Biomedical Engineering for Global Health

Lecture Twelve

WARNING: Insufficient Medical Research Can Be Hazardous To Your Health
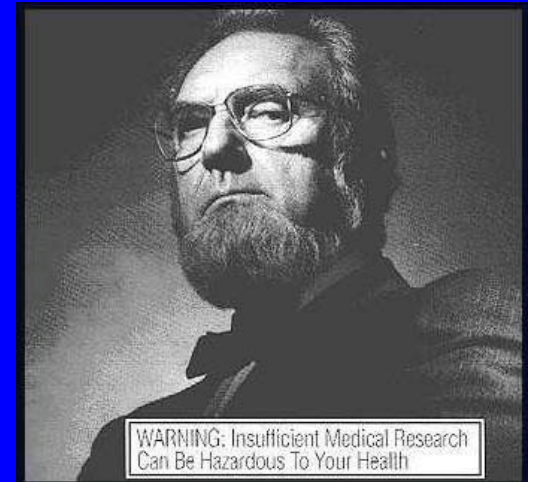
Four Questions

- What are the major health problems worldwide?

- Who pays to solve problems in health care?

- How can technology solve health care problems?

- How are health care technologies managed?

Three Case Studies

- Prevention of infectious disease
  - HIV/AIDS
- Early detection of cancer
  - Cervical Cancer
  - Ovarian Cancer
  - Prostate Cancer
- Treatment of heart disease
  - Atherosclerosis and heart attack
  - Heart failure

Outline

- The burden of cancer

- How does cancer develop?

- Why is early detection so important?

- Strategies for early detection

- Example cancers/technologies
    - Cervical cancer
    - Ovarian cancer
    - Prostate cancer

The Burden of Cancer: U.S.

- Cancer:
  - 2nd leading cause of death in US
  - 1 of every 4 deaths is from cancer
- 5-year survival rate for all cancers:
  - 62%
- Annual costs for cancer:
  - $172 billion
    - $61 billion - direct medical costs
    - $16 billion - lost productivity to illness
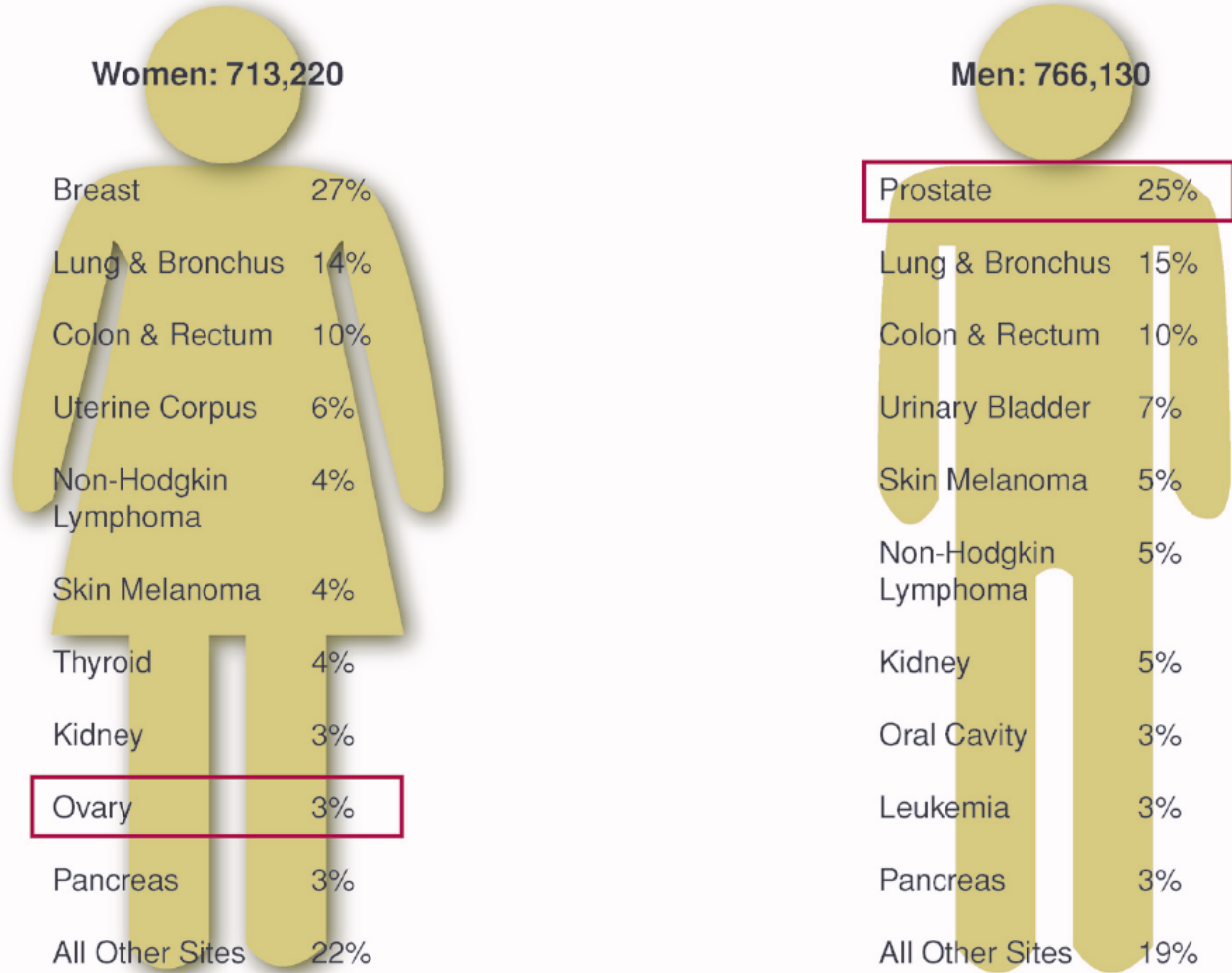   - $95 billion - lost productivity to premature death

U.S. Cancer Incidence & Mortality 2004

- New cases of cancer:
  - United States: 1,368,030
  - Texas: 84,530
- Deaths due to cancer:
  - United States: 563,700

www.cancer.org, Cancer Facts & Figures

Estimated US Cancer Cases in 2009*

Women: 713,220

Breast	27%
Lung & Bronchus	14%
Colon & Rectum	10%
Uterine Corpus	6%
Non-Hodgkin Lymphoma	4%
Skin Melanoma	4%
Thyroid	4%
Kidney	3%
Ovary	3%
Pancreas	3%
All Other Sites	22%

Men: 766,130
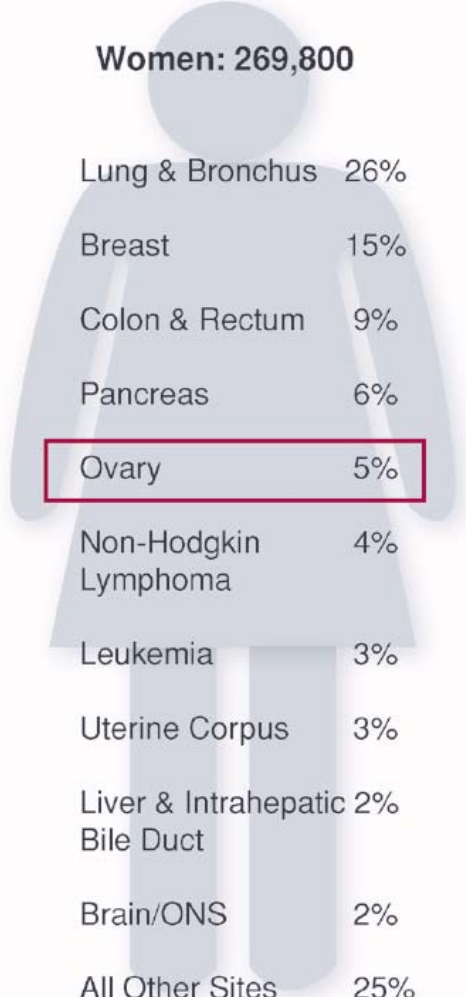
Prostate	25%
Lung & Bronchus	15%
Colon & Rectum	10%
Urinary Bladder	7%
Skin Melanoma	5%
Non-Hodgkin Lymphoma	5%
Kidney	5%
Oral Cavity	3%
Leukemia	3%
Pancreas	3%
All Other Sites	19%

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
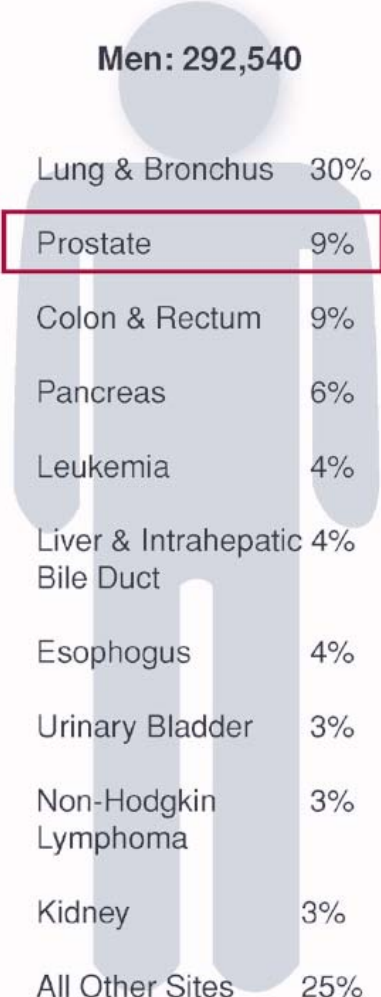
American Cancer Society

Estimated US Cancer Deaths in 2009*

Women: 269,800		Men: 292,540	
Lung & Bronchus	26%	Lung & Bronchus	30%
Breast	15%	Prostate	9%
Colon & Rectum	9%	Colon & Rectum	9%
Pancreas	6%	Pancreas	6%
Ovary	5%	Leukemia	4%
Non-Hodgkin Lymphoma	4%	Liver & Intrahepatic Bile Duct	4%
Leukemia	3%	Esophogus	4%
Uterine Corpus	3%	Urinary Bladder	3%
Liver & Intrahepatic Bile Duct	2%	Non-Hodgkin Lymphoma	3%
Brain/ONS	2%	Kidney	3%
All Other Sites	25%	All Other Sites	25%

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

American Cancer Society

Worldwide Burden of Cancer

- Today:
  - 11 million new cases every year
  - 6.2 million deaths every year (12% of deaths)
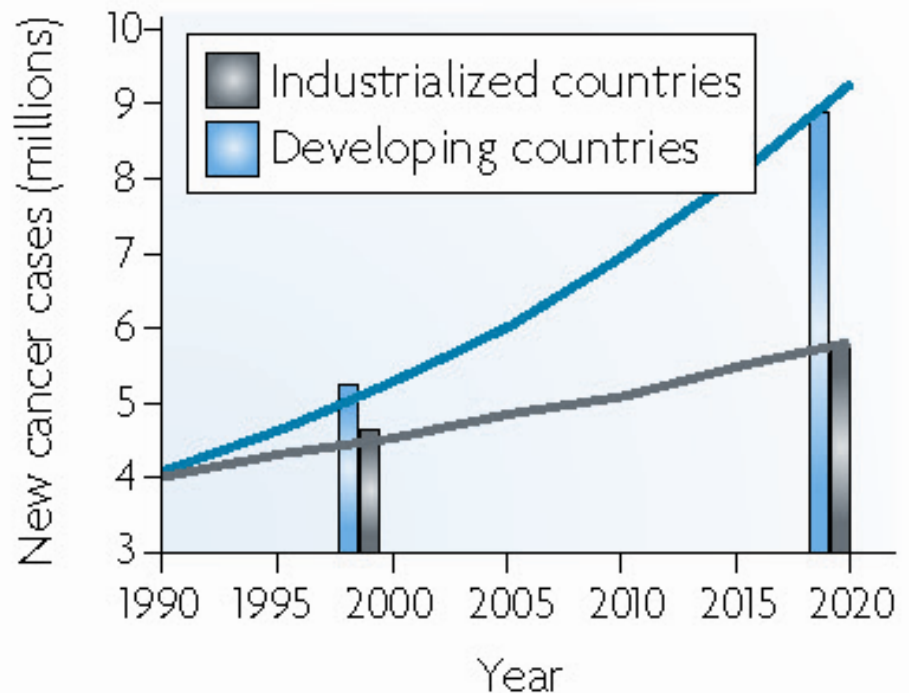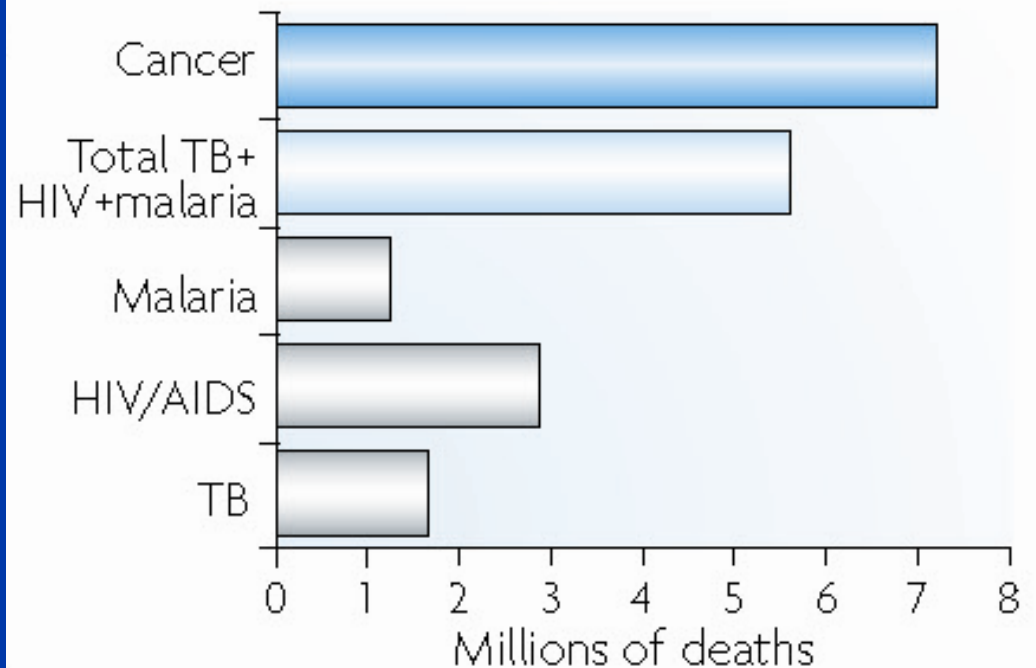- Can prevent 1/3 of these cases:
  - Reduce tobacco use
  - Implement existing screening techniques
  - Healthy lifestyle and diet
- In 2020:
  - 15 million new cases predicted in 2020
  - 10 million deaths predicted in 2020
  - Increase due to ageing population
  - Increase in smoking

Global Cancer Trends

Lingwood, et al;
The challenge of cancer control in Africa;
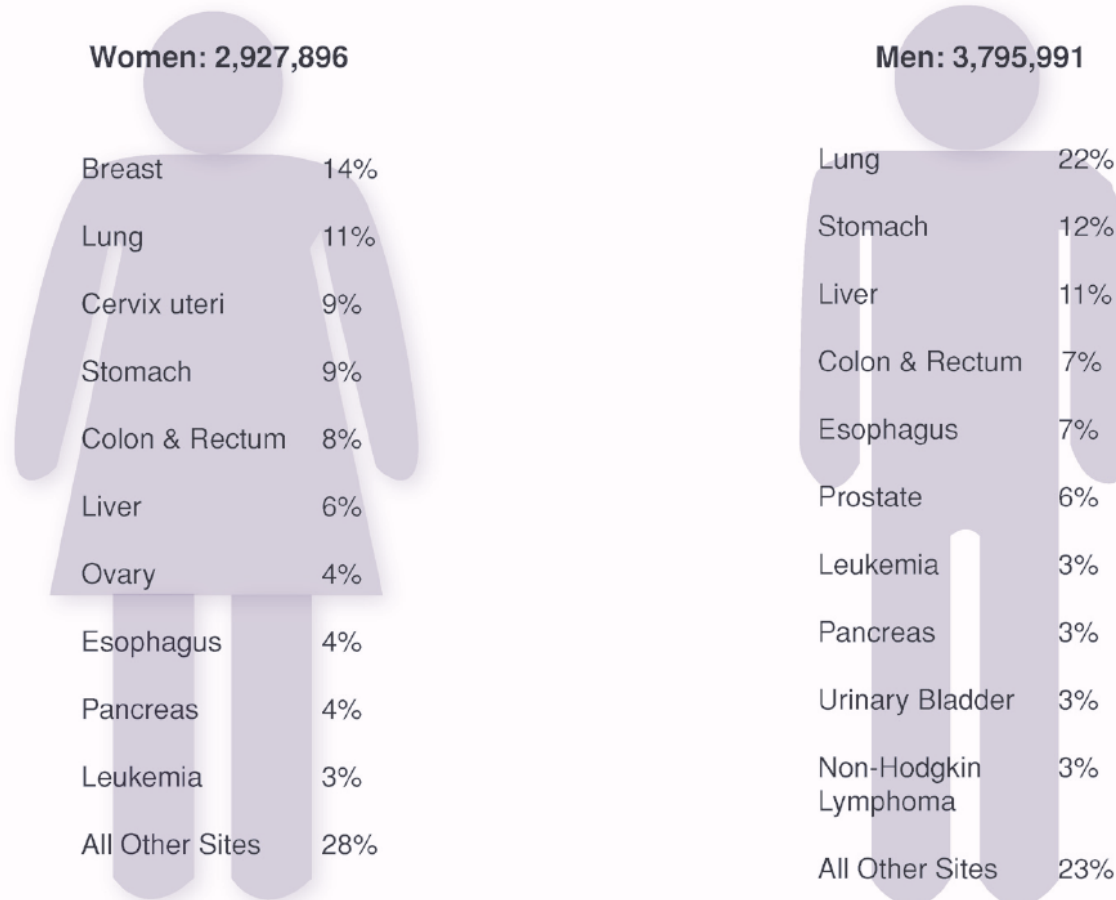Nat Rev CA, 8:398, 2008.

Worldwide Burden of Cancer

- 23% of cancers in developing countries caused by infectious agents
  - Hepatitis (liver)
  - HPV (cervix)
  - H. pylori (stomach)
- Vaccination could be key to preventing these cancers

Table 10.4. *The number of estimated cancer deaths worldwide in 2002 [6].*

Estimated Worldwide Cancer Deaths in 2002*

Women: 2,927,896

Breast	14%
Lung	11%
Cervix uteri	9%
Stomach	9%
Colon & Rectum	8%
Liver	6%
Ovary	4%
Esophagus	4%
Pancreas	4%
Leukemia	3%
All Other Sites	28%

Men: 3,795,991

|	
Lung	22%
Stomach	12%
Liver	11%
Colon & Rectum	7%
Esophagus	7%
Prostate	6%
Leukemia	3%
Pancreas	3%
Urinary Bladder	3%
Non-Hodgkin Lymphoma	3%
All Other Sites	23%

*Excludes basal and squamous cell skin cancers
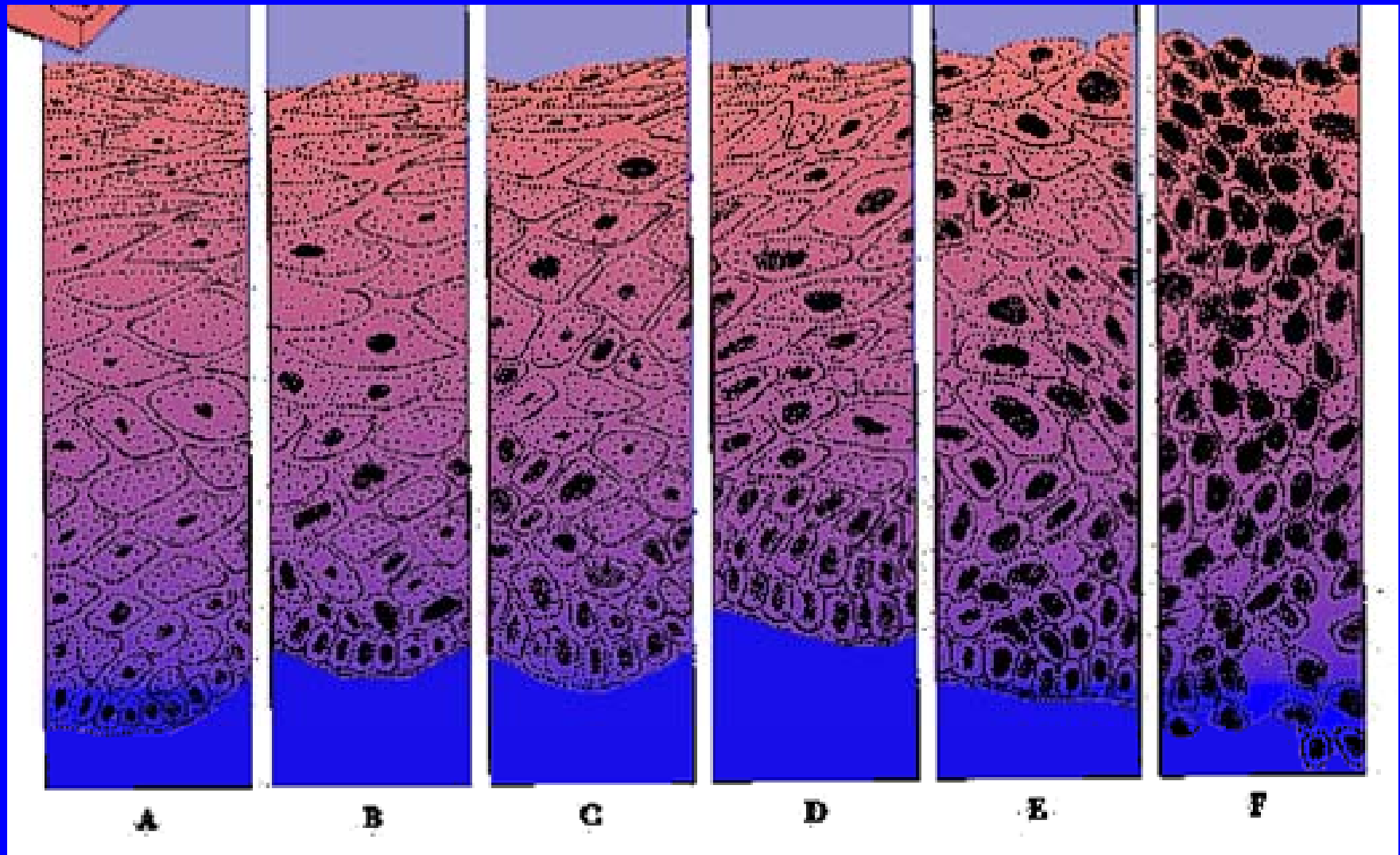
American Cancer Society

What is Cancer?

- Characterized by uncontrolled growth & spread of abnormal cells
- Can be caused by:
    - External factors:
        - Tobacco, chemicals, radiation, infectious organisms
    - Internal factors:
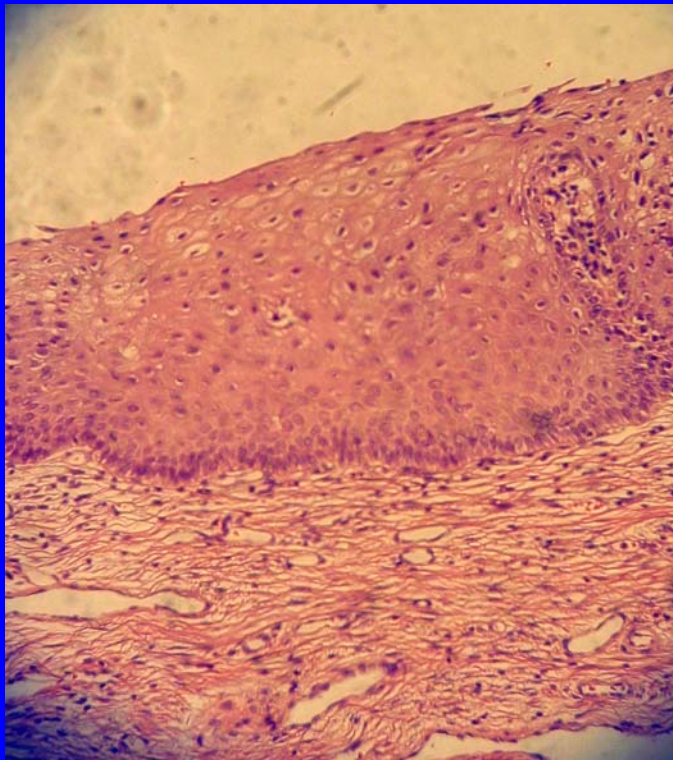   - Mutations, hormones, immune conditions
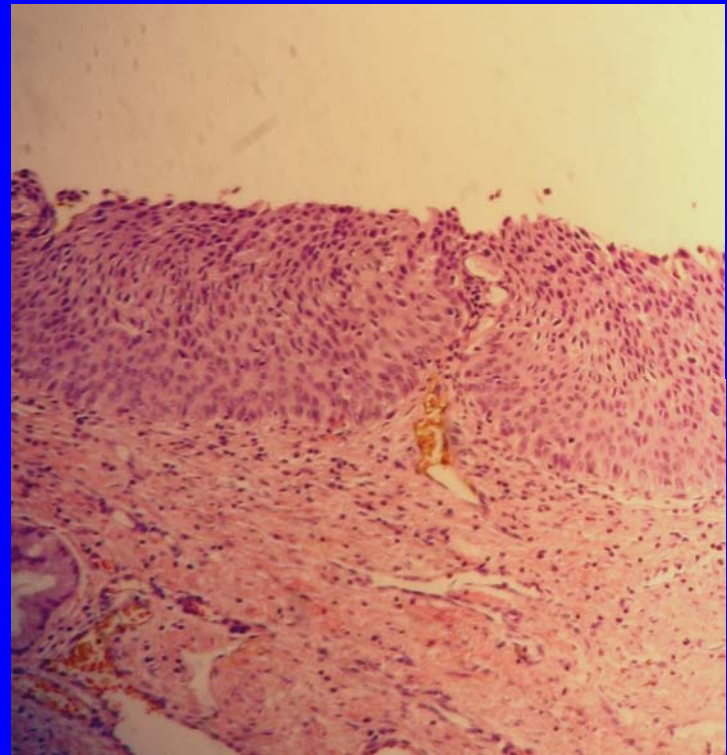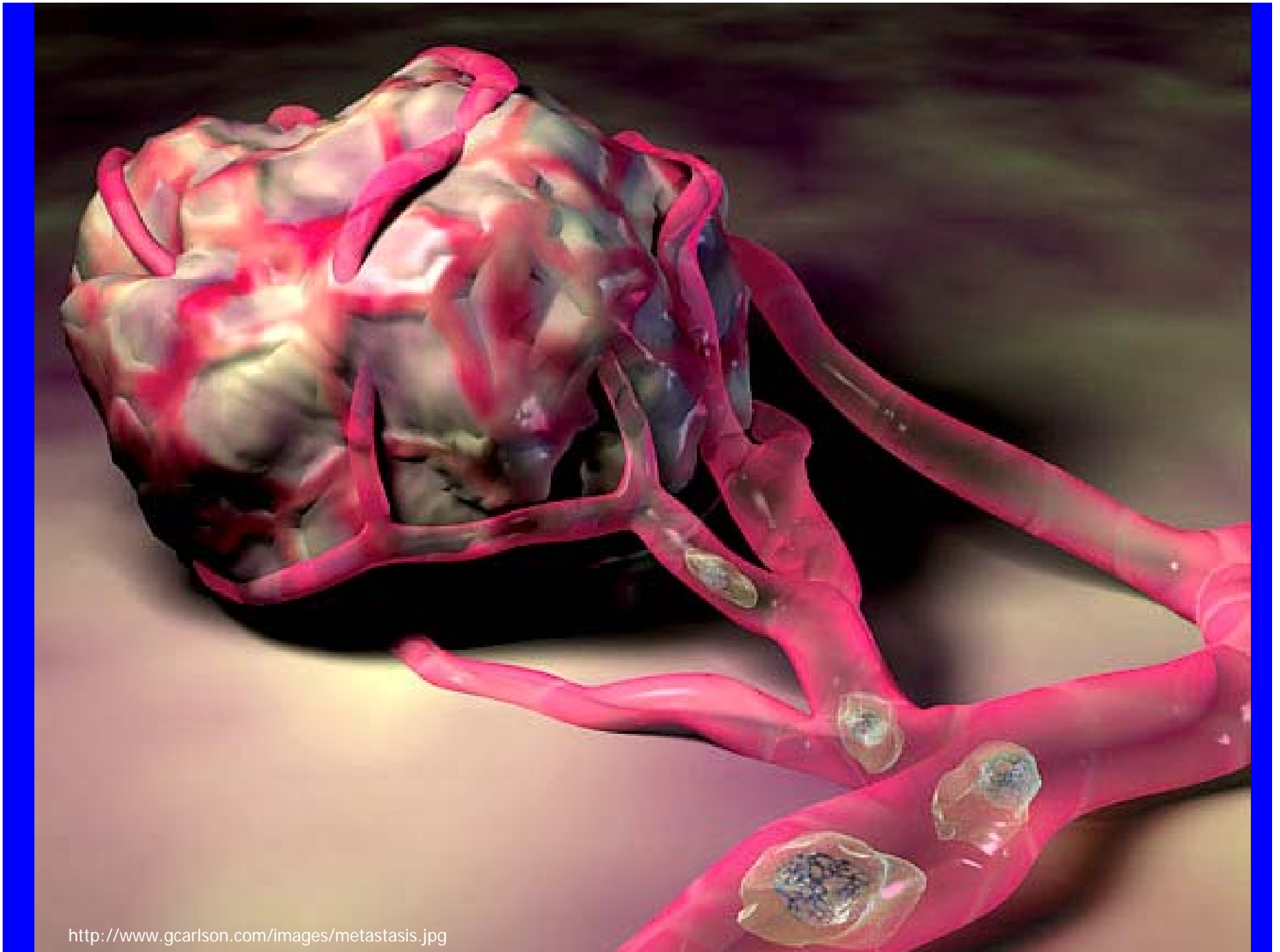
Squamous Epithelial Tissue
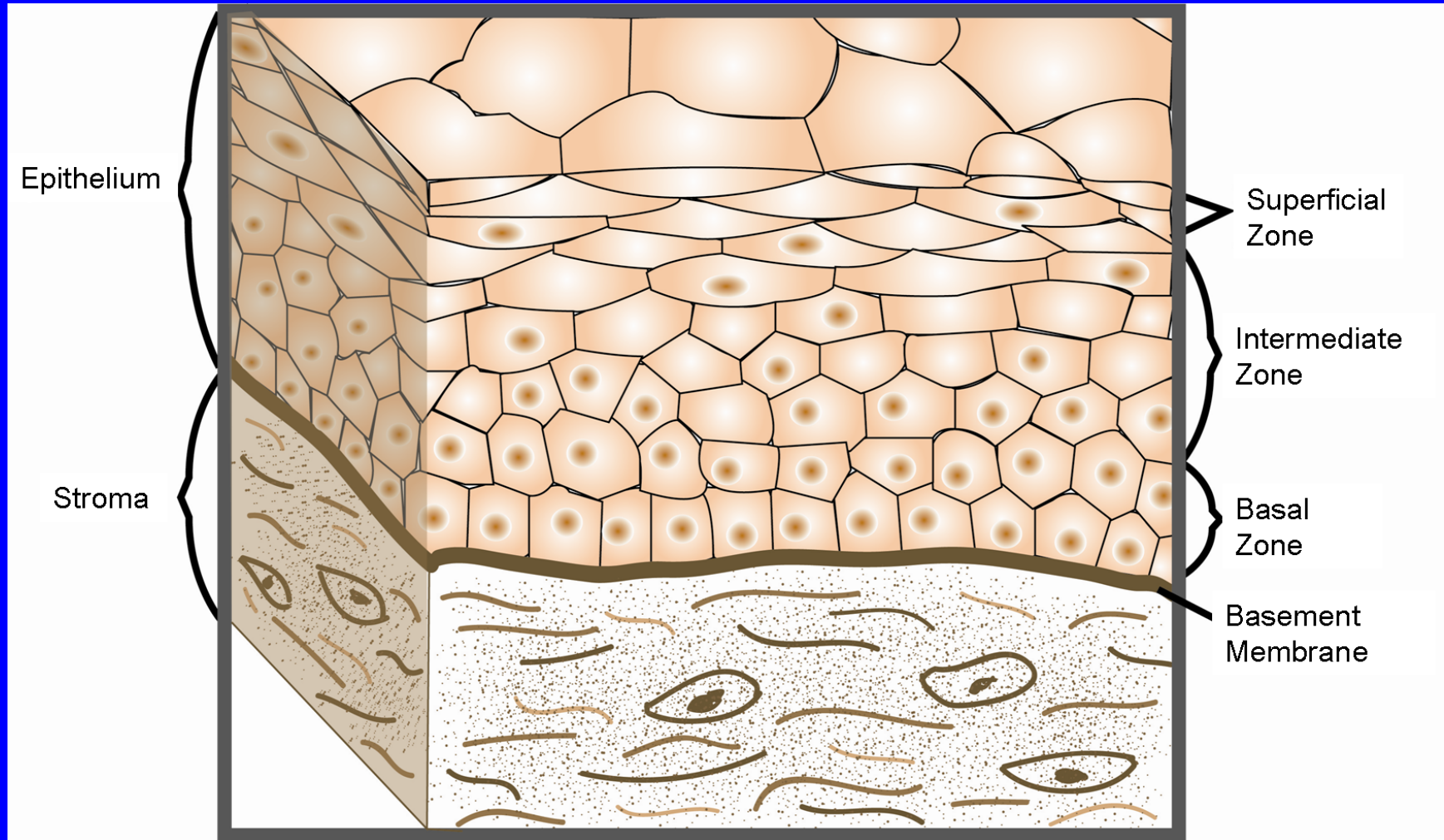
Precancer → Cancer Sequence

A   B   C   D   E   F

Histologic Images

Normal
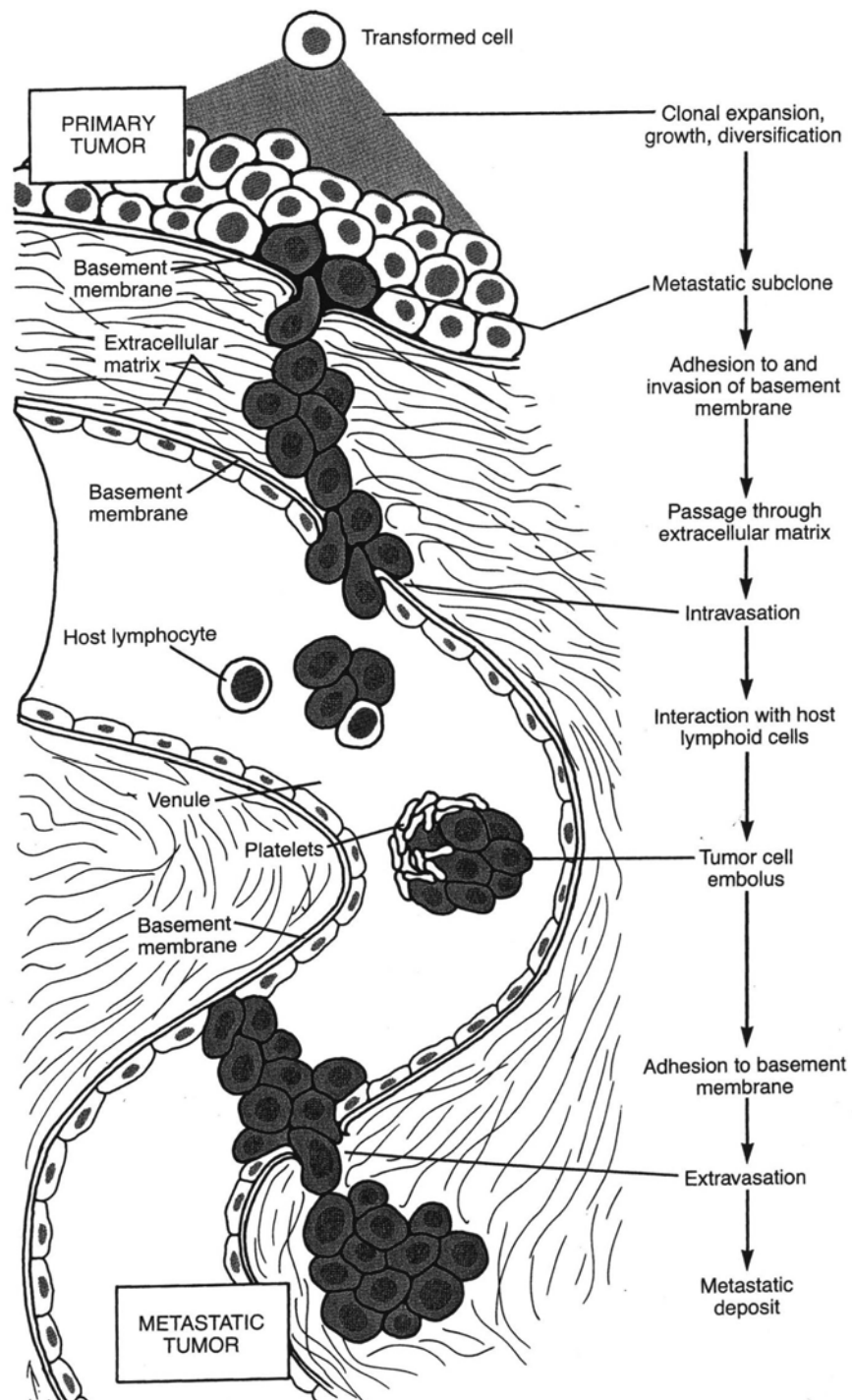
Cervical Pre-Cancer

http://www.gcarlson.com/images/metastasis.jpg

Fig 7.33 – The Metastatic cascade

Neoplasia

Progression of Malignant Cancer

NORMAL CELLS

ABNORMAL CELLS

ABNORMAL CELLS MULTIPLY

MALIGNANT / INVASIVE CANCER

BOUNDARY

LYMPH VESSEL

BLOOD VESSEL

PRIMARY CANCER

LOCAL INVASION

ANGIOGENESIS
Tumors grow their own blood vessels

LYMPH VESSEL

BOUNDARY

METASTASIS
Cells move away from primary tumor and invade other parts of the body via blood vessels and lymph vessels
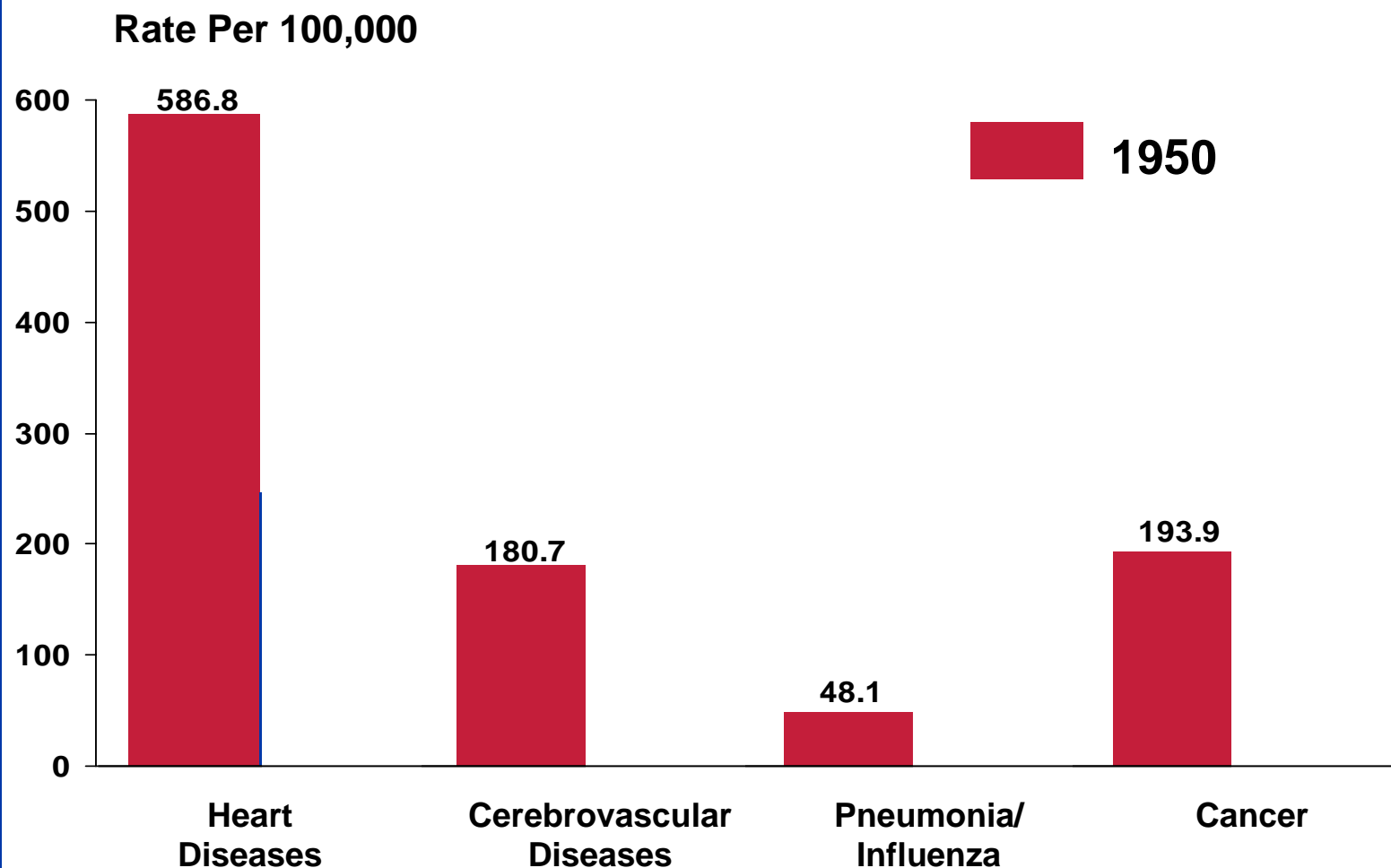
BLOOD VESSEL
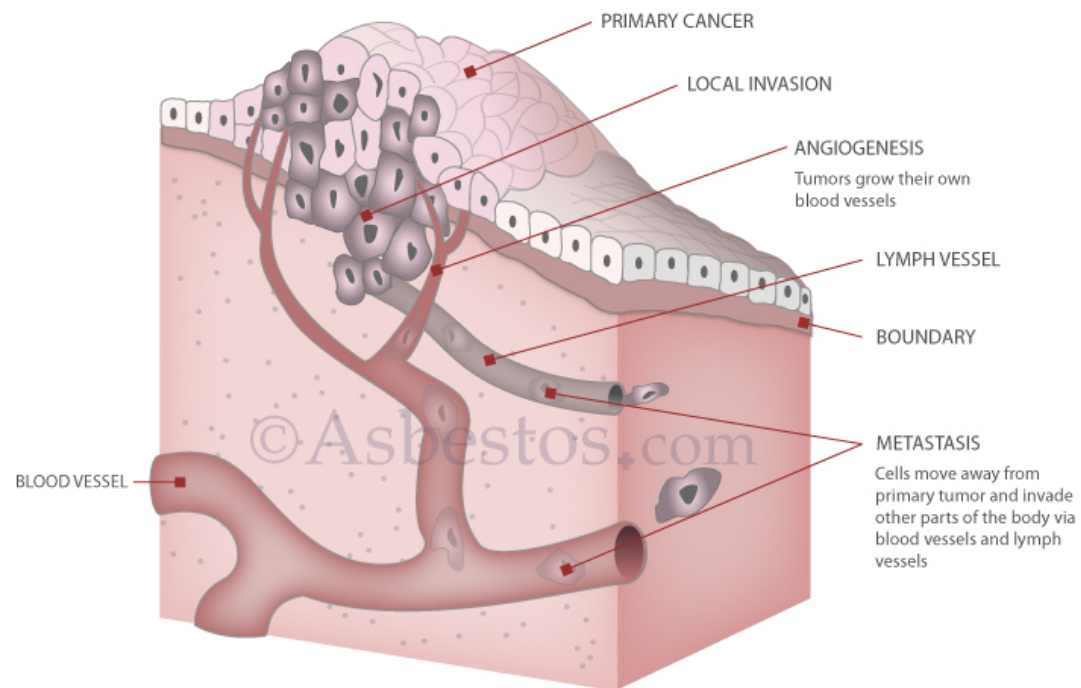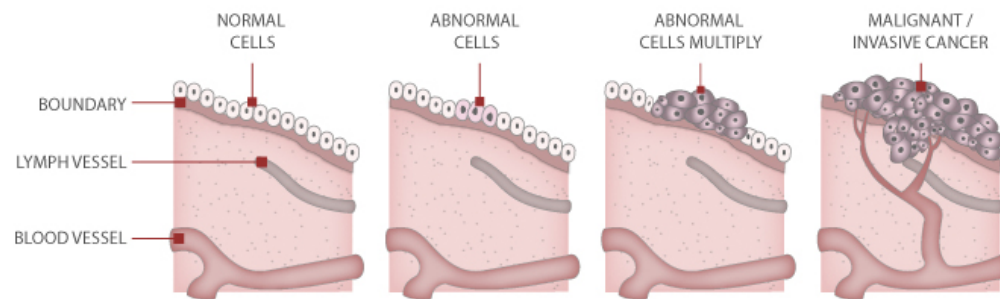
The War on Cancer

- **1971 State of Union address:**
  - President Nixon requested $100 million for cancer research
- **December 23, 1971**
  - Nixon signed National Cancer Act into law
  - "I hope in years ahead we will look back on this action today as the most significant action taken during my Administration."

Change in the US Death Rates* by Cause, 1950 & 2001

Rate Per 100,000

	1950

600

586.8

500

400

300

200

193.9
180.7

100

48.1

0

Heart Diseases	Cerebrovascular Diseases	Pneumonia/ Influenza	Cancer

Change in the US Death Rates* by Cause, 1950 & 2001

Rate Per 100,000

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

Change in the US Death Rates* by Cause, 1950 & 2001

Rate Per 100,000

Legend:
- 1950 (red)
- 2001 (blue)

Cause	1950	2001
Heart Diseases	586.8	245.8
Cerebrovascular Diseases	180.7	57.5
Pneumonia/Influenza	48.1	
Cancer	193.9	

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

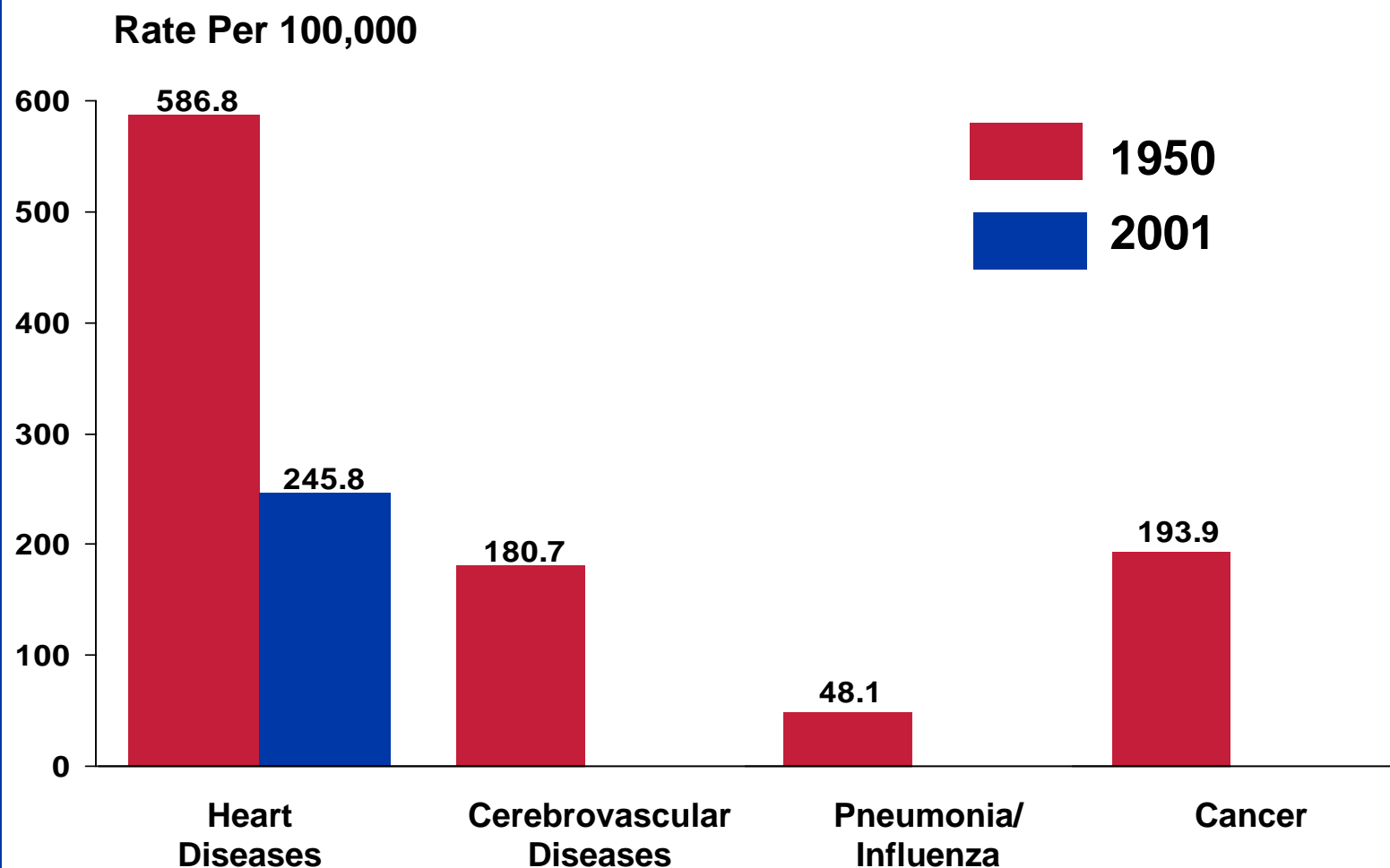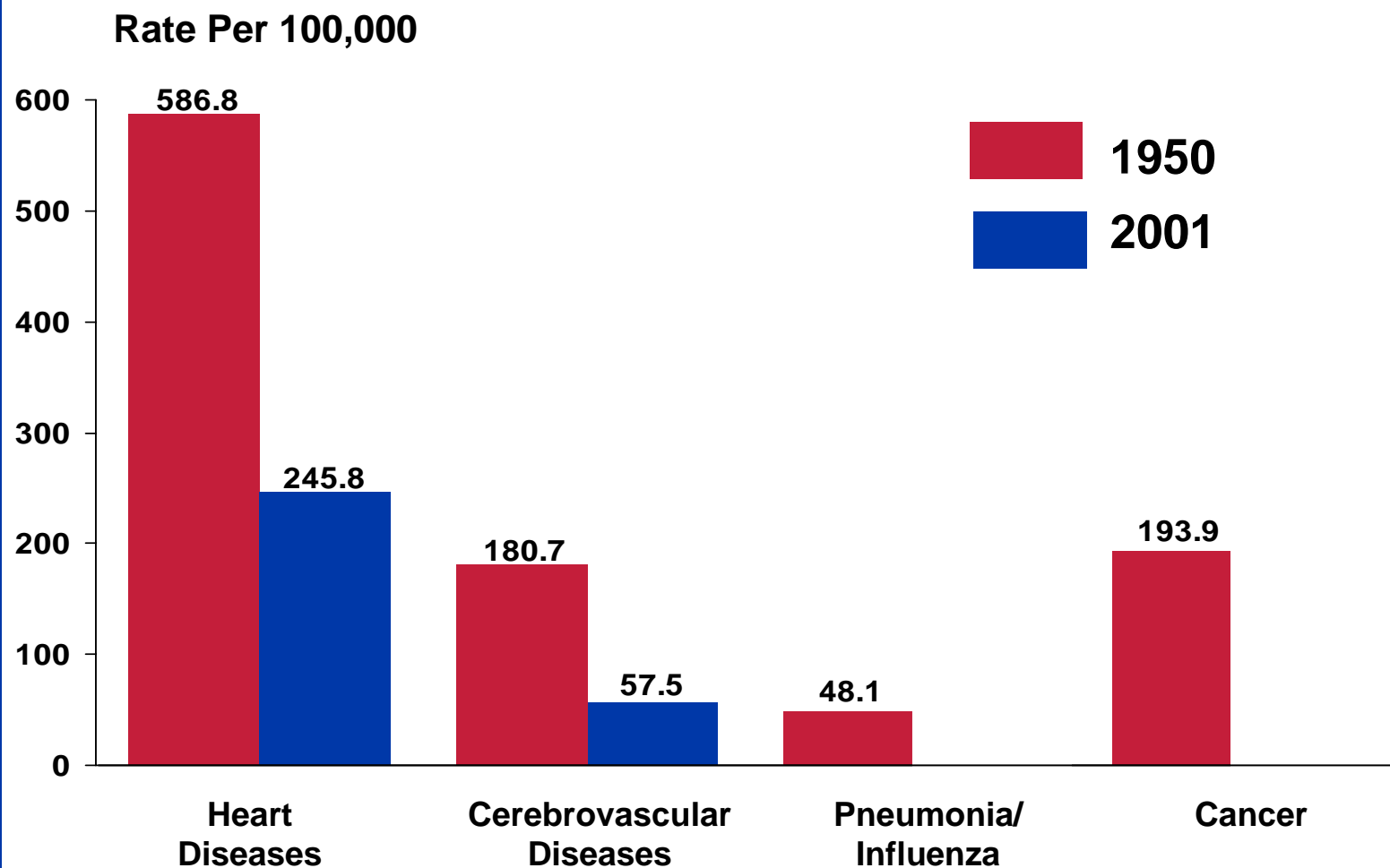# Change in the US Death Rates* by Cause, 1950 & 2001

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Rate Per 100,000

Legend:
- 1950 (red)
- 2001 (blue)

Cause	1950	2001
Heart Diseases	586.8	245.8
Cerebrovascular Diseases	180.7	57.5
Pneumonia/Influenza	48.1	21.8
Cancer	193.9	194.4

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
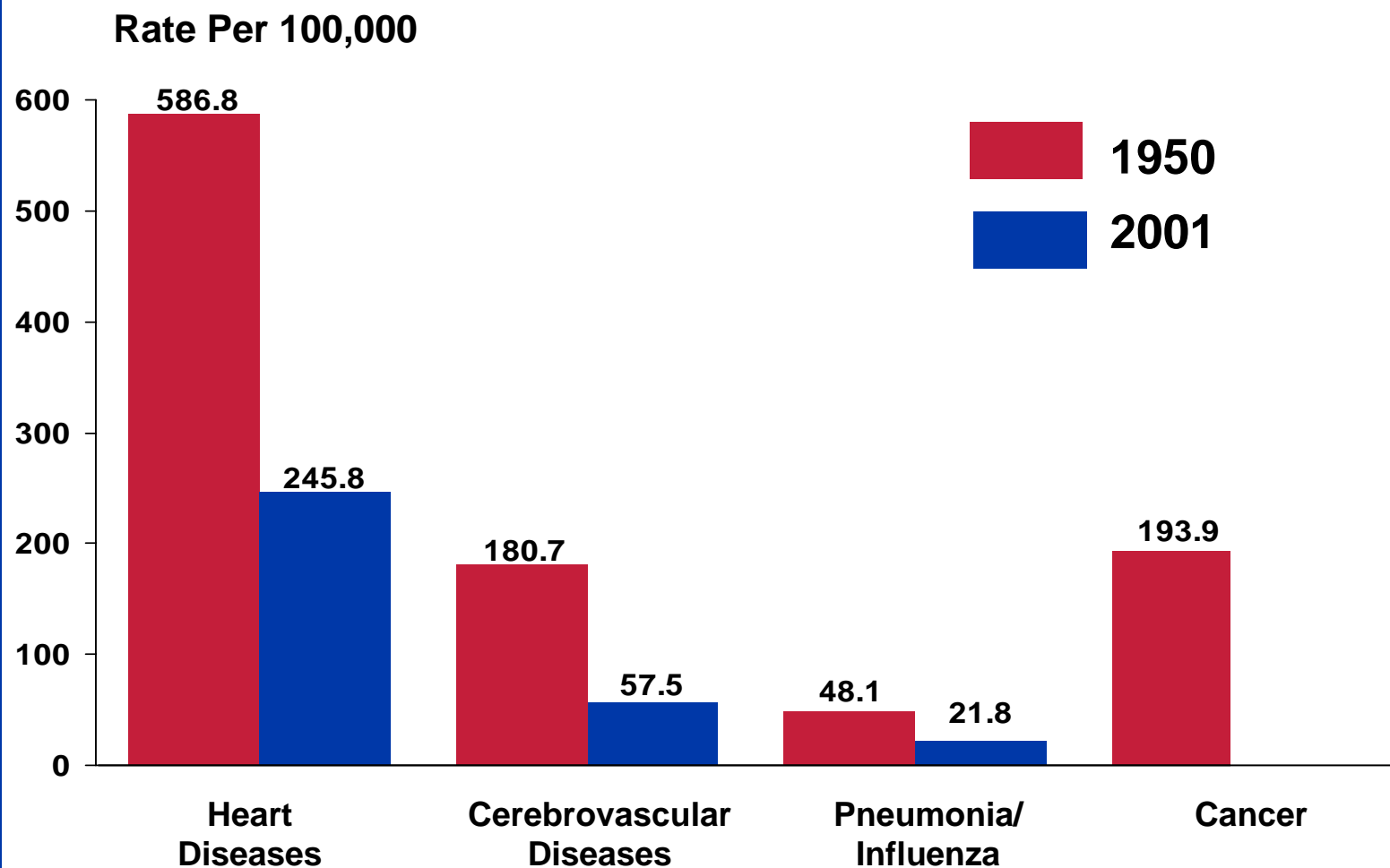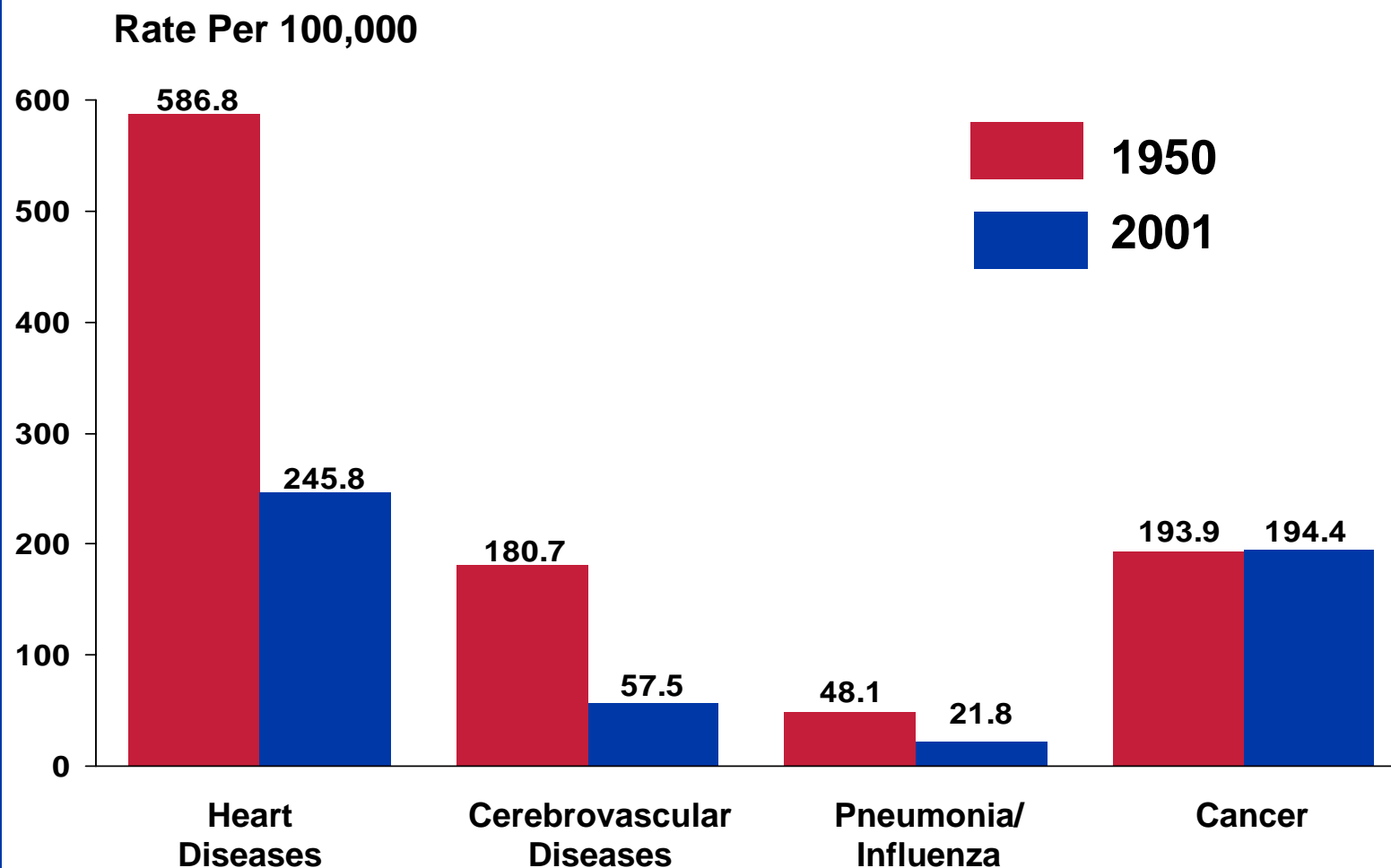2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

Cancer Death Rates*, for Men, US, 1930-2000
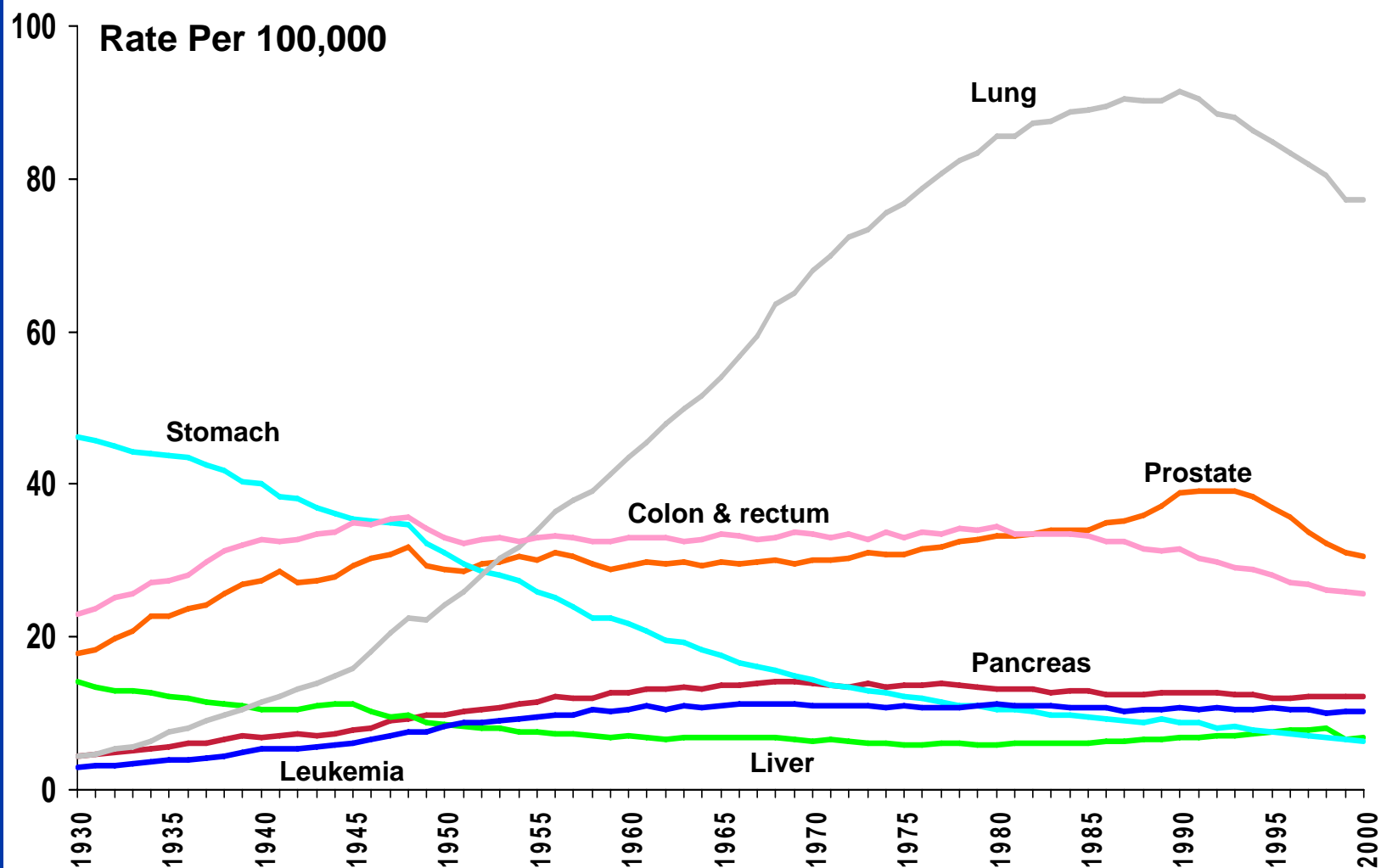
Rate Per 100,000

Lung

Stomach

Prostate

Colon & rectum

Pancreas

Leukemia

Liver

*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2000, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

Cancer Death Rates*, for Women, US, 1930-2000
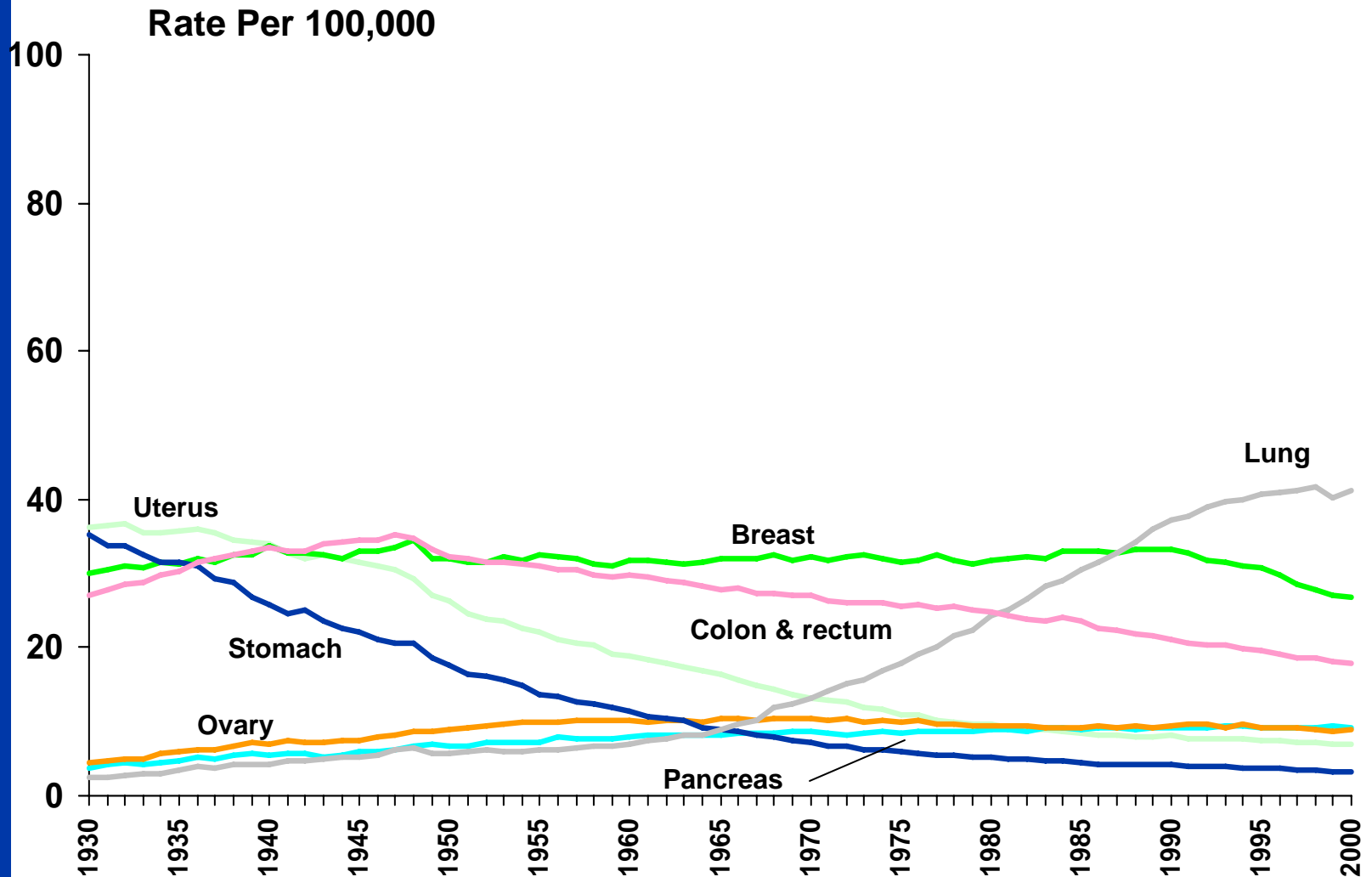
Rate Per 100,000

Uterus
Stomach
Ovary
Breast
Colon & rectum
Lung
Pancreas

100
80
60
40
20
0

1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000

*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2000, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

Cancer Incidence Rates* for Men, US, 1975-2000

Rate Per 100,000

Prostate

Lung

Colon and rectum

Urinary bladder

Non-Hodgkin lymphoma
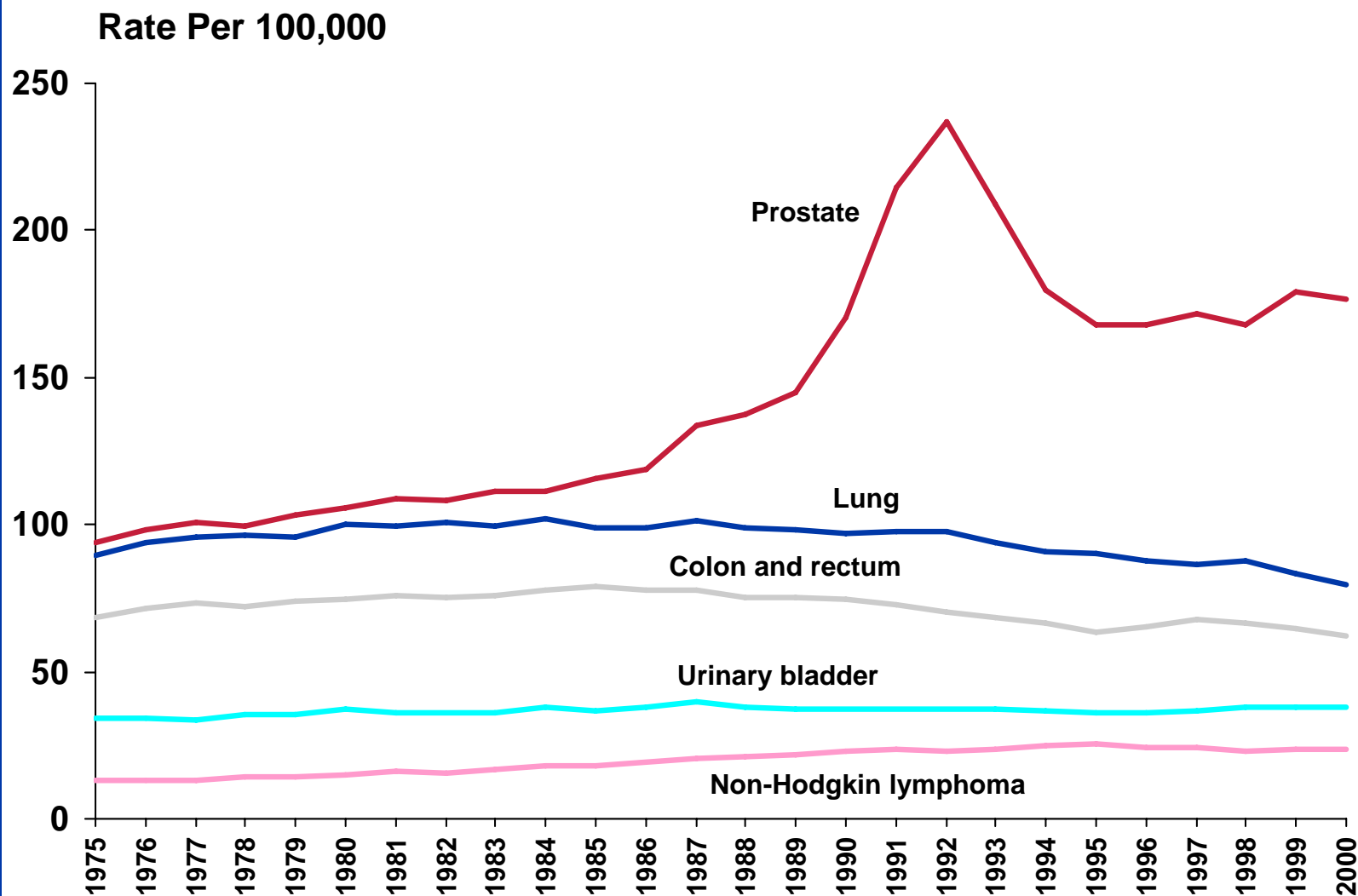
*Age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2000, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

Relative Survival* (%) during Three Time Periods by Cancer Site

Site	1974-1976	1983-1985	1992-1999
All sites	50	52	63
Breast (female)	75	78	87
Colon & rectum	50	57	62
Leukemia	34	41	46
Lung & bronchus	12	14	15
Melanoma	80	85	90
Non-Hodgkin lymphoma	47	54	56
Ovary	37	41	53
Pancreas	3	3	4
Prostate	67	75	98
Urinary bladder	73	78	82

*5-year relative survival rates based on follow up of patients through 2000.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2000, Division of Cancer Control and Population Sciences, National Cancer Institute, 2003.

Importance of Early Detection
Five Year Relative Survival Rates
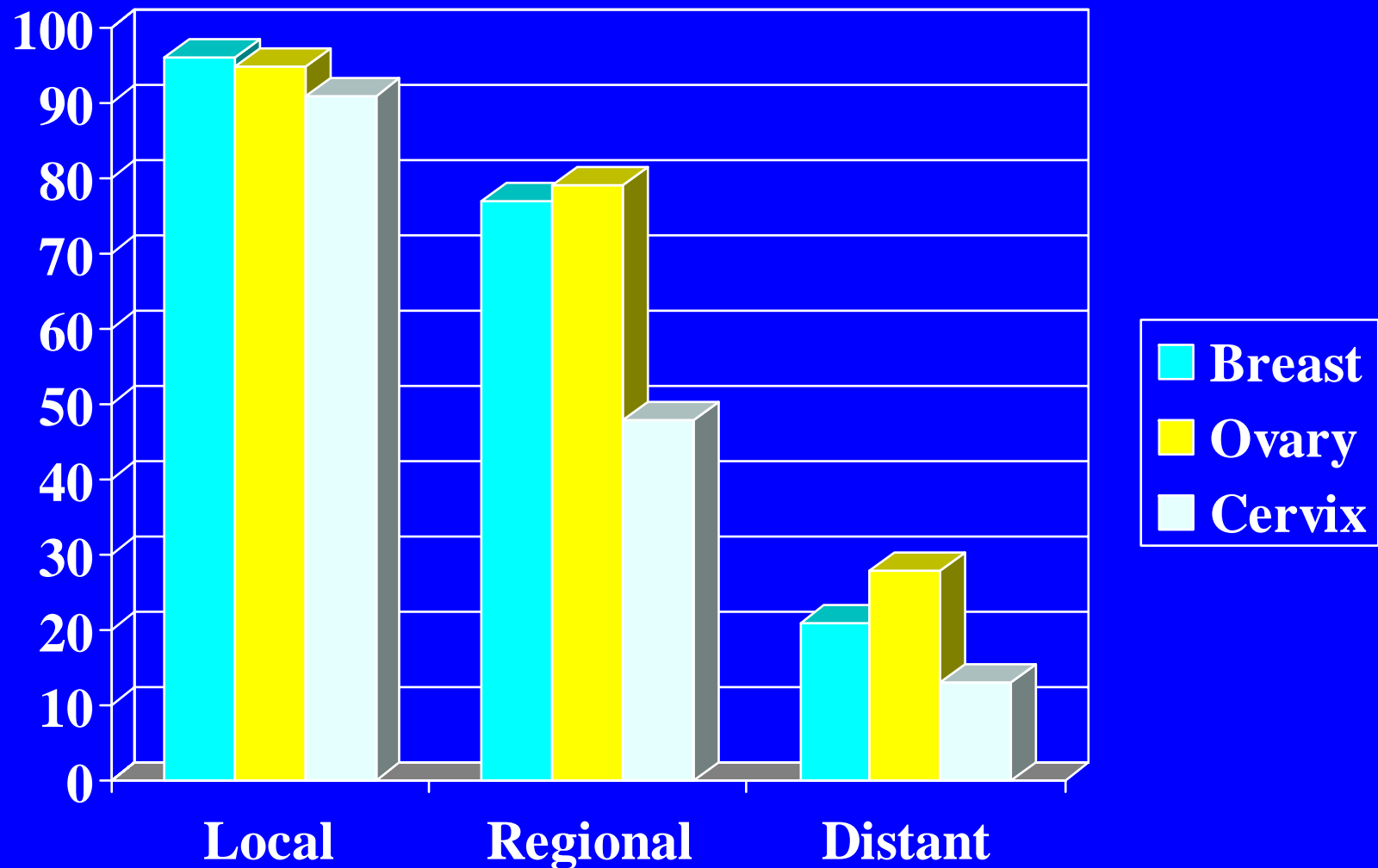
Screening

- Use of simple tests in a healthy population
- Goal:
    - Identify individuals who have disease, but do not yet have symptoms
- Should be undertaken only when:
    - Effectiveness has been demonstrated
    - Resources are sufficient to cover target group
    - Facilities exist for confirming diagnoses
    - Facilities exist for treatment and follow-up
    - When disease prevalence is high enough to justify effort and costs of screening

Cancer Screening

- We routinely screen for 4 cancers:
  - Female breast cancer
    - Mammography
  - Cervical cancer
    - Pap smear
  - Prostate cancer
    - Serum PSA
    - Digital rectal examination
  - Colon and rectal cancer
    - Fecal occult blood
    - Flexible sigmoidoscopy, Colonoscopy

Screening Guidelines for the Early Detection of Breast Cancer, American Cancer Society 2003

Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.

A clinical breast exam should be part of a periodic health exam, about every three years for women in their 20s and 30s, and every year for women 40 and older.

Women should know how their breast normally feel and report any breast changes promptly to their health care providers. Breast self-exam is an option for women starting in their 20s.

Women at increased risk (e.g., family history, genetic tendency, past breast cancer) should talk with their doctors about the benefits and limitations of starting mammography screening earlier, having additional tests (i.e., breast ultrasound and MRI), or having more frequent exams.

Mammogram Prevalence (%), by Educational Attainment and Health Insurance Status, Women 40 and Older, US, 1991-2002
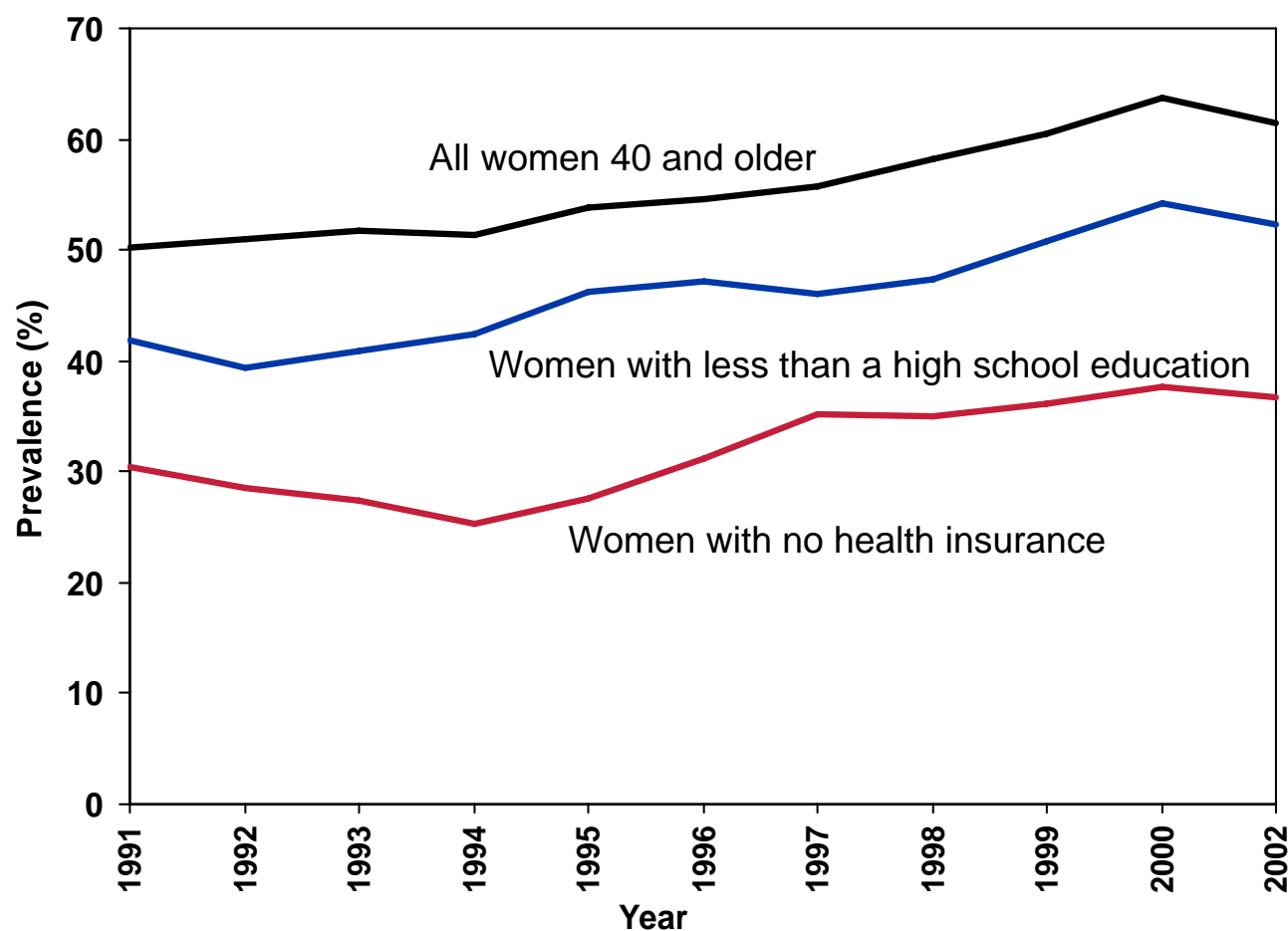
* A mammogram within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.
Source: Behavior Risk Factor Surveillance System CD-ROM (1984-1995, 1996-1997, 1998, 1999) and Public Use Data Tape (2000, 2002), National Centers for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention 1997, 1999, 2000, 2000, 2001,2003.

How do we judge efficacy of a screening test?

Sensitivity/Specificity

Positive/Negative Predictive Value

Sensitivity & Specificity

- ## Sensitivity
  - Probability that given DISEASE, patient tests POSITIVE
  - Ability to correctly detect disease
  - 100% - False Negative Rate

- ## Specificity
  - Probability that given NO DISEASE, patient tests NEGATIVE
  - Ability to avoid calling normal things disease
  - 100% - False Positive Rate

Possible Test Results

	Test Positive	Test Negative	
Disease Present	TP	FN	# with Disease = TP+FN
Disease Absent	FP	TN	#without Disease = FP+TN
	# Test Pos = TP+FP	# Test Neg = FN+TN	Total Tested = TP+FN+FP+TN

Se = TP/(# with disease) = TP/(TP+FN)

Sp = TN/(# without disease) = TN/(TN+FP)

Amniocentesis Example

- Amniocentesis:
  - Procedure to detect abnormal fetal chromosomes
- Efficacy:
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive
- Calculate:
  - Sensitivity & Specificity

Possible Test Results

	Test Positive	Test Negative	
Disease Present	25	3	# with Disease = 28
Disease Absent	7	965	#without Disease = 972
	# Test Pos = 32	# Test Neg = 968	Total Tested = 1,000

Se = 25/28 = 89%   Sp =965/972 = 99.3%

As a patient:

What Information Do You Want?

Predictive Value

- **Positive Predictive Value**
    - Probability that given a POSITIVE test result, you have DISEASE
    - Ranges from 0-100%
- **Negative Predictive Value**
    - Probability that given a NEGATIVE test result, you do NOT HAVE DISEASE
    - Ranges from 0-100%
- **Depends on the prevalence of the disease**

Possible Test Results

	Test Positive	Test Negative	
Disease Present	TP 25	FN 3	# with Disease = TP+FN = 28
Disease Absent	FP 7	TN 965	#without Disease = FP+TN = 972
	# Test Pos = TP+FP = 32	# Test Neg = FN+TN = 968	Total Tested = TP+FN+FP+TN = 25+3+7+965 = 1000

PPV = TP/(# Test Pos) = TP/(TP+FP) = 25/(25+7) = .781

NPV = TN/(# Test Neg) = TN/(FN+TN) = 965/(3+965) = .997

Amniocentesis Example

- **Amniocentesis:**
  - Procedure to detect abnormal fetal chromosomes
- **Efficacy:**
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive
- **Calculate:**
  - Positive & Negative Predictive Value

Dependence on Prevalence

- Prevalence – is a disease common or rare?
    - p = (# with disease)/total #
    - p = (TP+FN)/(TP+FP+TN+FN) = (25+3)/(25+7+965+3) = 28/1000 = .028
- Does our test accuracy depend on p?
    - Se/Sp do not depend on prevalence
    - PPV/NPV are highly dependent on prevalence
- PPV = pSe/[pSe + (1-p)(1-Sp)] = .781
- NPV = (1-p)Sp/[(1-p)Sp + p(1-Se)] = .997

Is it Hard to Screen for Rare Disease?

- **Amniocentesis:**
  - Procedure to detect abnormal fetal chromosomes
- **Efficacy:**
  - 1,000 40-year-old women given the test
  - 28 children born with chromosomal abnormalities
  - 32 amniocentesis test were positive, and of those 25 were truly positive
- **Calculate:**
  - Prevalence of chromosomal abnormalities

Is it Hard to Screen for Rare Disease?

- **Amniocentesis:**
    - Usually offered to women > 35 yo
- **Efficacy:**
    - 1,000 20-year-old women given the test
    - Prevalence of chromosomal abnormalities is expected to be 2.8/1000
- **Calculate:**
    - Sensitivity & Specificity
    - Positive & Negative Predictive Value
    - Suppose a 20 yo woman has a positive test. What is the likelihood that the fetus has a chromosomal abnormality?

Summary of Lecture 12

- **The burden of cancer**
  - Contrasts between developed/developing world
- **How does cancer develop?**
  - Cell transformation → Angiogenesis → Motility → Microinvasion → Embolism → Extravasation
- **Why is early detection so important?**
  - Treat before cancer develops → Prevention
- **Accuracy of screening/detection tests**
  - Se, Sp, PPV, NPV