BIOE 301

Lecture Twelve
Nadhi Thekkek
Graduate Student
Bioengineering
February 19, 2008

Review of Lecture 11

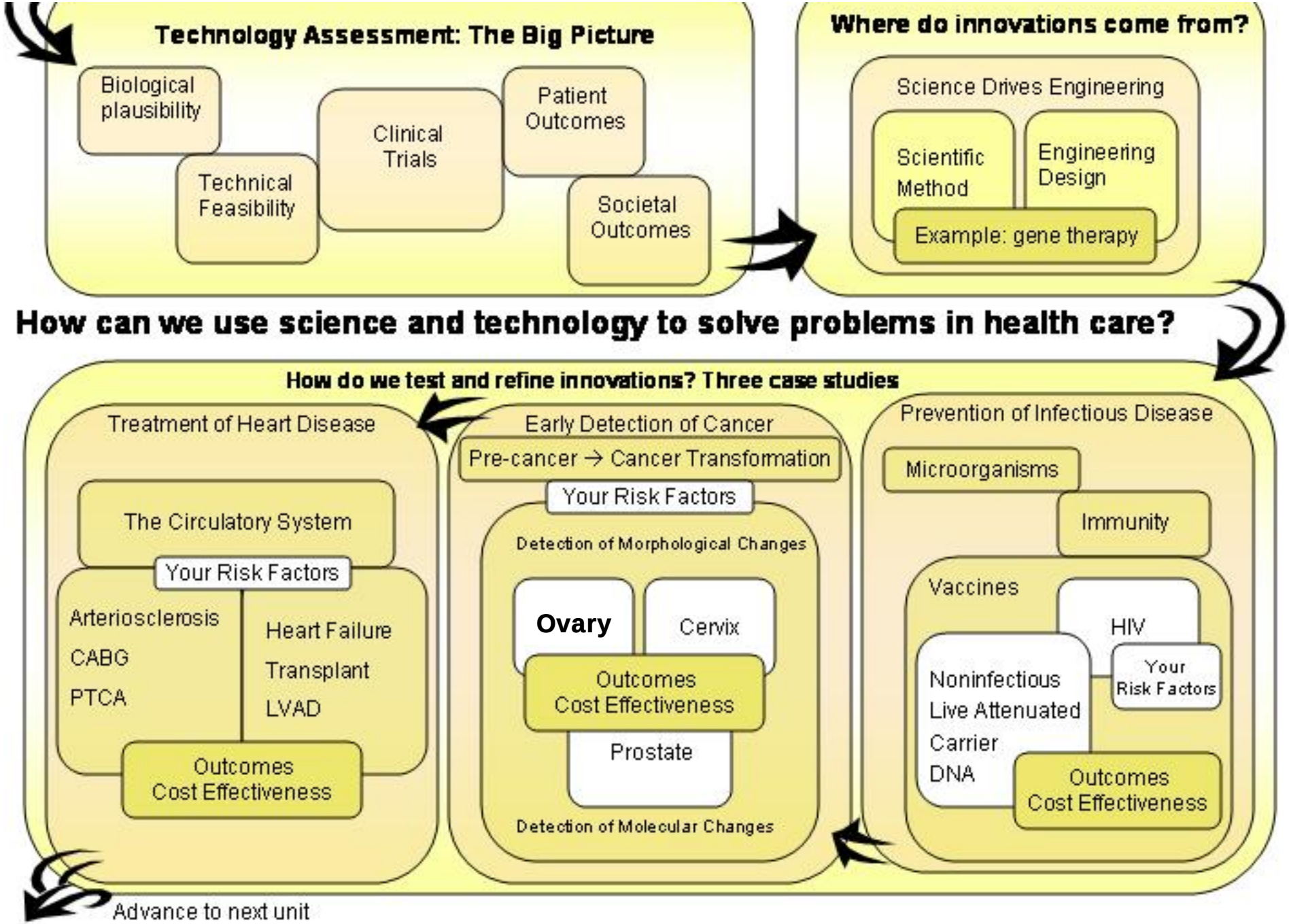
- Belmont Report
  - Respect for persons
  - Beneficence
  - Justice
  - Process of informed consent

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
  - Prostate Cancer
  - Ovarian and Lung Cancer
- Treatment of heart disease
  - Atherosclerosis and heart attack
  - Heart failure


Technology Assessment: The Big Picture
Biological plausibility
Technical Feasibility
Clinical Trials
Patient Outcomes
Societal Outcomes
Where do innovations come from?
Science Drives Engineering
Scientific Method
Engineering Design
Example: gene therapy
How can we use science and technology to solve problems in health care?
How do we test and refine innovations? Three case studies
Treatment of Heart Disease
The Circulatory System
Your Risk Factors
Arteriosclerosis
CABG
PTCA
Heart Failure
Transplant
LVAD
Outcomes
Cost Effectiveness
Early Detection of Cancer
Pre-cancer → Cancer Transformation
Your Risk Factors
Detection of Morphological Changes
Ovary
Cervix
Outcomes
Cost Effectiveness
Prostate
Detection of Molecular Changes
Prevention of Infectious Disease
Microorganisms
Immunity
Vaccines
HIV
Noninfectious
Live Attenuated
Carrier
DNA
Your
Risk Factors
Outcomes
Cost Effectiveness
Advance to next unit

Outline

- The burden of cancer
- How does cancer develop?
- Why is early detection so important?
- Strategies for early detection
- Example cancers/technologies
  - Cervical cancer
  - Prostate cancer
  - Ovarian and lung 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

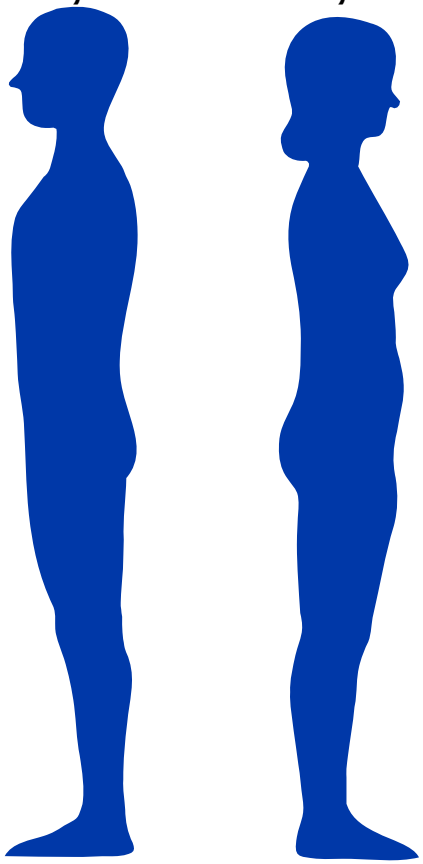
US Mortality, 2001

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	700,142	29.0
2.	**Cancer**	**553,768**	**22.9**
3.	Cerebrovascular diseases	163,538	6.8
4.	Chronic lower respiratory diseases	123,013	5.1
5.	Accidents (Unintentional injuries)	101,537	4.2
6.	Diabetes mellitus	71,372	3.0
7.	Influenza and Pneumonia	62,034	2.6
8.	Alzheimer's disease	53,852	2.2
9.	Nephritis	39,480	1.6
10.	Septicemia	32,238	1.3

Source: US Mortality Public Use Data Tape 2001, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

2004 Estimated US Cancer Cases*

Men 699,560	
Prostate	33%
Lung & bronchus	13%
Colon & rectum	11%
Urinary bladder	6%
Melanoma of skin	4%
Non-Hodgkin lymphoma	4%
Kidney	3%
Oral Cavity	3%
Leukemia	3%
Pancreas	2%
All Other Sites	18%

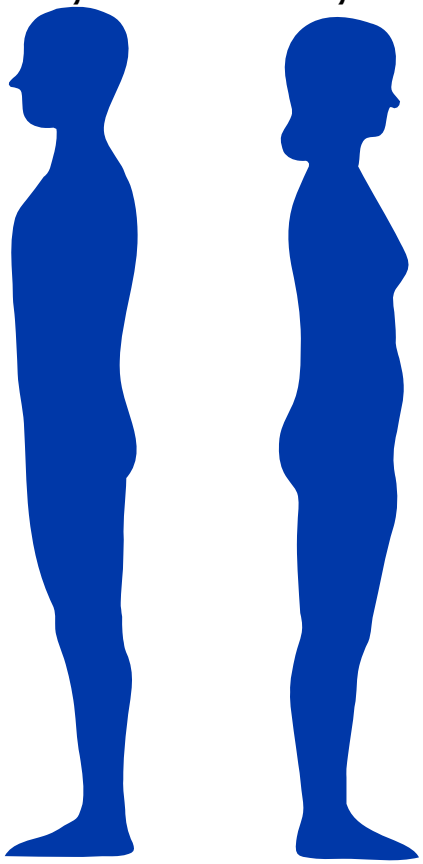


Women 668,470	
32%	Breast
12%	Lung & bronchus
11%	Colon & rectum
6%	Uterine corpus
4%	Ovary
4%	Non-Hodgkin lymphoma
4%	Melanoma of skin
3%	Thyroid
2%	Pancreas
2%	Urinary bladder
20%	All Other Sites

***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2004.

2004 Estimated US Cancer Deaths*

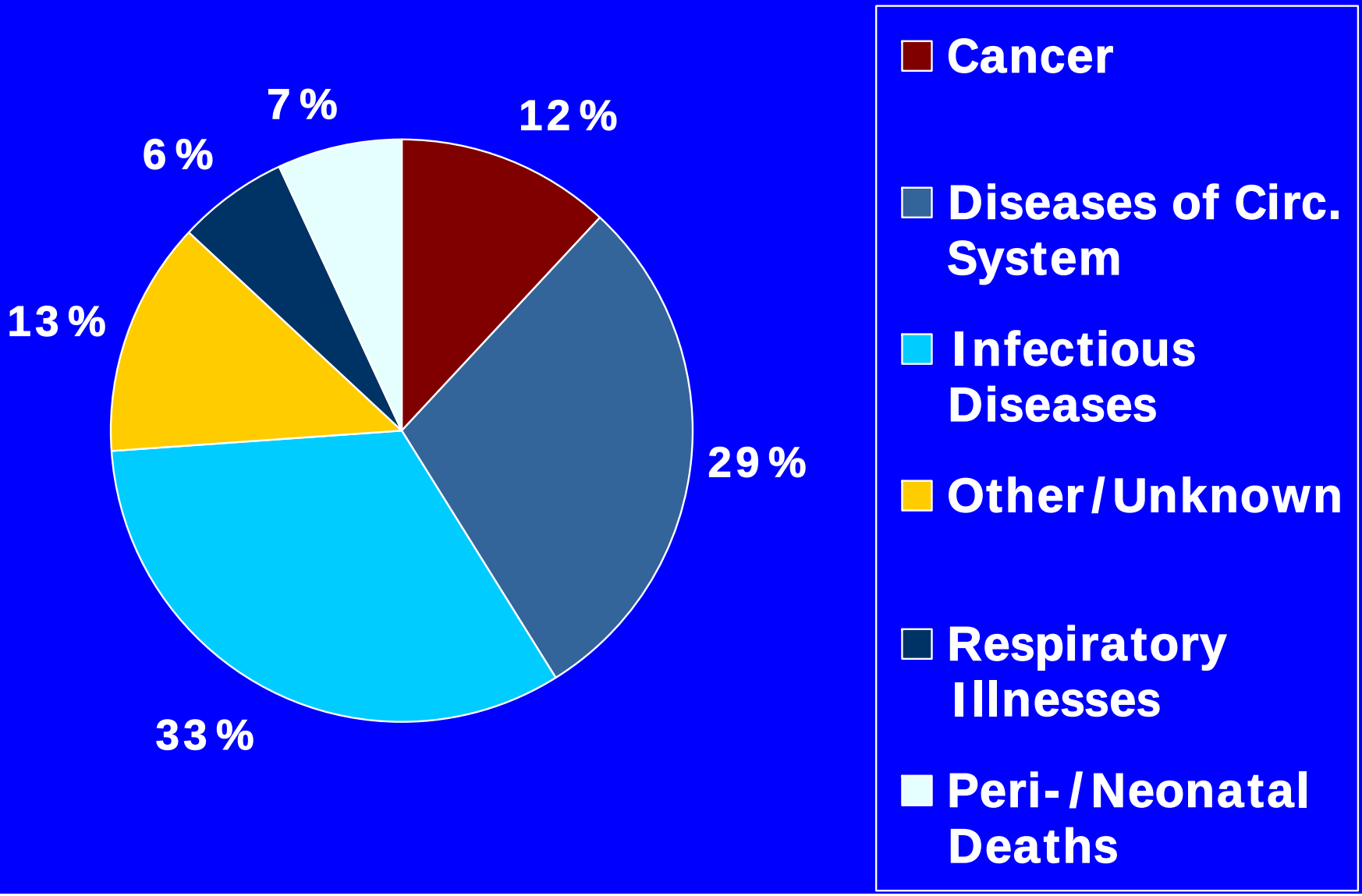
Men 290,890	
Lung & bronchus	32%
Prostate	10%
Colon & rectum	10%
Pancreas	5%
Leukemia	5%
Non-Hodgkin lymphoma	4%
Esophagus	4%
Liver & intrahepatic bile duct	3%
Urinary bladder	3%
Kidney	3%
All other sites	21%



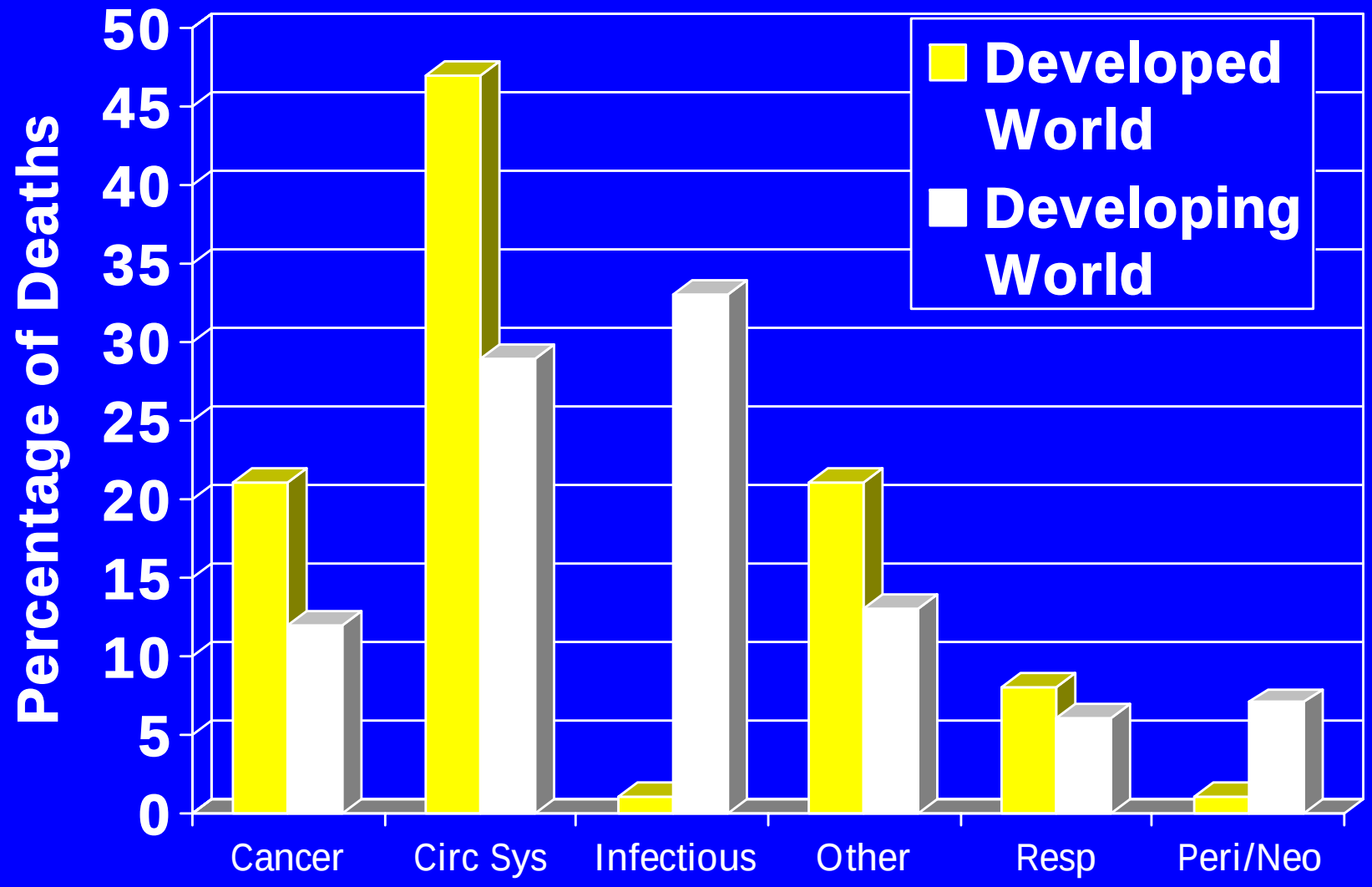
Women 272,810	
25%	Lung & bronchus
15%	Breast
10%	Colon & rectum
6%	Ovary
6%	Pancreas
4%	Leukemia
3%	Non-Hodgkin lymphoma
3%	Uterine corpus
2%	Multiple myeloma
2%	Brain/ONS
24%	All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2004.

Worldwide Causes of Death, 1996



Causes of Mortality, 1996



Worldwide Burden of Cancer

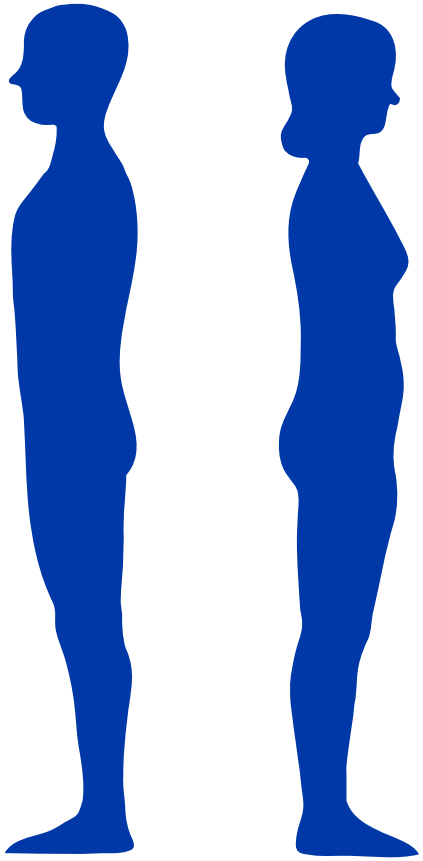
- Today:
  - 11 million new cases every year
  - 6.2 million deaths every year (12% of deaths)
- Can prevent 1/3 of these cases:
  - Reduce tobacco use
  - Implement existing screening techniques
  - Healthy lifestyle and diet
- In 2020:
  - 15 million new cases predicted in 2020
  - 10 million deaths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

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

1996 Estimated Worldwide Cancer Cases*

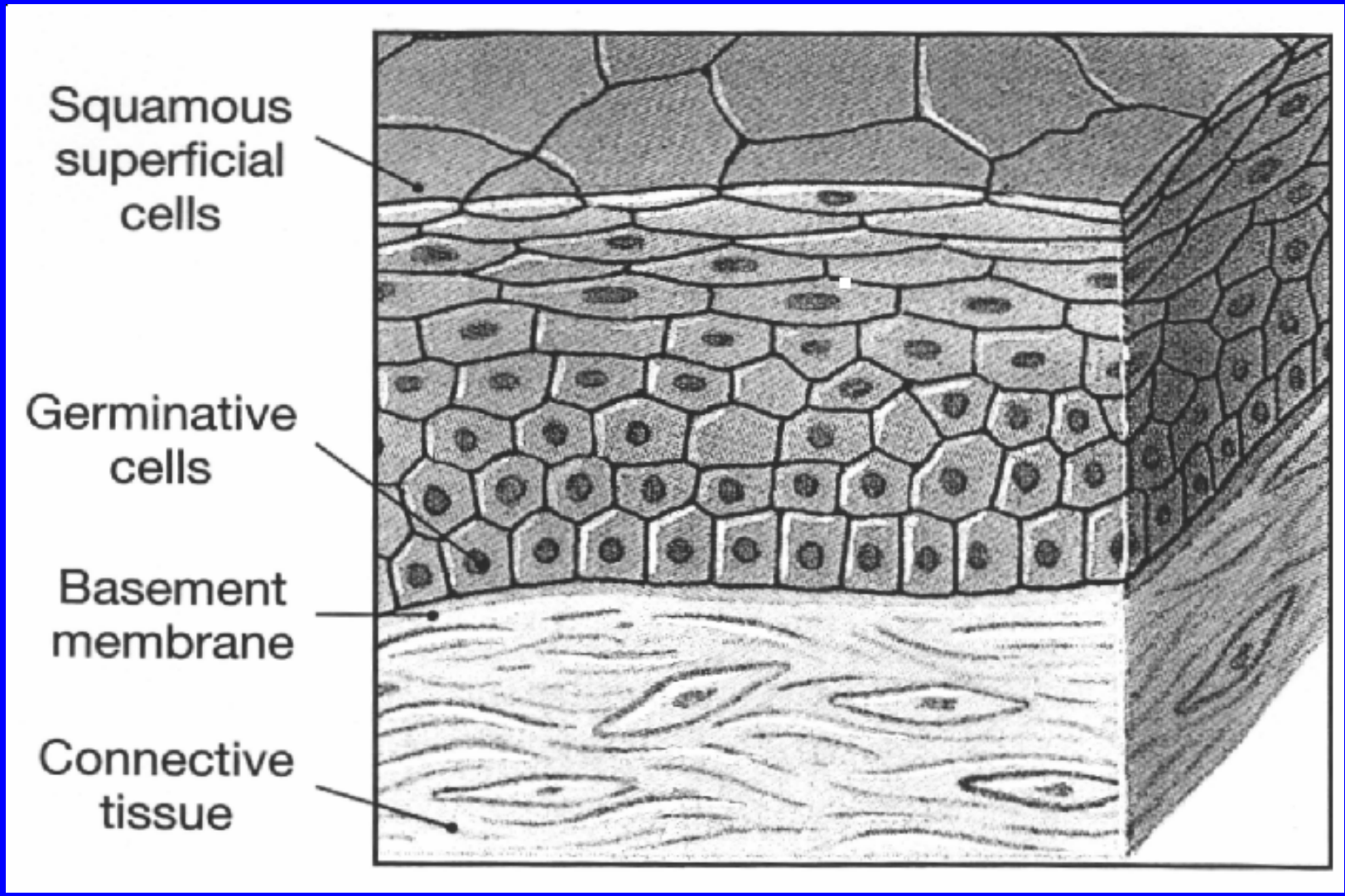
Men		Women	
Lung & bronchus	988	910	Breast
Stomach	634	524	Cervix
Colon & rectum	445	431	Colon & rectum
Prostate	400	379	Stomach
Mouth	384	333	Lung & bronchus
Liver	374	192	Mouth
Esophagus	320	191	Ovary
Urinary bladder	236	172	Uterine corpus



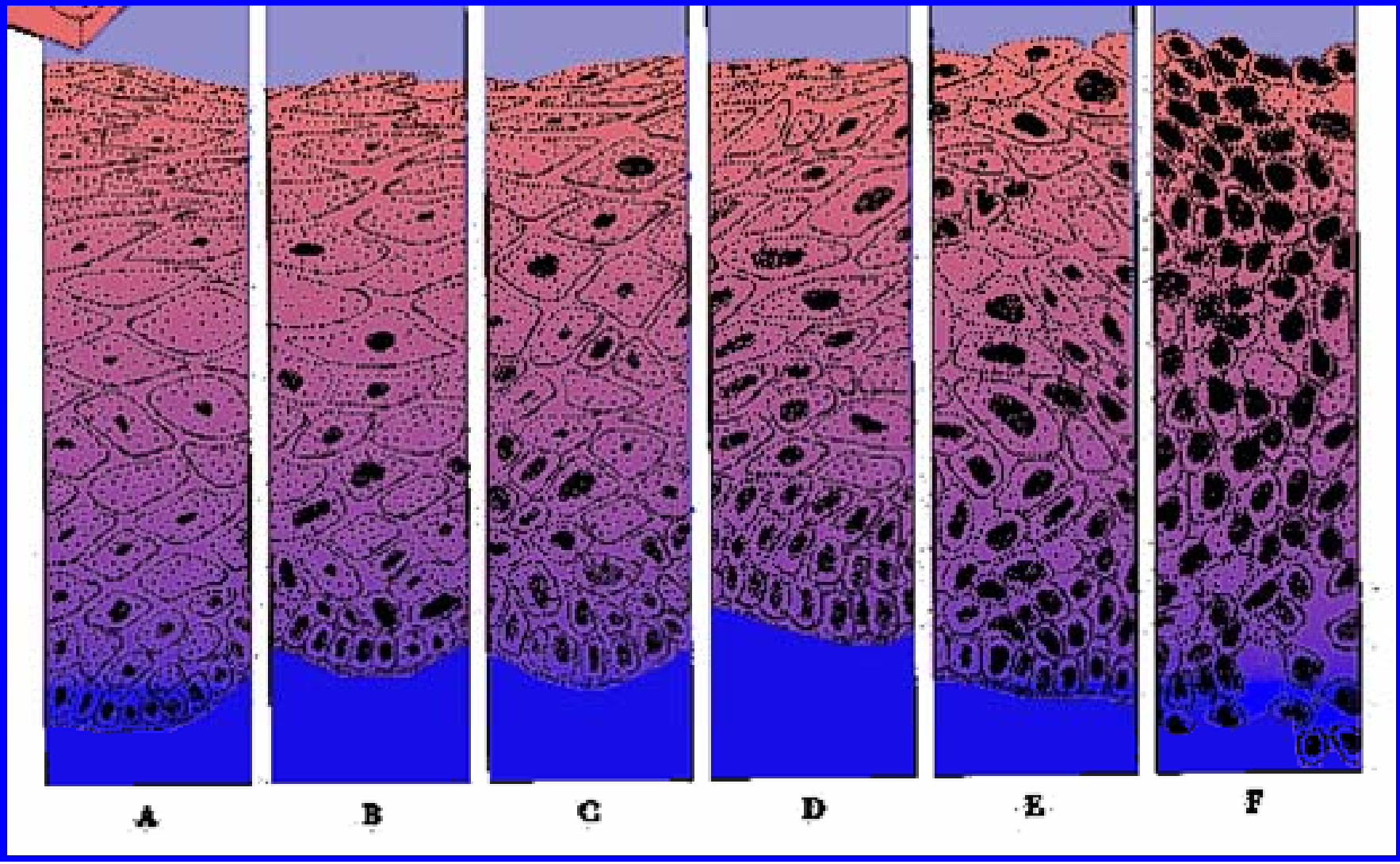
What is Cancer?

- 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

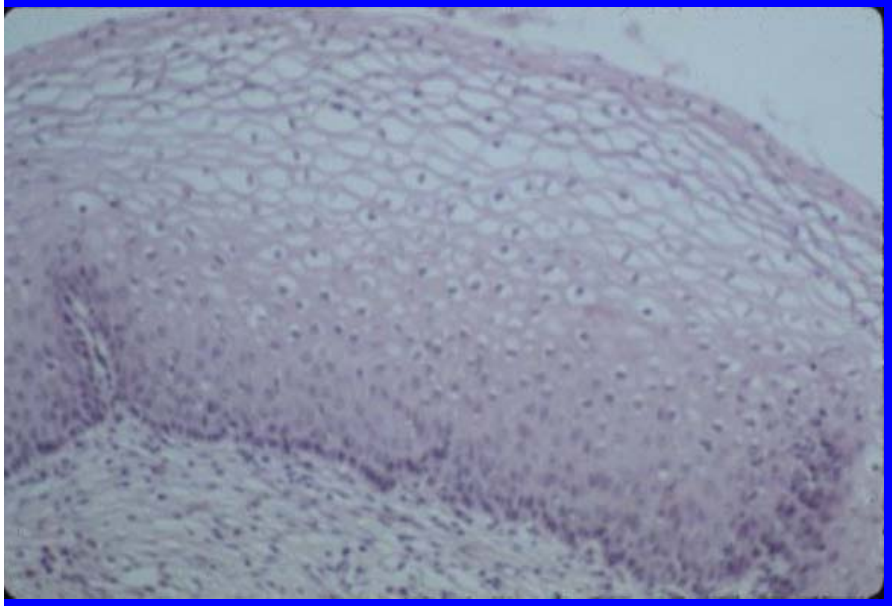


Precancer → Cancer Sequence

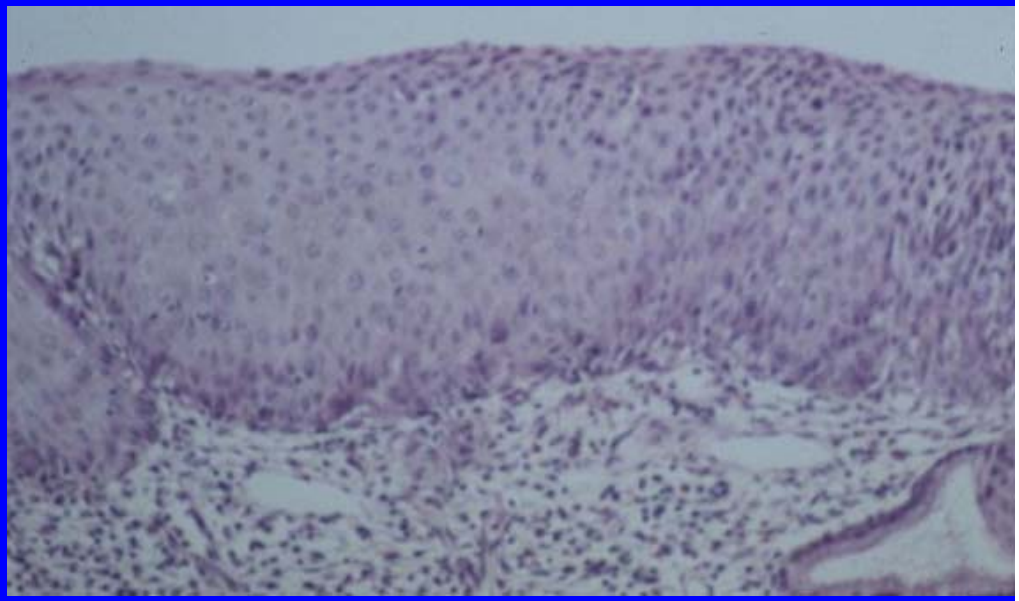


Histologic Images

Normal



Cervical Pre-Cancer




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

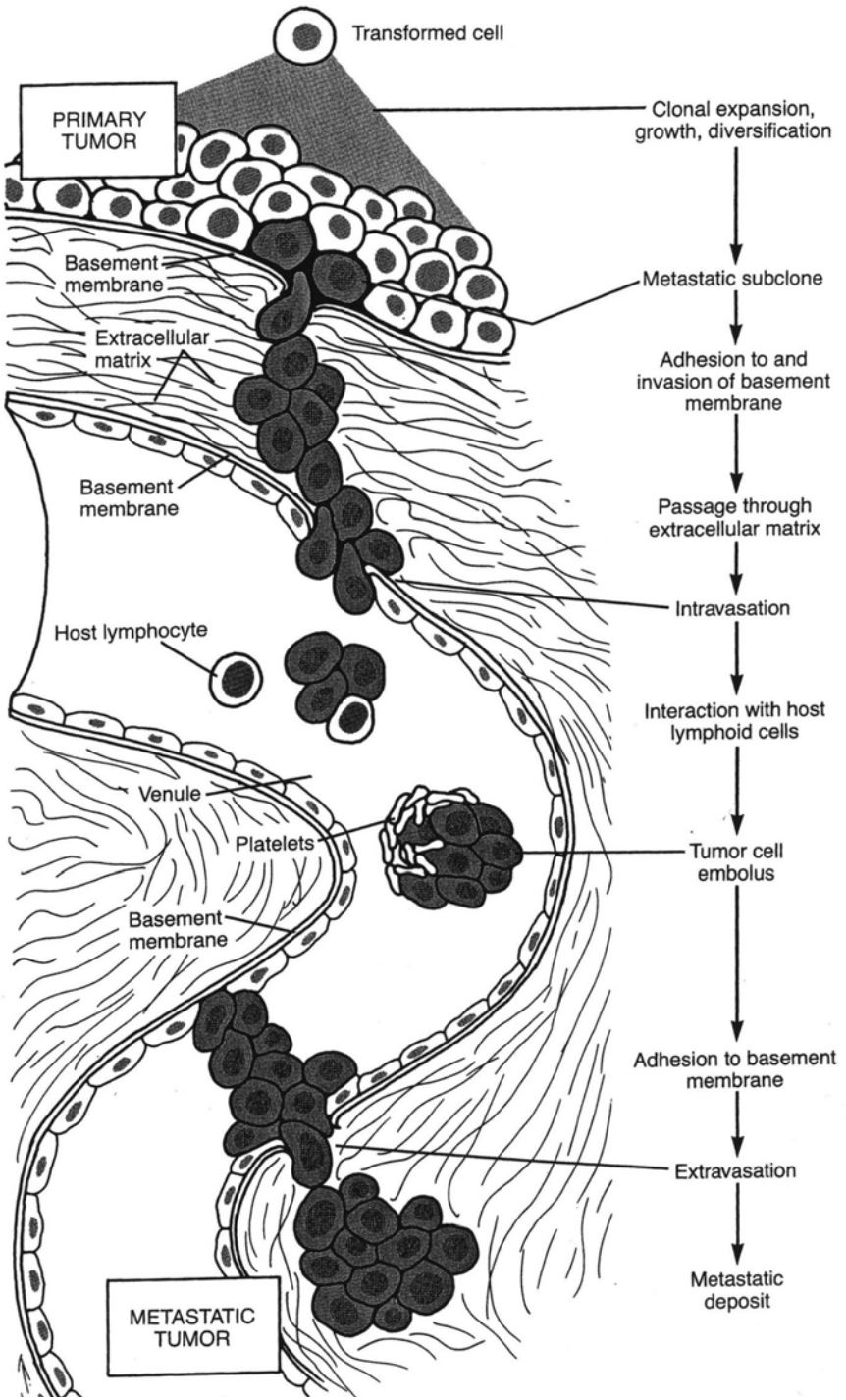
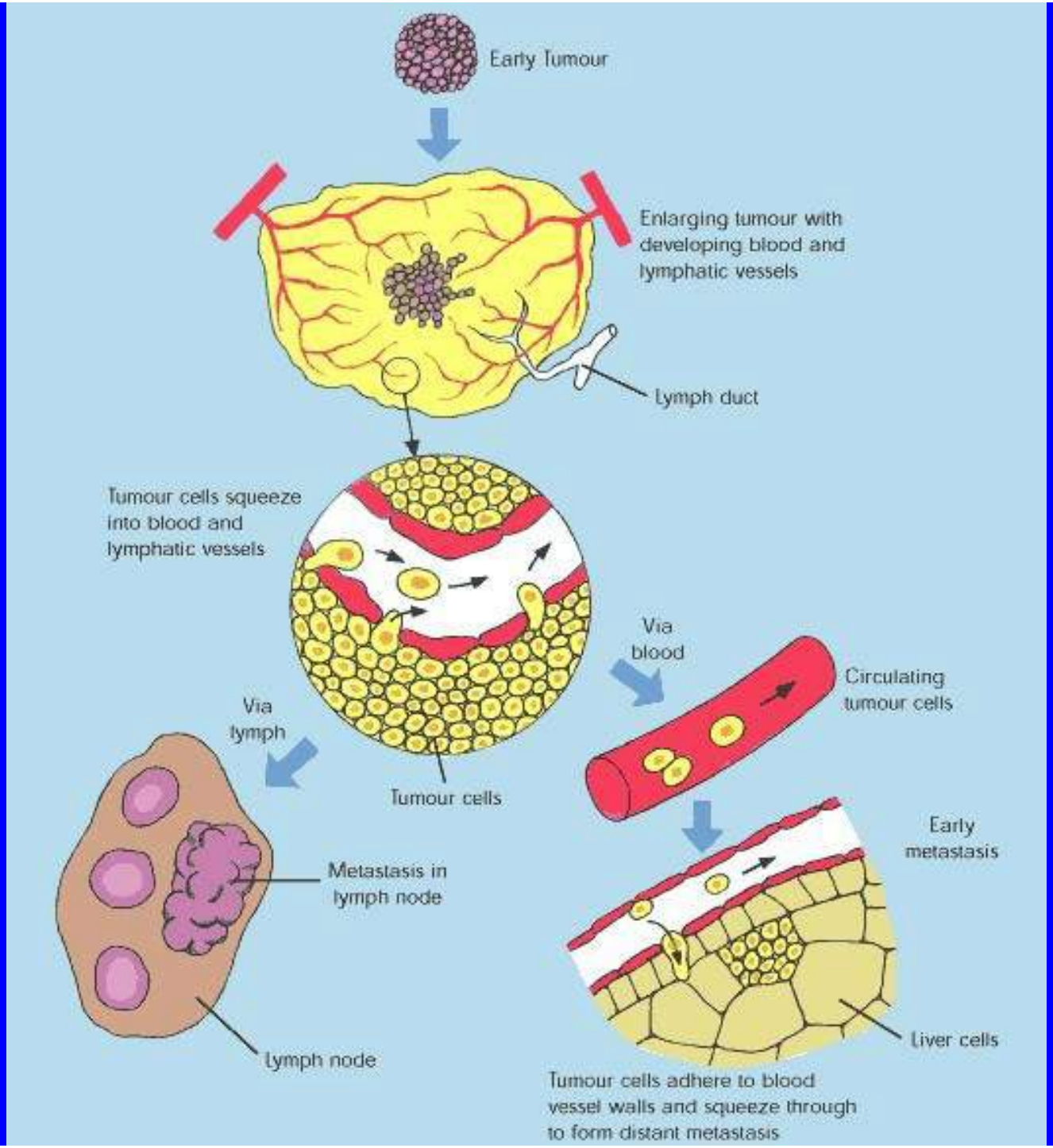
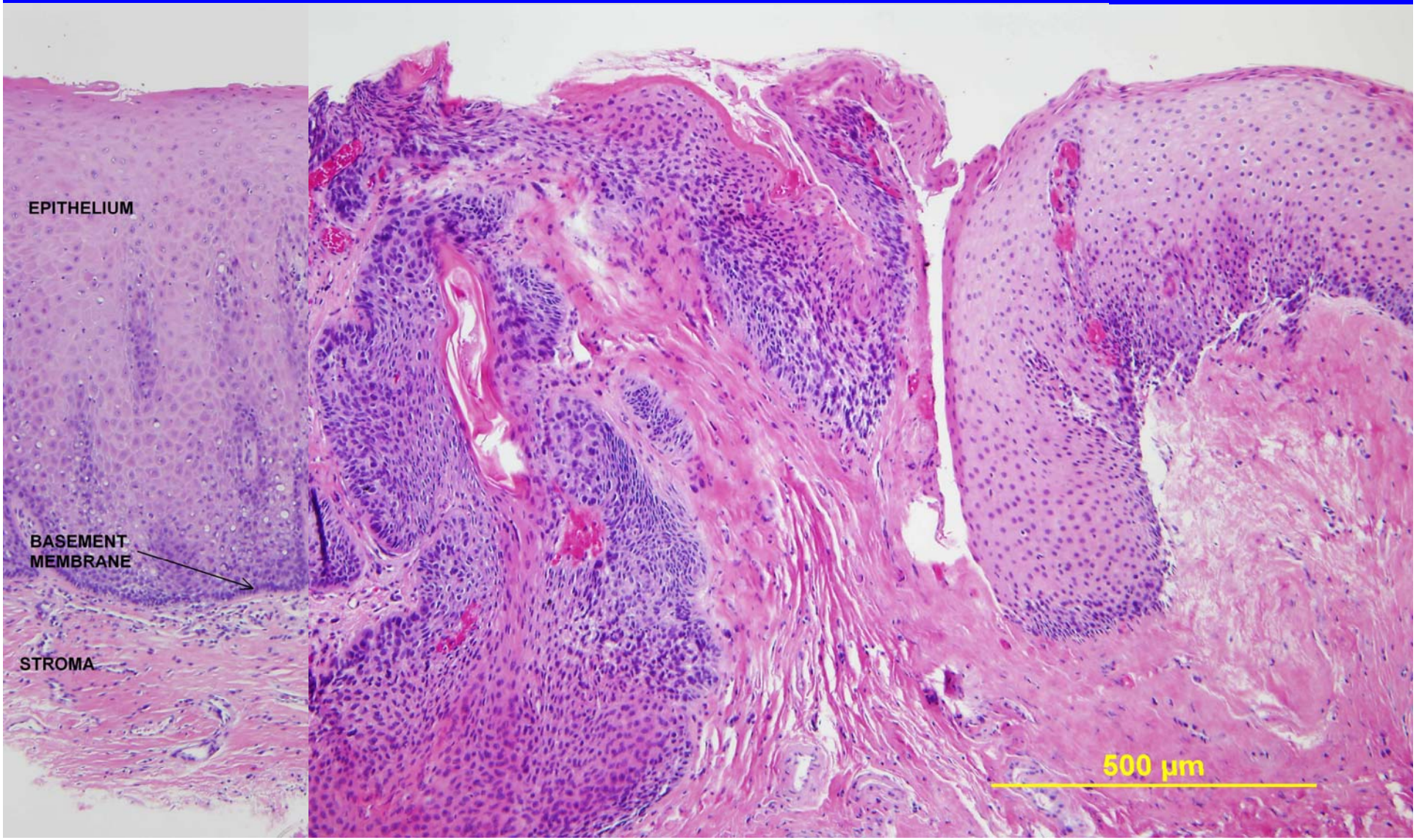


Fig 7.33 – The Metastatic cascade



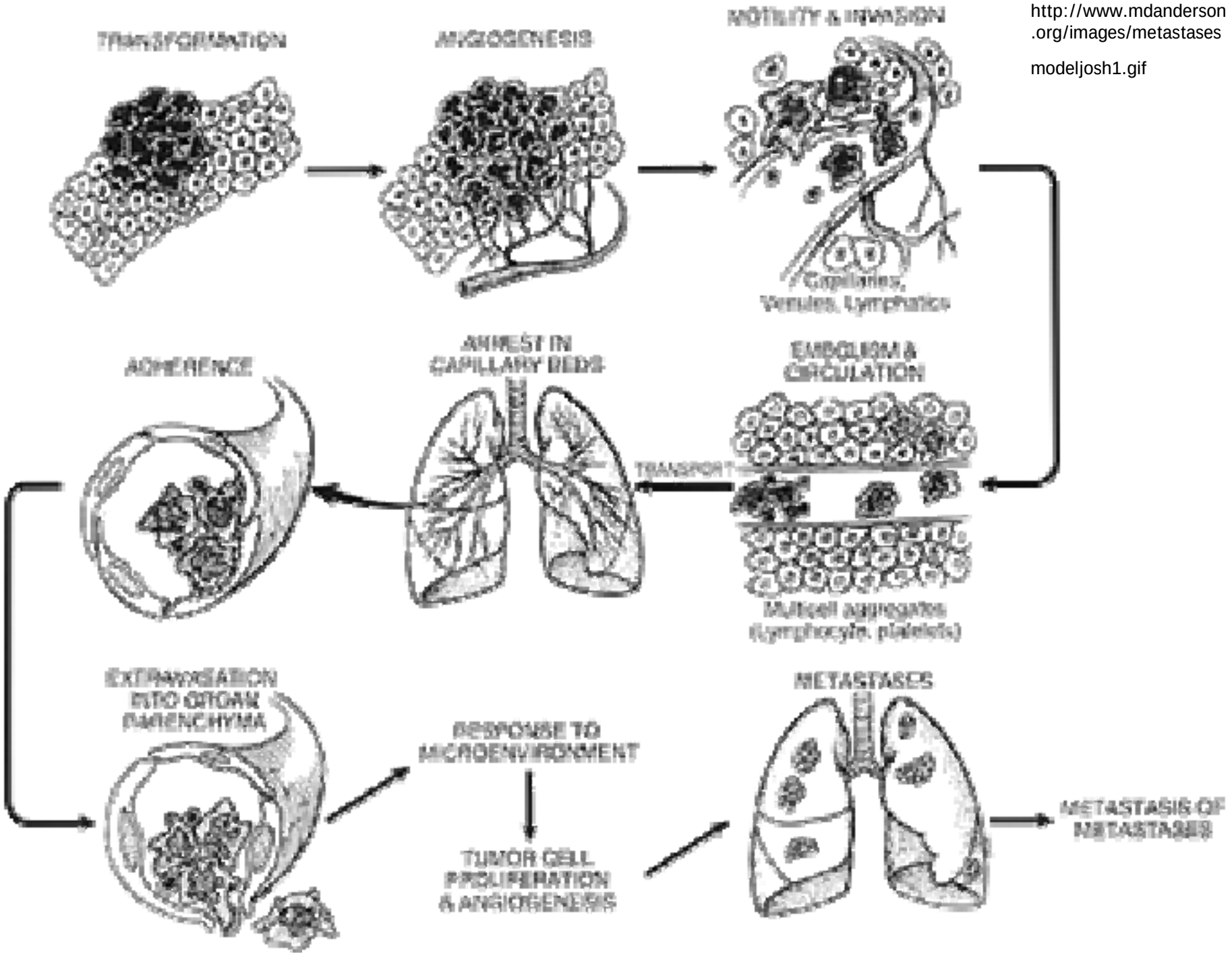
http://www.drugdevelopment-technology.com/projects/avastin/avastin2.html

Microscopic Appearance



http://www.mdanderson
.org/images/metastases

modeljosh1.gif



Clinical Liver Metastases

http://www.pathology.vcu.edu/education/pathogenesis/images/6d.b.jpg

What is Your Lifetime Cancer Risk?

Lifetime Probability of Developing Cancer, by Site, Men, US, 1998-2000

Site	Risk
All sites	1 in 2
Prostate	1 in 6
Lung & bronchus	1 in 13
Colon & rectum	1 in 17
Urinary bladder	1 in 29
Non-Hodgkin lymphoma	1 in 48
Melanoma	1 in 55
Leukemia	1 in 70
Oral cavity	1 in 72
Kidney	1 in 69
Stomach	1 in 81

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 5.1 Statistical Research and Applications Branch, NCI, 2003. http://srab.cancer.gov/devcan

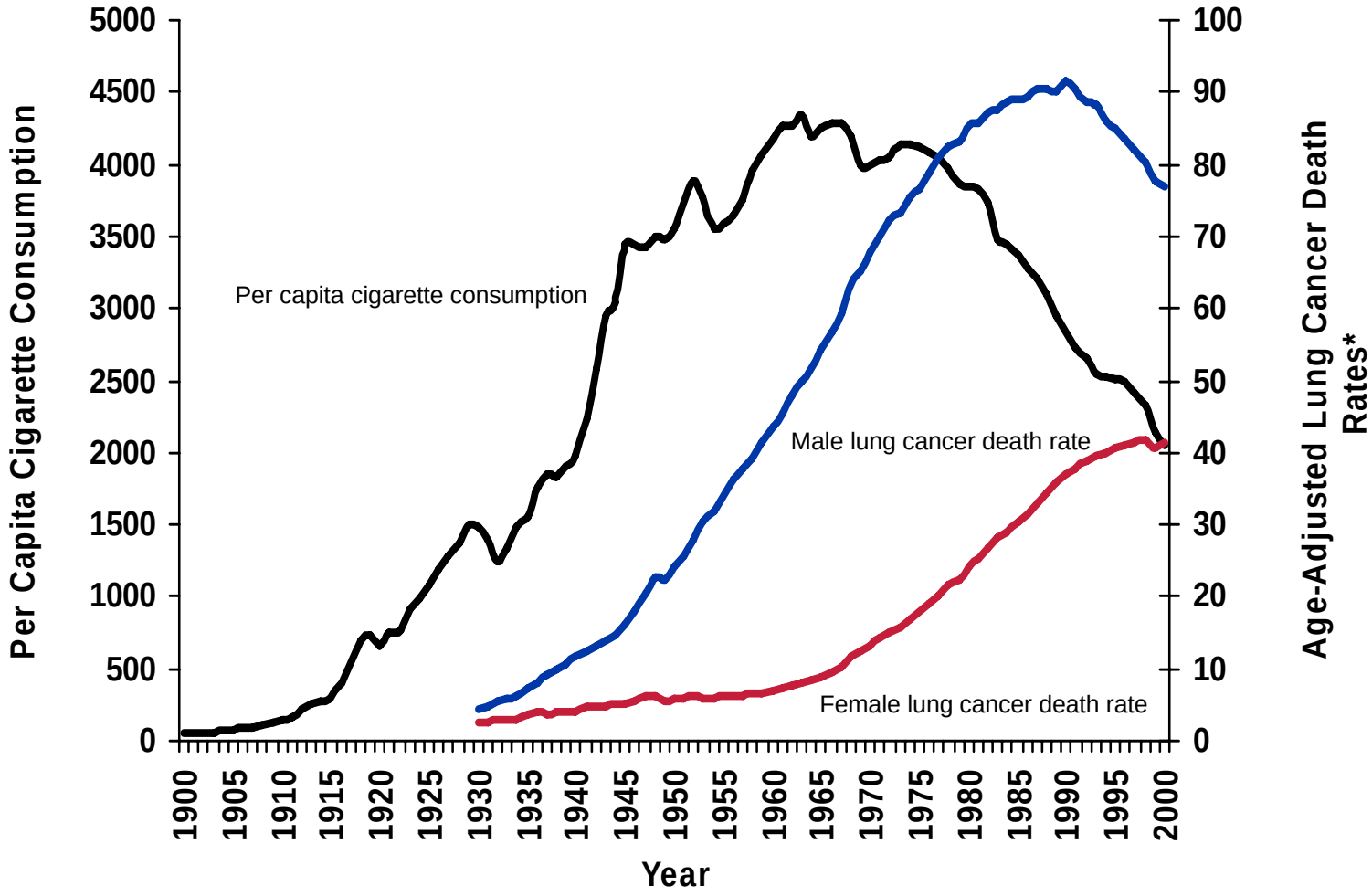
Lifetime Probability of Developing Cancer, by Site, Women, US, 1998-2000

Site	Risk
All sites	1 in 3
Breast	1 in 7
Lung & bronchus	1 in 17
Colon & rectum	1 in 18
Uterine corpus	1 in 38
Non-Hodgkin lymphoma	1 in 57
Ovary	1 in 59
Pancreas	1 in 83
Melanoma	1 in 82
Urinary bladder	1 in 91
Uterine cervix	1 in 128

Source:DevCan: Probability of Developing or Dying of Cancer Software, Version 5.1 Statistical Research and Applications Branch, NCI, 2003. http://srab.cancer.gov/devcan

How Can You Reduce Your Cancer Risk?

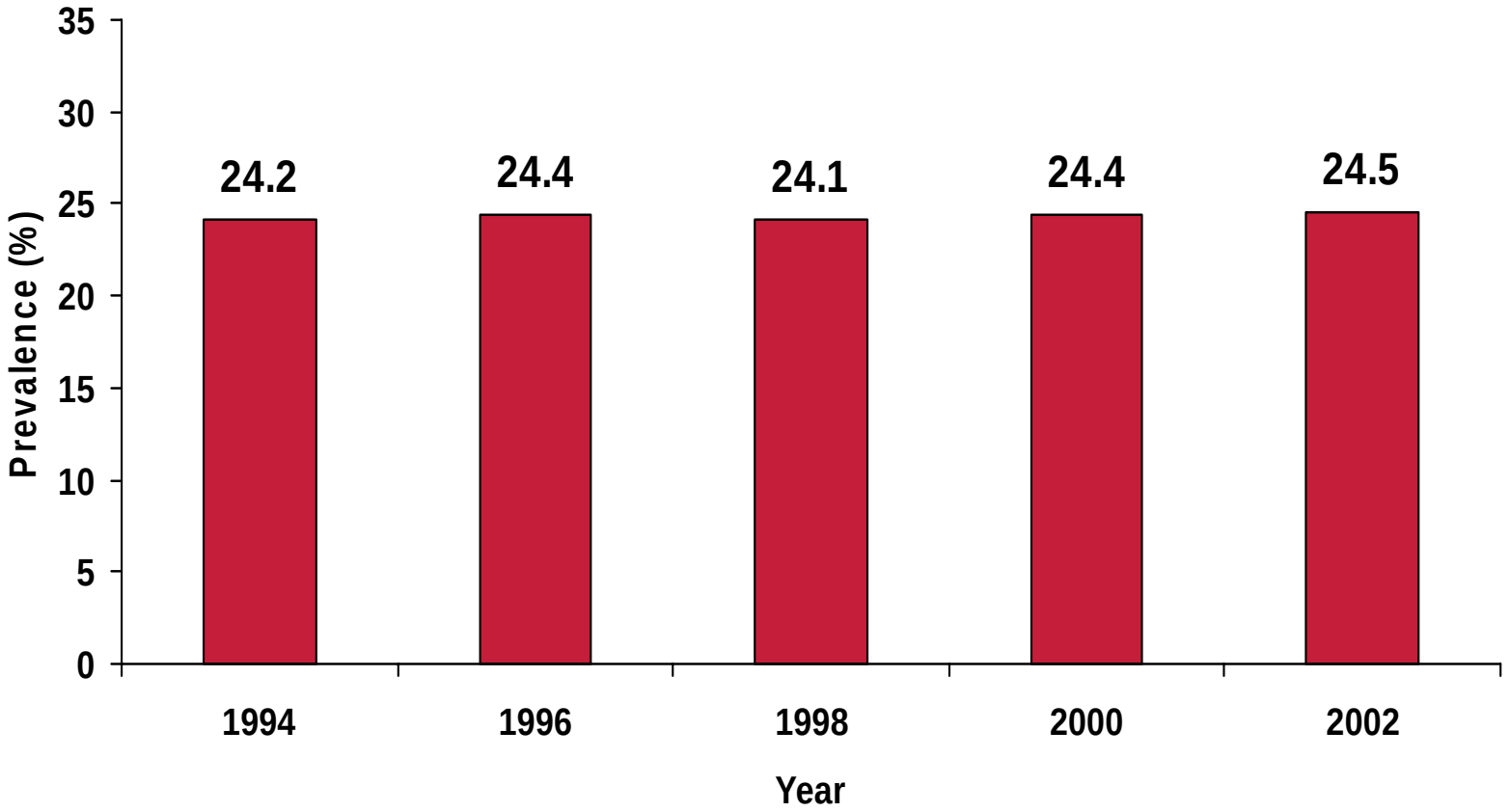
Tobacco Use in the US, 1900-2000



***Age-adjusted to 2000 US standard population.**

Source: Death rates: US Mortality Public Use Tapes, 1960-2000, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002. Cigarette consumption: US Department of Agriculture, 1900-2000.

Trends in Consumption of Five or More Recommended Vegetable and Fruit Servings for Cancer Prevention, Adults 18 and Older, US, 1994-2002



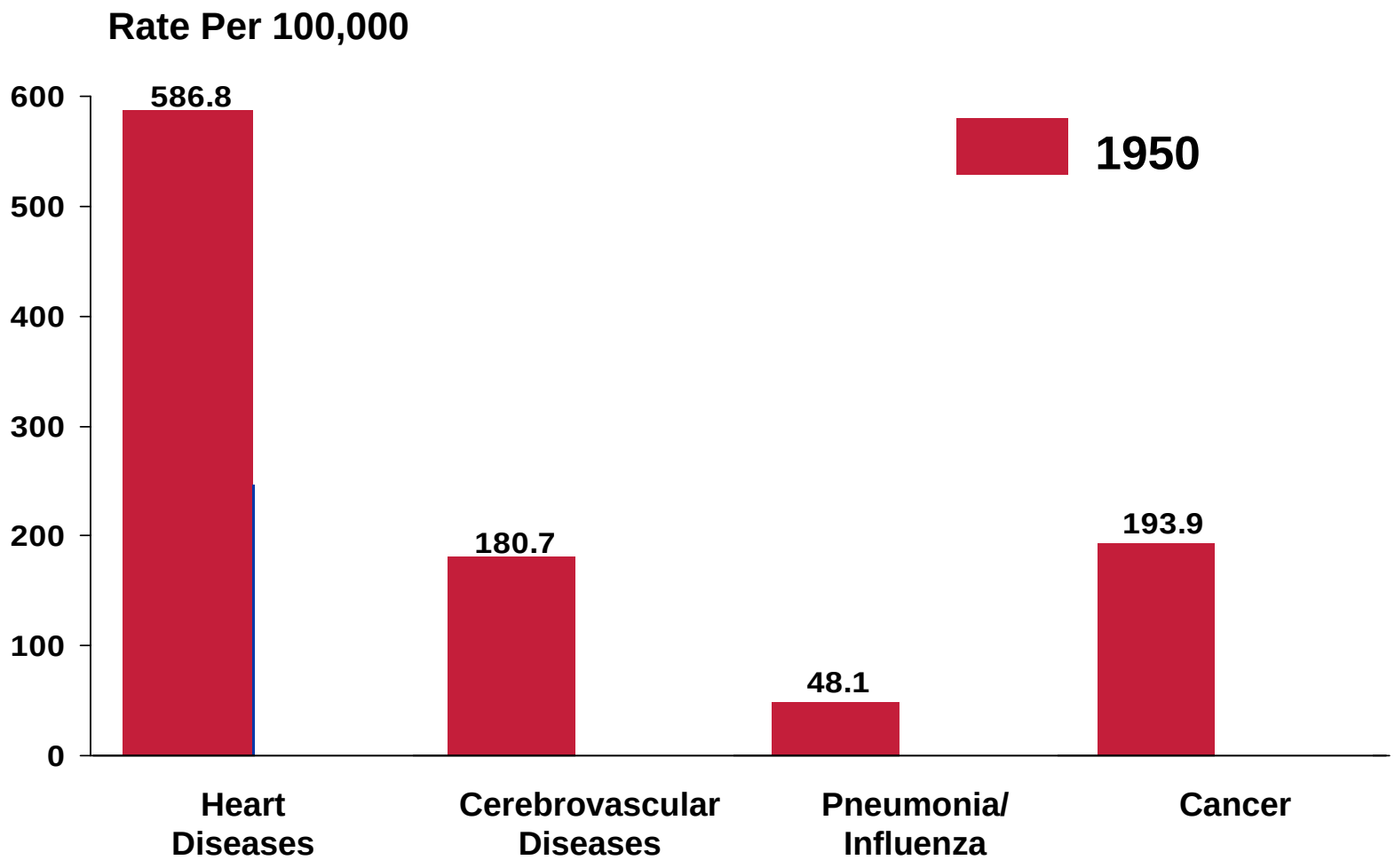
Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

Source: Behavioral Risk Factor Surveillance System CD-ROM (1984-1995, 1996, 1998) and Public Use Data Tape (2000), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1997, 1999, 2000, 2001.

The War on Cancer

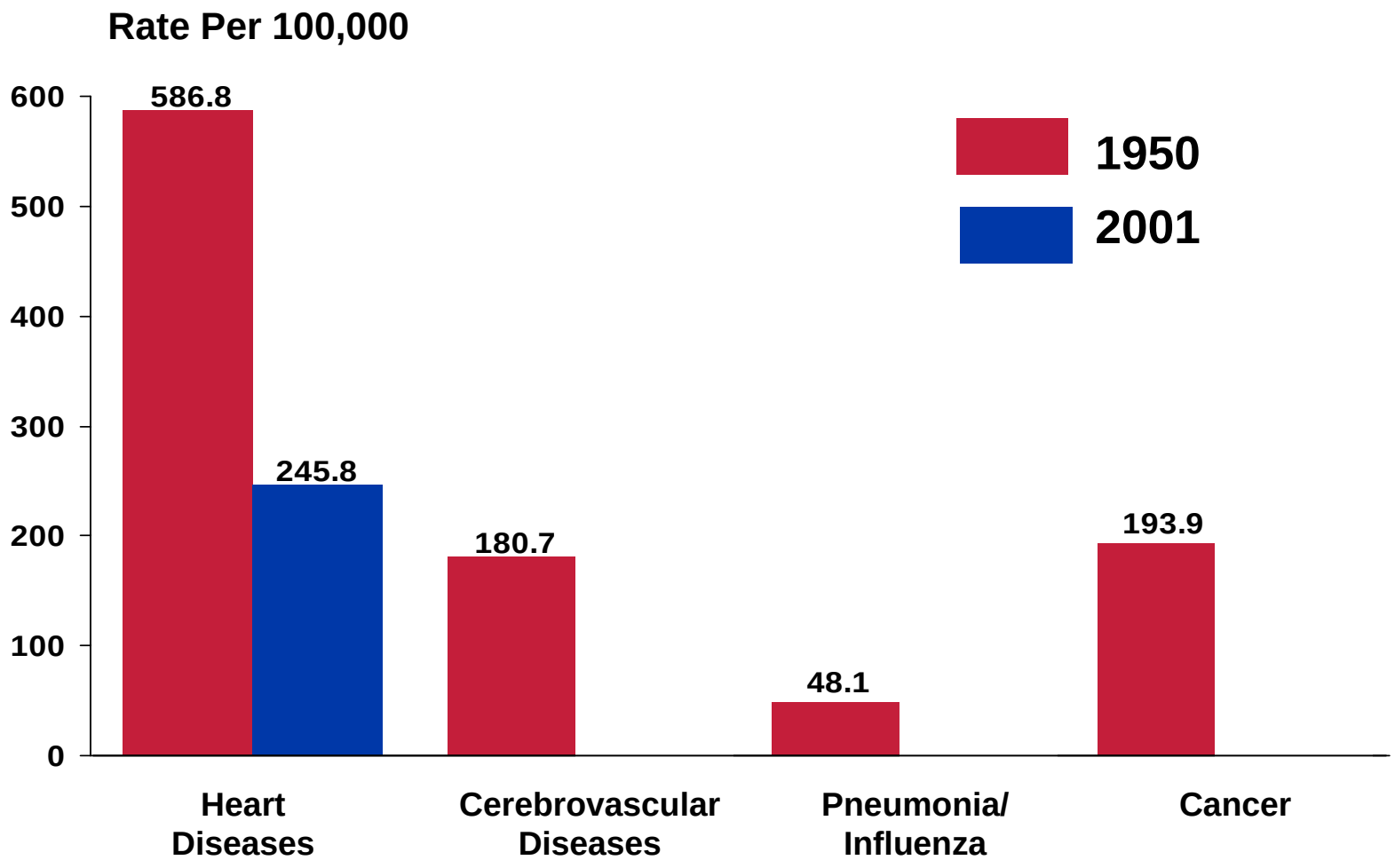
- 1971 State of Union address:
  - President Nixon requested $100 million for cancer research
- December 23, 1971
  - Nixon signed National Cancer Act into law
  - "I hope in years ahead we will look back on this action today as the most significant action taken during my Administration."

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



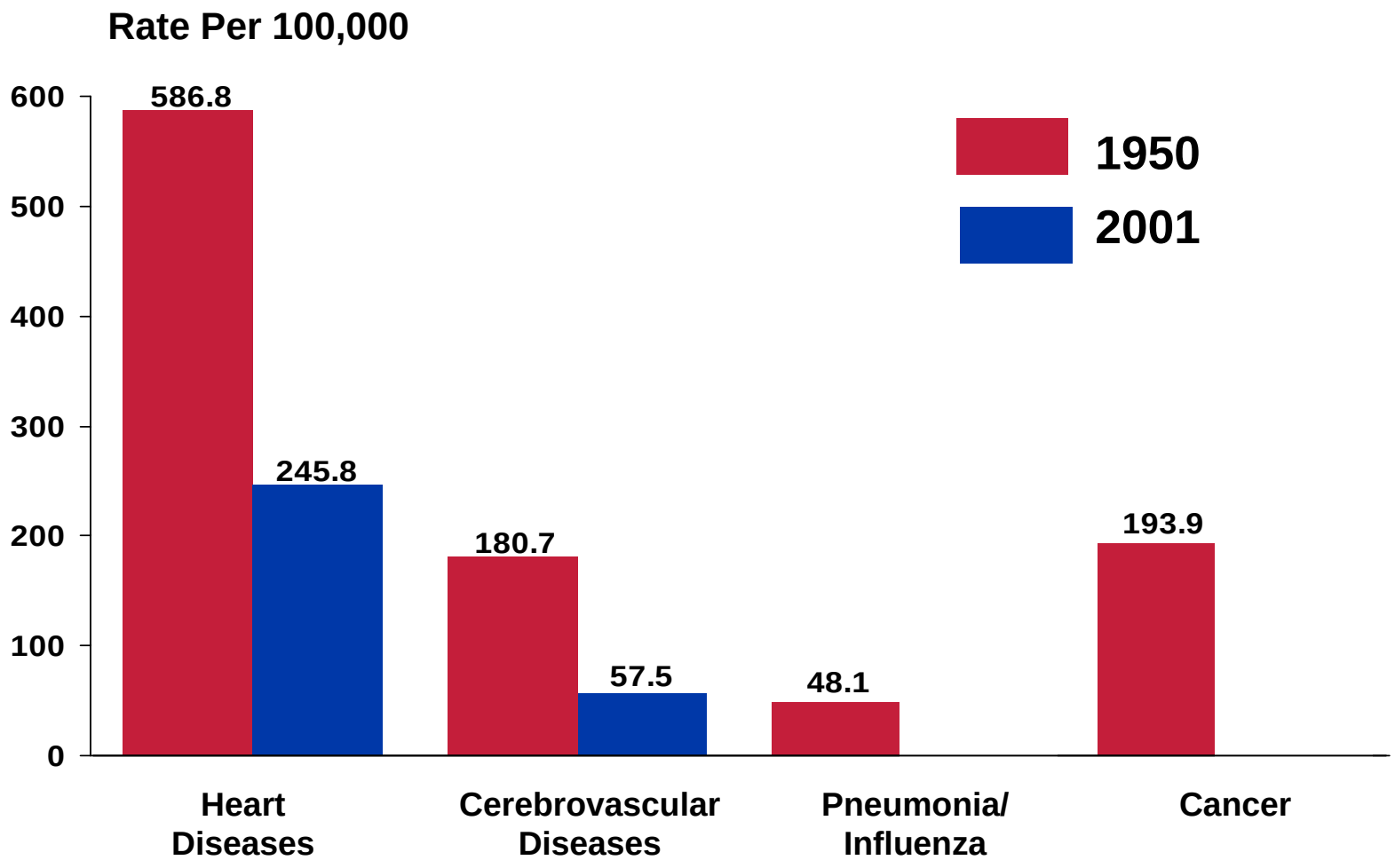
*** Age-adjusted to 2000 US standard population.**
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

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



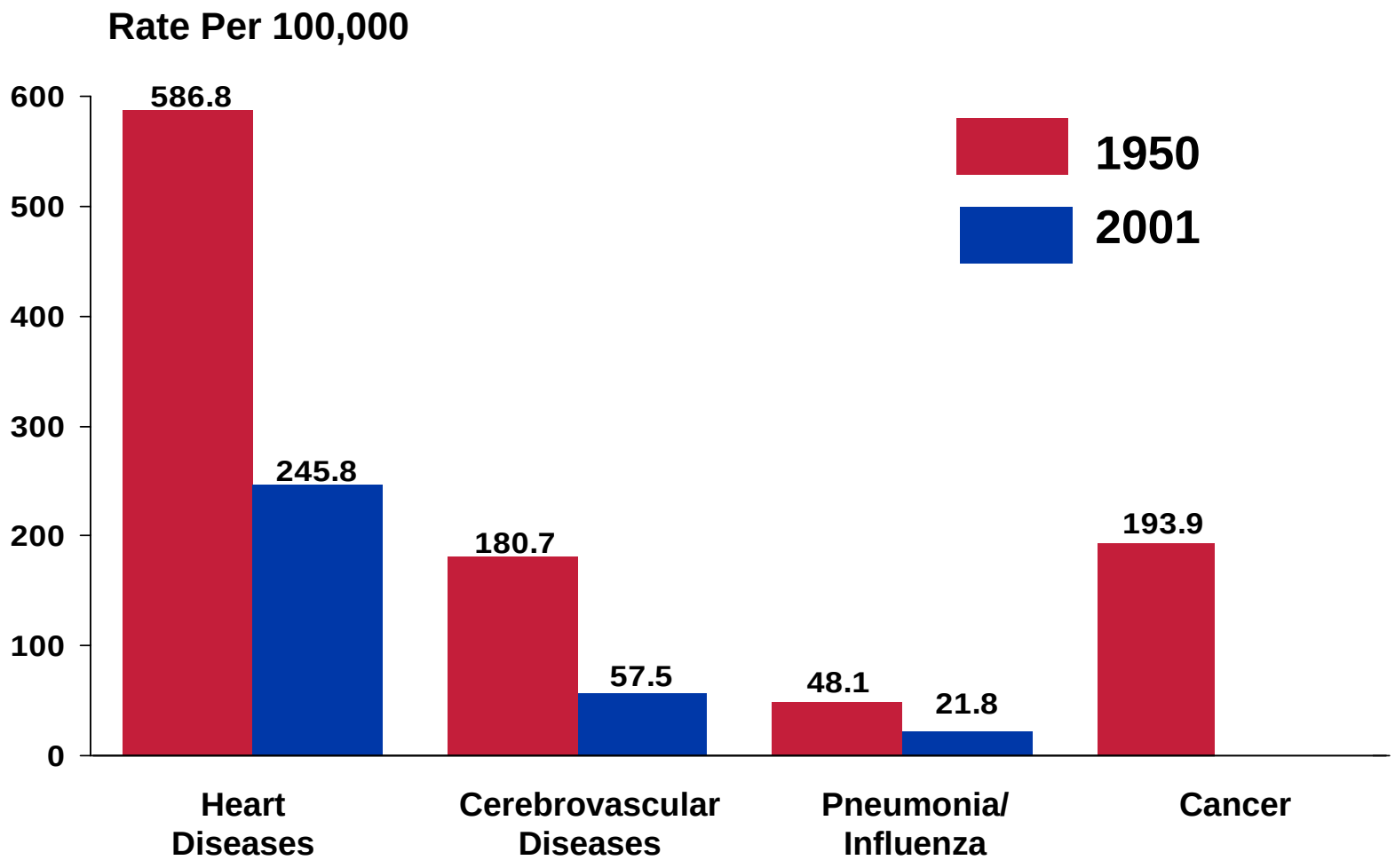
*** Age-adjusted to 2000 US standard population.**
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

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



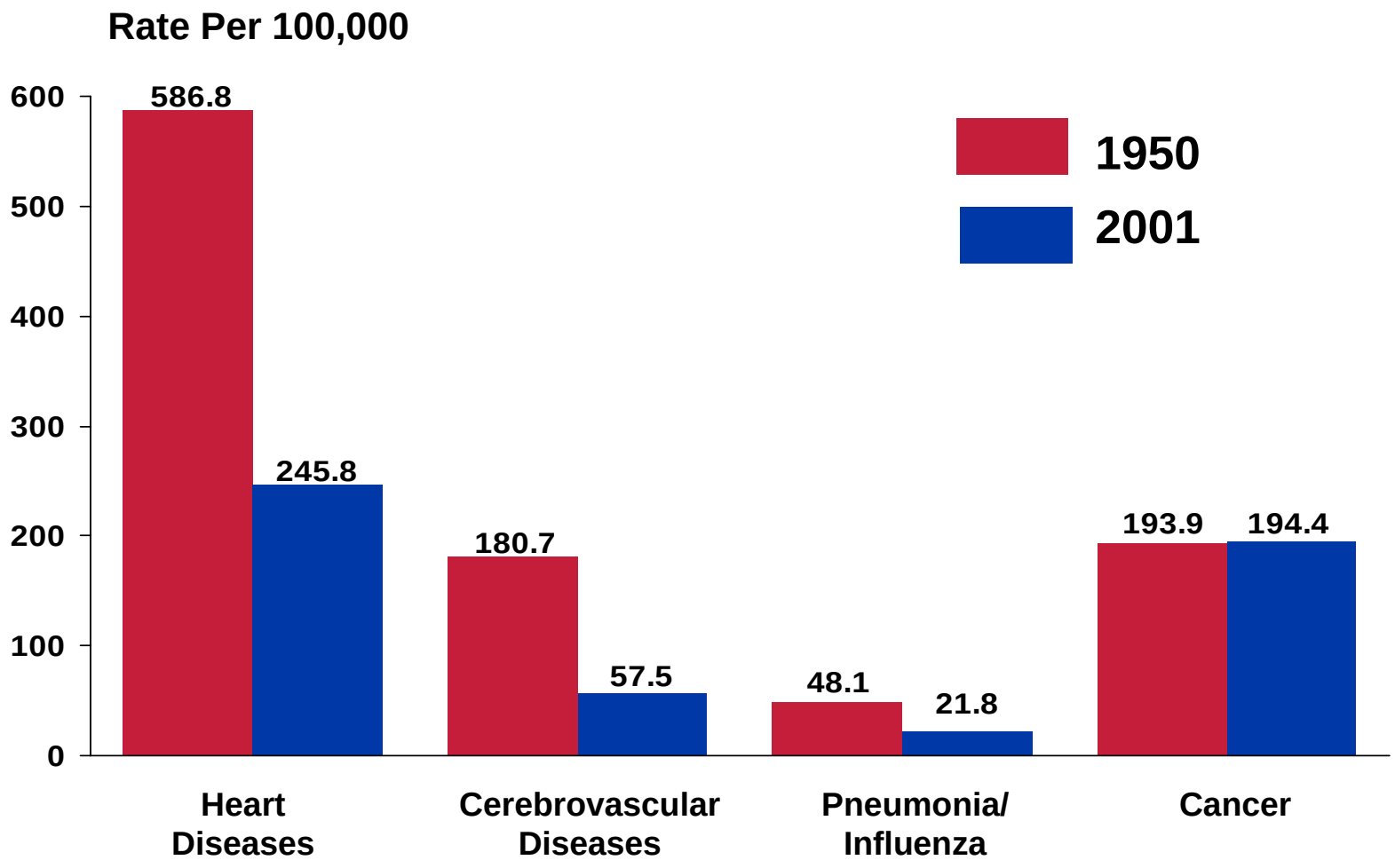
*** Age-adjusted to 2000 US standard population.**
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

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



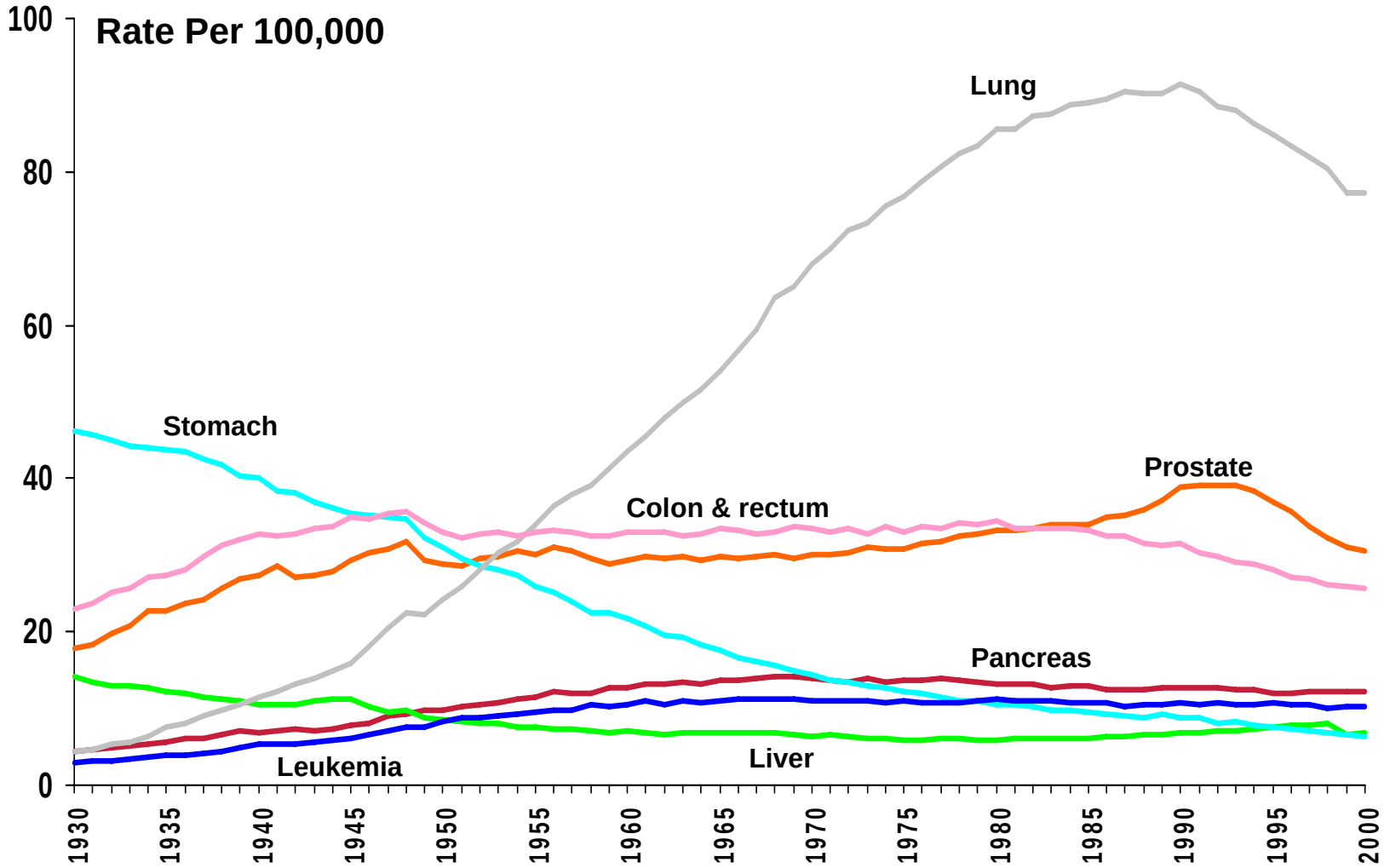
*** Age-adjusted to 2000 US standard population.**
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

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



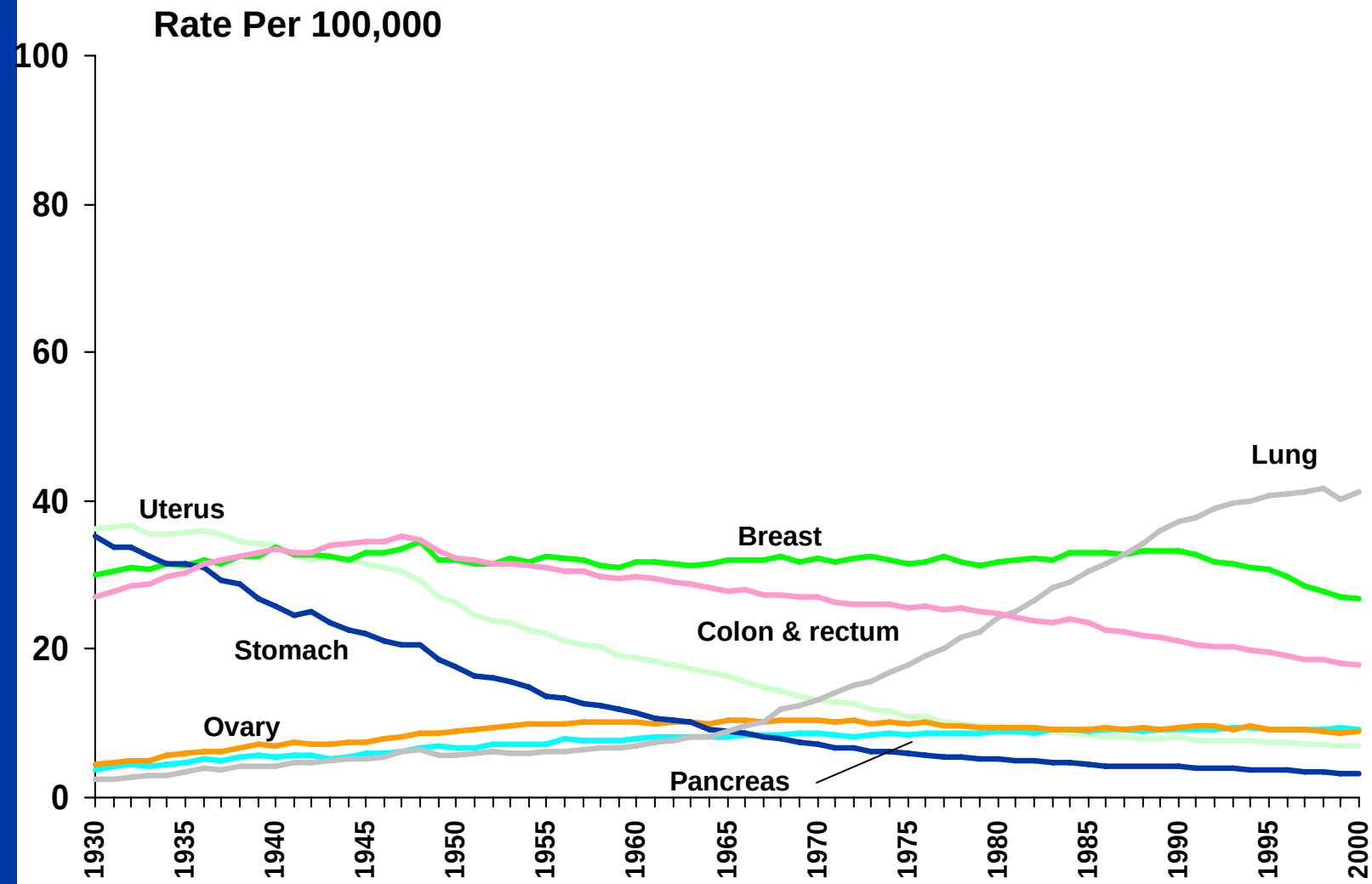
*** Age-adjusted to 2000 US standard population.**
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

Cancer Death Rates*, for Men, US, 1930-2000



*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.

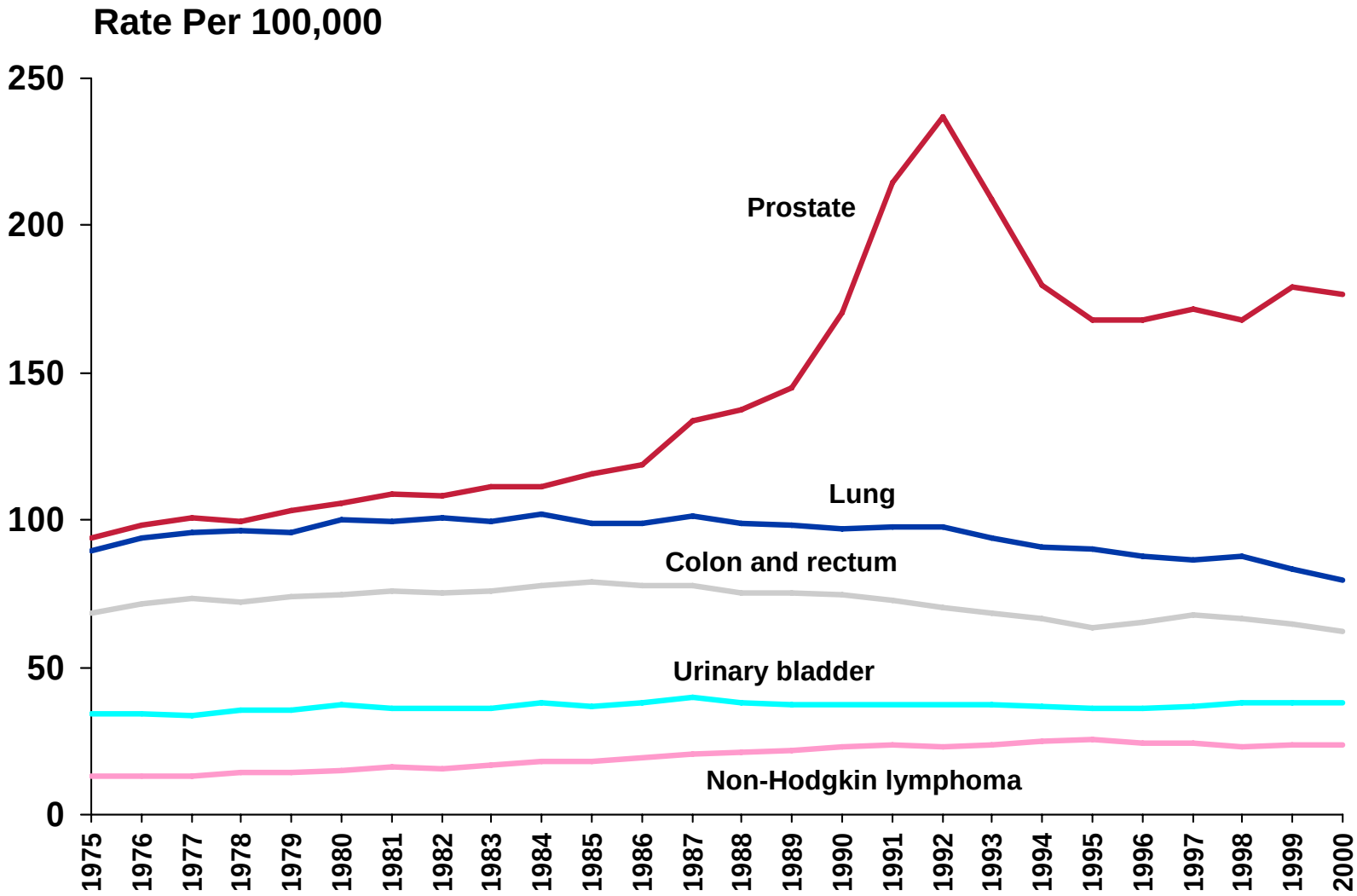
Cancer Death Rates*, for Women, US, 1930-2000



*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.

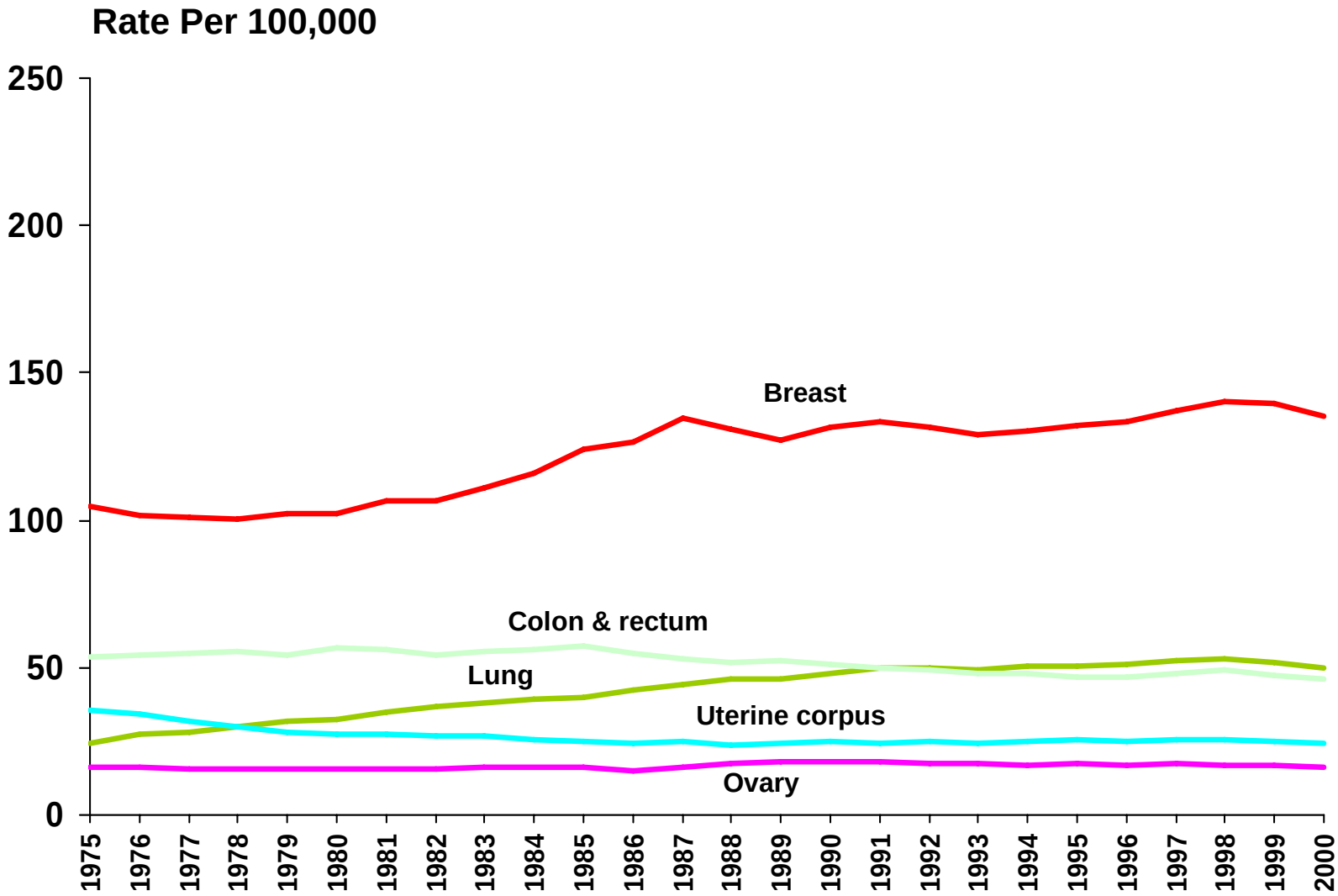
Cancer Incidence Rates* for Men, US, 1975-2000



*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.

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



*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

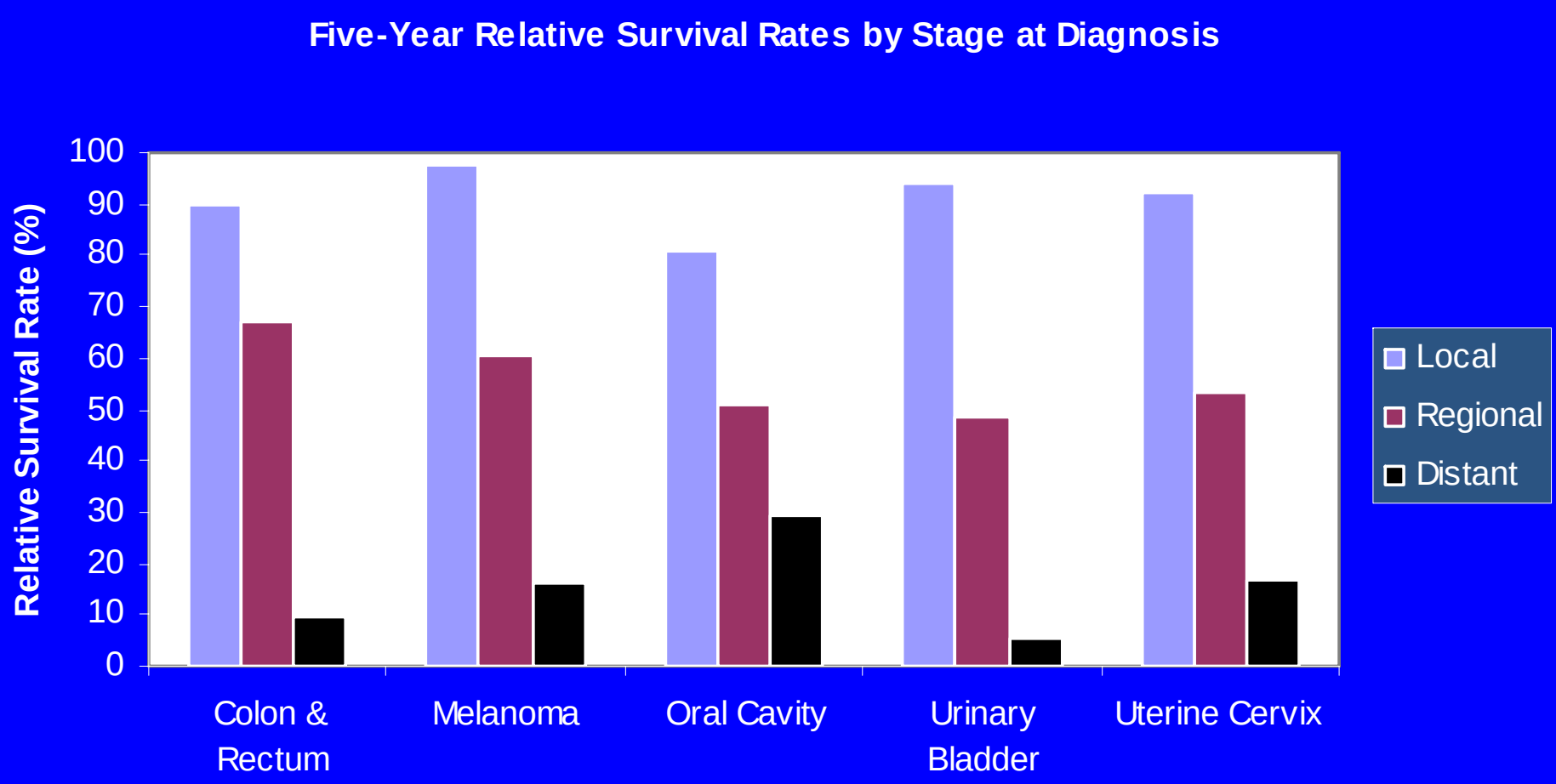
Site	1974-1976	1983-1985	1992-1999
All sites	50	52	63
Breast (female)	75	78	87
Colon & rectum	50	57	62
Leukemia	34	41	46
Lung & bronchus	12	14	15
Melanoma	80	85	90
Non-Hodgkin lymphoma	47	54	56
Ovary	37	41	53
Pancreas	3	3	4
Prostate	67	75	98
Urinary bladder	73	78	82

***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.

Mission: National Cancer Institute

- Eliminate suffering and death due to cancer by 2015
- Budget Request 2004: $**5,986,000,000**

Importance of Cancer Screening



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

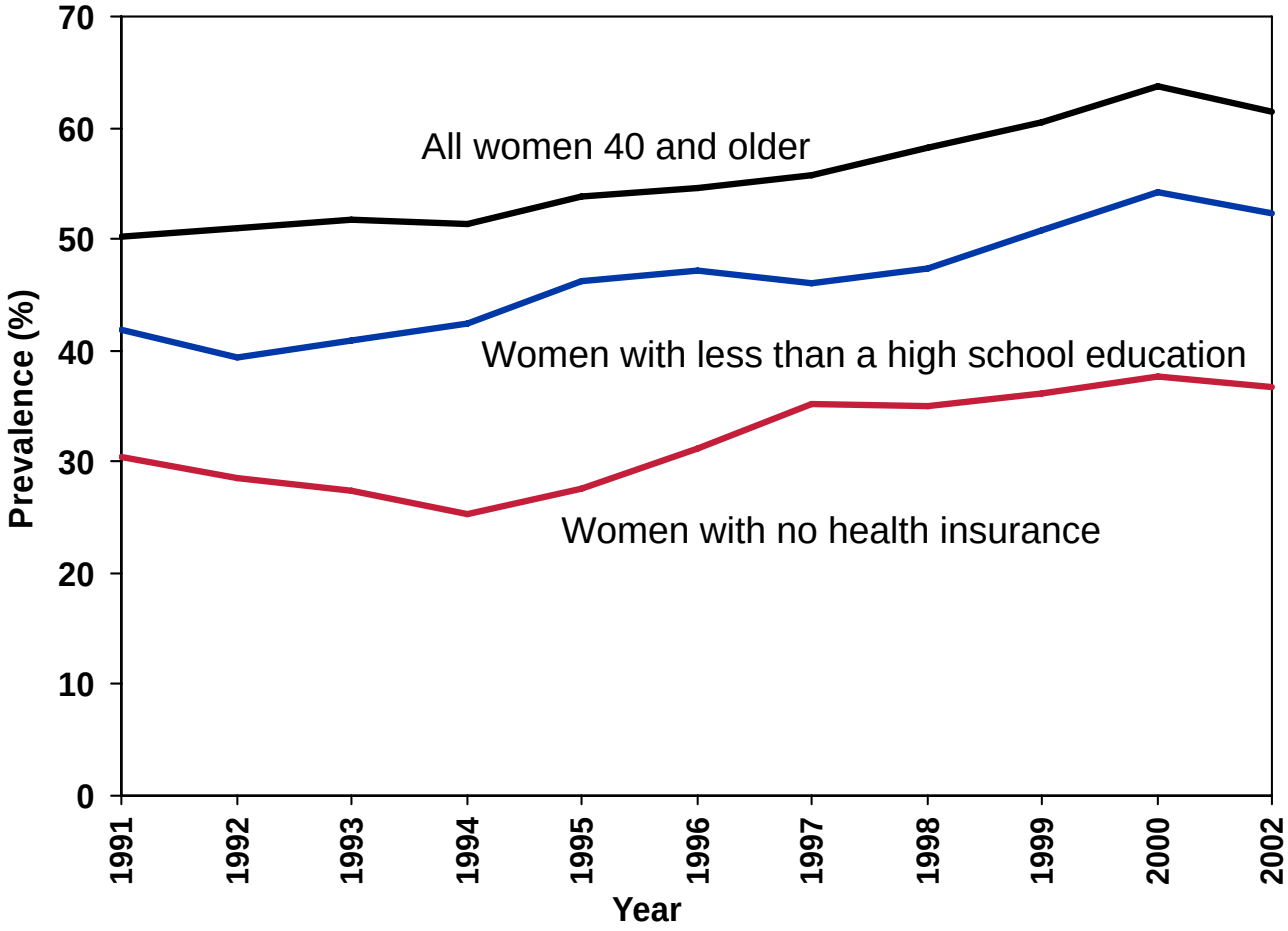
Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.

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.

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

Beginning at age 50, men and women should follow one of the following examination schedules:

A fecal occult blood test (FOBT) every year

A flexible sigmoidoscopy (FSIG) every five years

Annual fecal occult blood test and flexible sigmoidoscopy every five years*

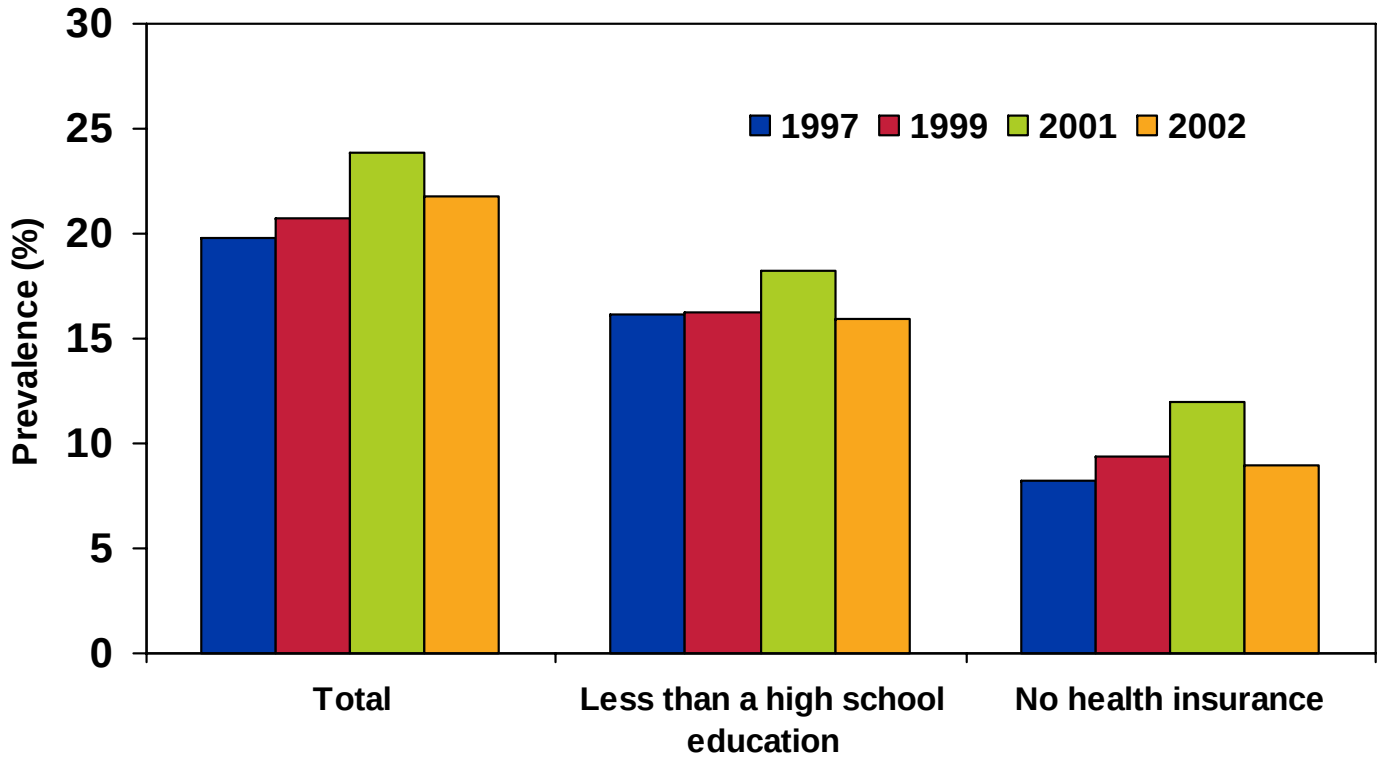
A double-contrast barium enema every five years

A colonoscopy every ten years

*Combined testing is preferred over either annual FOBT, or FSIG every 5 years alone.

People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule

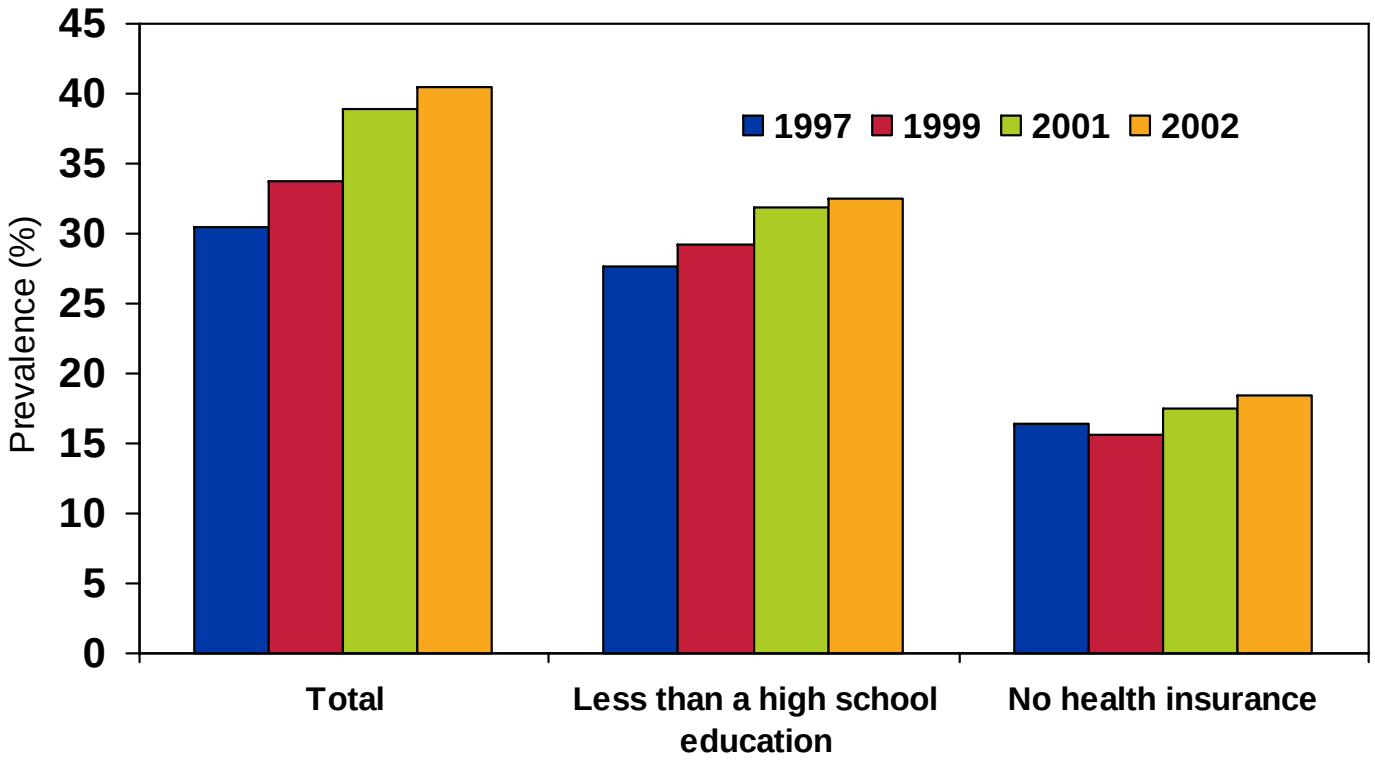
Trends in Recent* Fecal Occult Blood Test Prevalence (%), by Educational Attainment and Health Insurance Status, Adults 50 Years and Older, US, 1997-2002



***A fecal occult blood test within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.**

Source: Behavioral Risk Factor Surveillance System CD-ROM (1996-1997, 1999) and Public Use Data Tape (2001, 2002), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention and Prevention, 1999, 2000, 2002, 2003.

Trends in Recent* Flexible Sigmoidoscopy Prevalence (%), by Educational Attainment and Health Insurance Status, Adults 50 Years and Older, US, 1997-2002



***A flexible sigmoidoscopy or colonoscopy within the past five years. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.**
Source: Behavioral Risk Factor Surveillance System CD-ROM (1996-1997, 1999) and Public Use Data Tape (2001, 2002), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention and Prevention, 1999, 2000, 2002, 2003.

How do we judge efficacy of a screening test?

Sensitivity/Specificity

Positive/Negative Predictive Value

Screening for Diabetes

- Questionnaire
  - Se=72-78%
  - Sp=50-51%
- Capillary Blood Glucose
  - >140 mg/dL
    - Se=56-65%
    - Sp=95-96%
  - >120 mg/dL
    - Se=75-84%
    - Sp=86-90%

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 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 = 1000

Se = TP/(# with disease) = TP/(TP+FN) = 25/(25+3) = .893

Sp = TN/(# without disease) = TN/(TN+FP) = 965/(965+7) = .992

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

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