Long-term exposure to some drugs**

Diet and the Cancer Process

Initiation

Harmful: Dietary carcinogens; reactive oxygen species --> DNA damage

Protective: Bioactive compounds in fruits and vegetables

Promotion

Harmful: Diet-related promoters--fat, total energy intake, obesity

Protective: Bioactive compounds in fruits and vegetables

Progression

Harmful : ?---fat, total energy intake, obesity

Protective: Bioactive compounds in fruits and vegetables

Cancer Promoter: Dietary Fat

- Cancers most associated with high fat intake: prostate, colon, breast
- Mechanism of Action:
  - increase bile acid production
  - increase steroid hormone production
  - suppress immune function
  - promote obesity

  Note: Saturated (animal) fat appears to be most harmful; monounsaturated (olive oil) least harmful.

Cancer Promoter: Obesity

- Cancers most associated with obesity: colon, breast, prostate, cervix, ovary
- Mechanism of Action:
  - increased levels of steroid hormones (estrogens), growth factors (IGF-1)
  - increased oxidative stress

Cancer Protectors in the Diet

- **Foods associated with decreased cancer risk**
  - ◆ **Fruits and vegetables**
  - ◆ **Whole grain products**
  - ◆ **Beans, legumes, seeds**

- **Cancers most associated with protective effects of plant foods: lung, head and neck, colon, breast, bladder, prostate**

What is an Antioxidant?

Microconstituents of the diet that protect DNA, proteins and cell membranes against oxidative damage, including that induced by carcinogens.

What is a Phytoestrogen?

Microconstituents of the diet (generally plant-derived compounds) with weak estrogenic properties, and thus the ability to interfere with the activity of endogenous estrogens.

Potentially Protective Nutrients in Fruits and Vegetables

Nutrient	Proposed Mechanism
Carotenoids (β-carotene)	antioxidant
Vitamin C	antioxidant
Vitamin E	antioxidant
Folic acid	prevents DNA hypomethylation
Selenium	antioxidant

Other Potentially Protective Phyto (plant) Compounds

Compound	Source	Proposed Mechanism
Isoflavones (genistein)	soy	phytoestrogen; antioxidant
Flavonoids	variety	phytoestrogen; antioxidant
Alliums	onion; garlic	alter carcinogen metabolism
Polyphenols	tea	antioxidant
Coumarins	citrus	alter carcinogen metabolism
Lignans	grains	phytoestrogen
Isothiocyantaes	crucifers	alter carcinogen metabolism
Dietary fiber	grains	bind carcinogens; alters bile acid, hormone metabolism

Other Diet-Cancer Issues

- **Food contaminants:** no convincing evidence that chemical residues sometimes present in food and drink (fertilizer, pesticide, herbicide, hormones) increases cancer risk

- **Food additives:** no convincing evidence that any food additive (preservative, emulsifier, dye, flavoring) increases cancer risk (possible concern: nitrites)

- **Supplements vs. Foods:** evidence thus far from clinical trials suggest supplementation with high doses of isolated nutrients is probably unnecessary and possibly unhelpful for cancer prevention. The balance of multiple nutrients from a diet containing a variety of fruits, vegetables and grains may be very important

# 1999 American Institute for Cancer Research Dietary Recommendations

1. Choose diets rich in plant-based foods including a variety of fruits and vegetables, reduce processed, starchy foods.

2. Avoid being overweight or underweight.

3. If occupational activity is low or moderate, take a brisk walk (or similar exercise) every day and also exercise vigorously at least one hour per week.

1999 American Institute for Cancer Research Dietary Recommendations *(continued)*
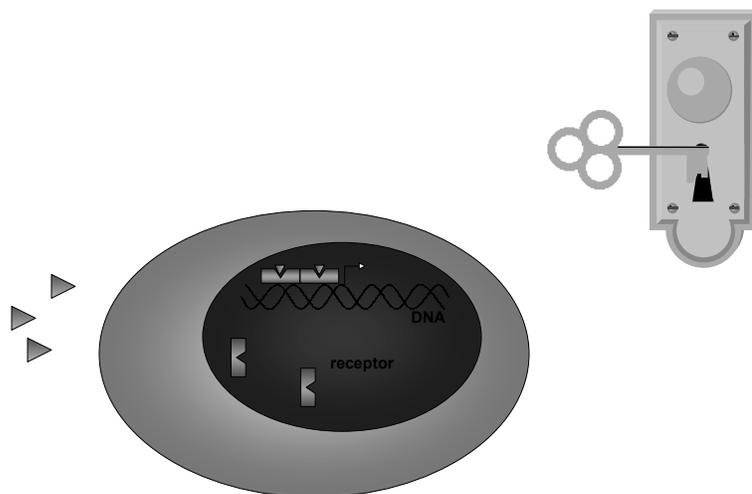
4. Eat 7 or more servings/day of cereals, pulses, roots or tubers, and limit consumption of refined sugar.

5. If consumed at all, limit alcoholic drinks to no more than than two drinks/ day for men and one for women.

6. Limit intake of red meat to less than 3 ounces; when possible, choose fish or poultry in place of red meat

7. Limit consumption of fatty foods, particularly those of animal origin. Choose modest amounts of appropriate vegetable oils, particularly olive oil.
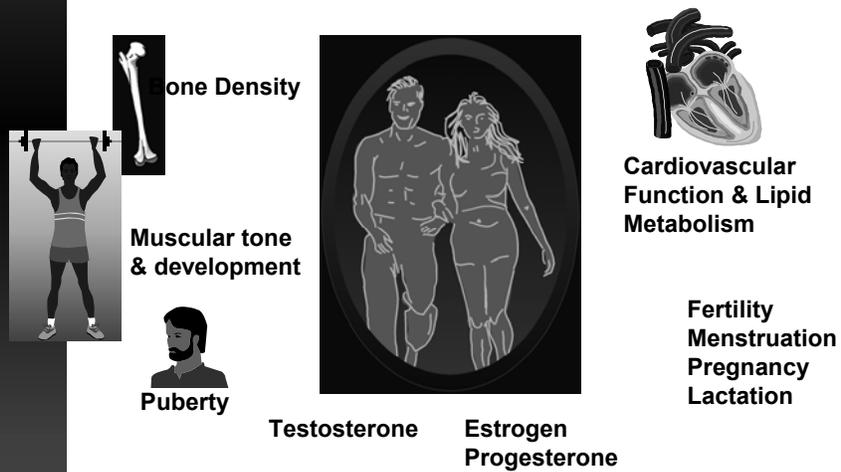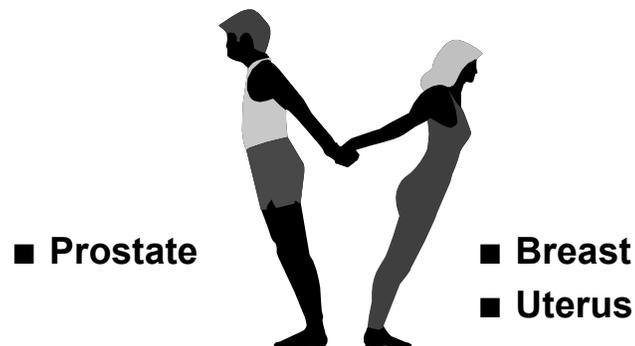
The Endocrine System
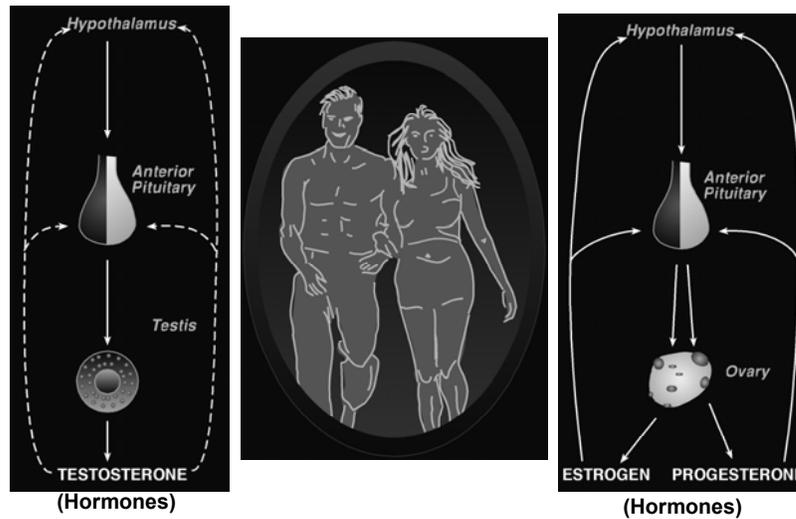
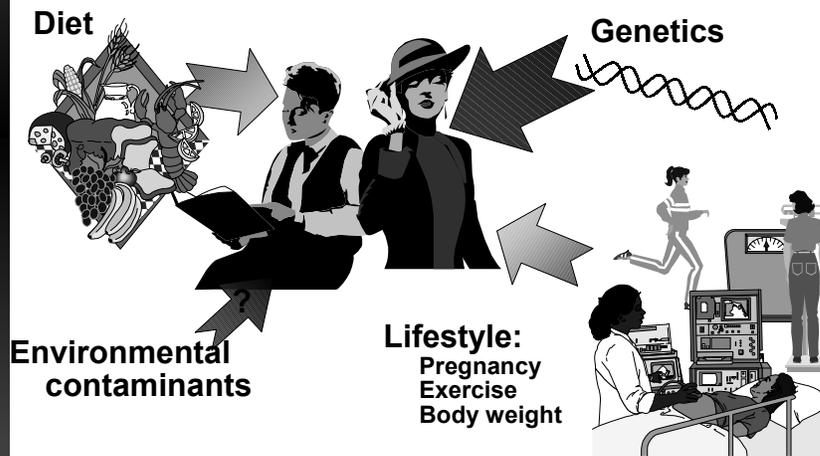# Hormones Bind to Specific Receptors like a Key Fits a Lock

Steroid Hormones Play an Important Role in Many Biological Processes

Bone Density

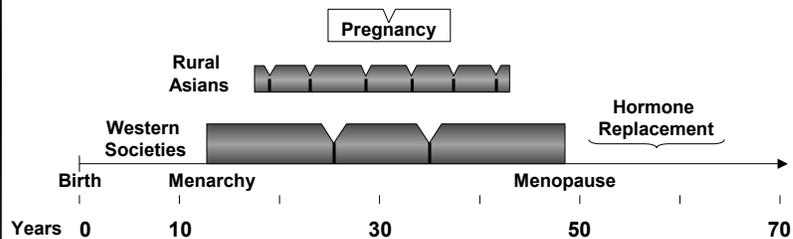Muscular tone & development

Puberty

Testosterone

Estrogen
Progesterone

Cardiovascular Function & Lipid Metabolism

Fertility
Menstruation
Pregnancy
Lactation

Common Tumors Occurring In Hormonally Regulated Tissues:

■ Prostate

■ Breast
■ Uterus

A Variety of Factors Impact Risk of Hormonally Dependent Cancers

Diet

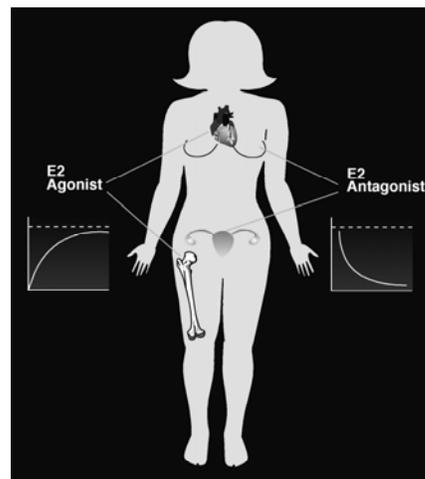**Genetics**

Environmental contaminants

Lifestyle:
Pregnancy
Exercise
Body weight

Evidence Suggests that Lifetime Risk of Breast & Endometrial Cancer is Proportional to Total Estrogen Exposure

Pregnancy

Rural Asians

Western Societies

Hormone Replacement

Birth   Menarchy   Menopause

Years   0   10   30   50   70

Hormonal Exposure From Internal & External Sources

DDT
Kepone

Pesticides

Dioxane
PCBs

Some
Medicines

Industrial Processes
& Products

Hormone
replacement
BCPs

Soy

Diet

Bisphenol
(Plastics)
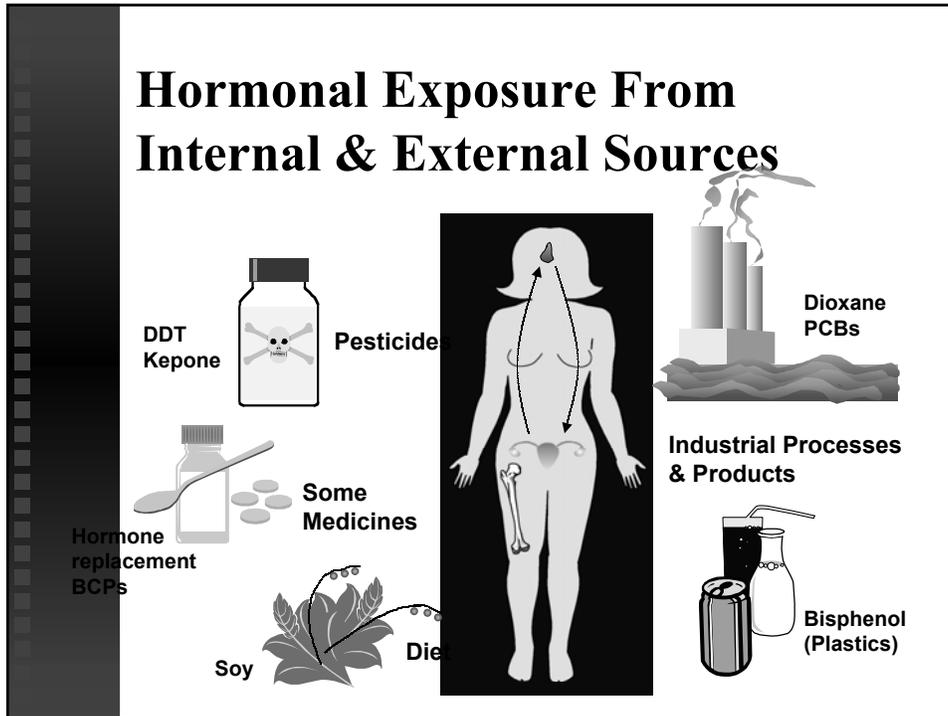
Medicines Can Act Like Hormones or Can Inhibit Hormonal Action

E2
Agonist

E2
Antagonist

| Compound	Use
Tamoxifen	Breast Cancer
Raloxifene	Osteoporosis
Hormone	Hot flash
Replacement	Cardiovascular
Therapy	Osteoporosis

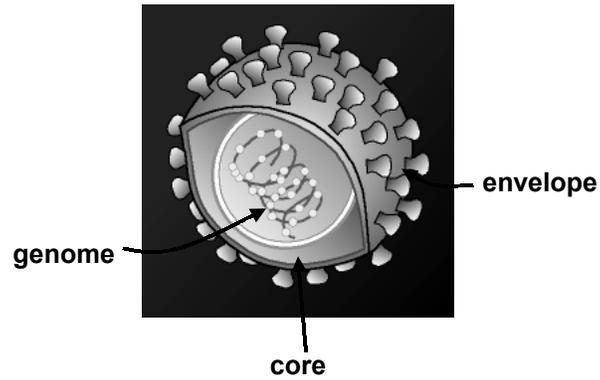# Q: Can You Catch Cancer as a Result of a Viral Infection?

Yes or No

Viruses and Human Cancer

■ **Viruses are now believed to be an important risk factor for cancer in humans.**
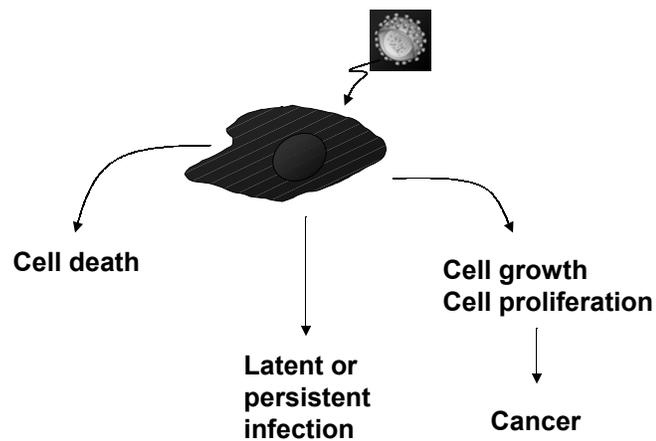
~ 10% - 15% of human cancer can be linked to virus infections
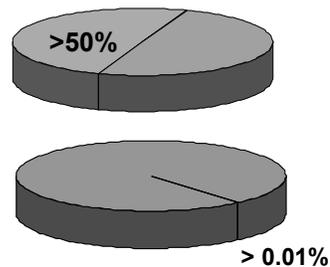
Virus Particle

envelope

genome
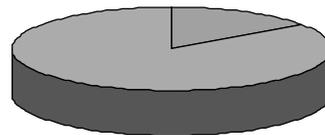
core

Fates of Virus-Infected Cells

Cell death

Cell growth
Cell proliferation

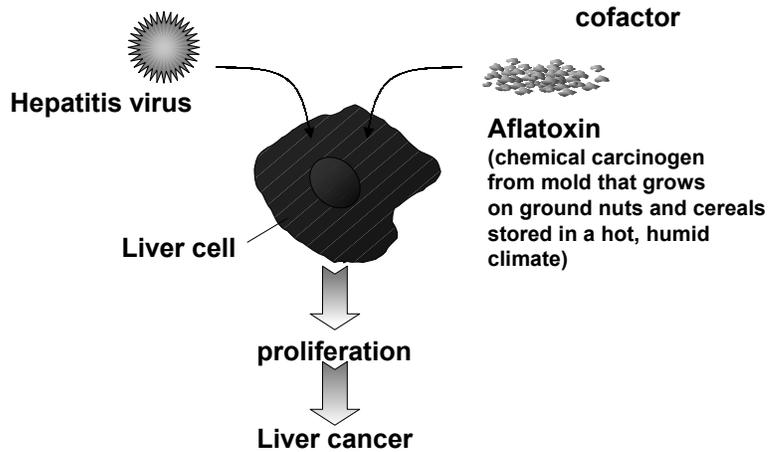Latent or
persistent
infection

Cancer

Different Viruses have Different Effects

■ Human Viruses With Oncogenic Potential
- ◆ Human Papilloma Viruses (HPV)
- ◆ Hepatitis B Virus (HBV)
- ◆ Human Herpes Virus 8
- ◆ Epstein-Bar Viruses
- ◆ Human T-lymphotropic Viruses (HTLV)
- ◆ Human immunodeficiency Viruses (HIV)

■ Common Characteristics
- ◆ Cause persistent infection
- ◆ Can directly or indirectly promote carcinogenesis
- ◆ Can inactivate tumor suppressors
- ◆ DNA or RNA viruses with a DNA phase in lifecycle

■ Viruses That Do Not Participate in Cancer Development
- ◆ Influenza viruses
- ◆ Common cold viruses
- ◆ Polio
- ◆ Chicken pox
- ◆ Measles
- ◆ Mumps
- ◆ Rubella
- ◆ Yellow fever

■ Common Characteristics
- ◆ Cause acute infection
- ◆ Do not promote carcinogenesis
- ◆ Usually cause cell death
- ◆ Mostly RNA viruses

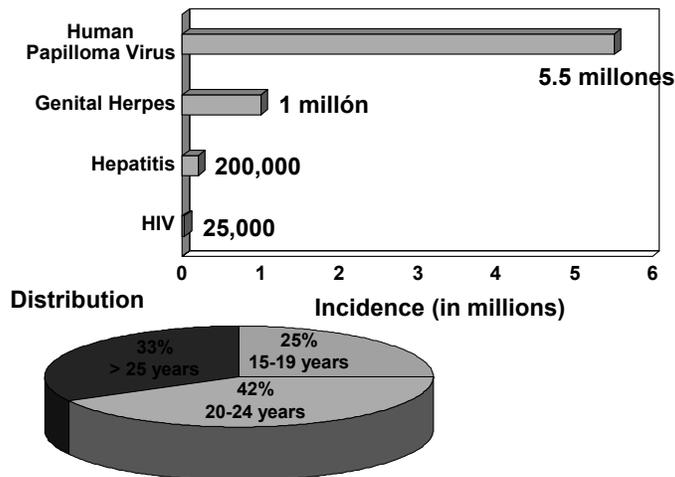**■ More than 50% of cases physicians encounter daily involve viral infections**

■ Fortunately, only a very small % of people infected with specific types of viruses develop cancer

■ Because this % is so low, cofactors, such as the genetic make-up of the host, environmental factors, and/or secondary viral infections are suspected to be needed for cancer to develop

>50%

> 0.01%

Virus Interaction with Environmental Factors

cofactor

Hepatitis virus

Aflatoxin
(chemical carcinogen
from mold that grows
on ground nuts and cereals
stored in a hot, humid
climate)

Liver cell

proliferation

Liver cancer

Estimated Annual New Cases of Viral Sexually Transmitted Diseases in U.S.

Human Papilloma Virus — 5.5 millones

Genital Herpes — 1 millón

Hepatitis — 200,000

HIV — 25,000

0 1 2 3 4 5 6

Incidence (in millions)

Distribution

25% 15-19 years
42% 20-24 years
33% > 25 years

Important Points to Remember:

- About 15% of cancer is linked to viral infections
- Only a very small % of viral infections will lead to cancer
- Cancer itself is not contagious
- Virus is contagious but viral infection is preventable
- Cancer associated with viruses therefore can be prevented

What Can be Done?

- Chances of contracting a sexually transmitted virus can be reduced by practicing safe sex
- It is possible to prevent cancers associated with viruses by reducing exposure to environmental carcinogens
- Some viral infections can be prevented by immunization, this practice should also lower the worldwide cancer burden

One Change Can Change Your Life

Stop Smoking   **Improve Diet**

Quitting smoking lowers risk by 30%   **Improving diet lowers risk by 30%**

Acknowledgement of Contributions

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- Michael C. Macleod, Ph.D.
- David L. Mitchell, Ph.D.
- Rodney S. Nairn, Ph.D.
- Paul K.Y.Wong, Ph.D.
- Don Cook M.S.

Graphics by Chris Yone

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER