Biomedical Engineering for Global Health

Lecture Eleven

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.

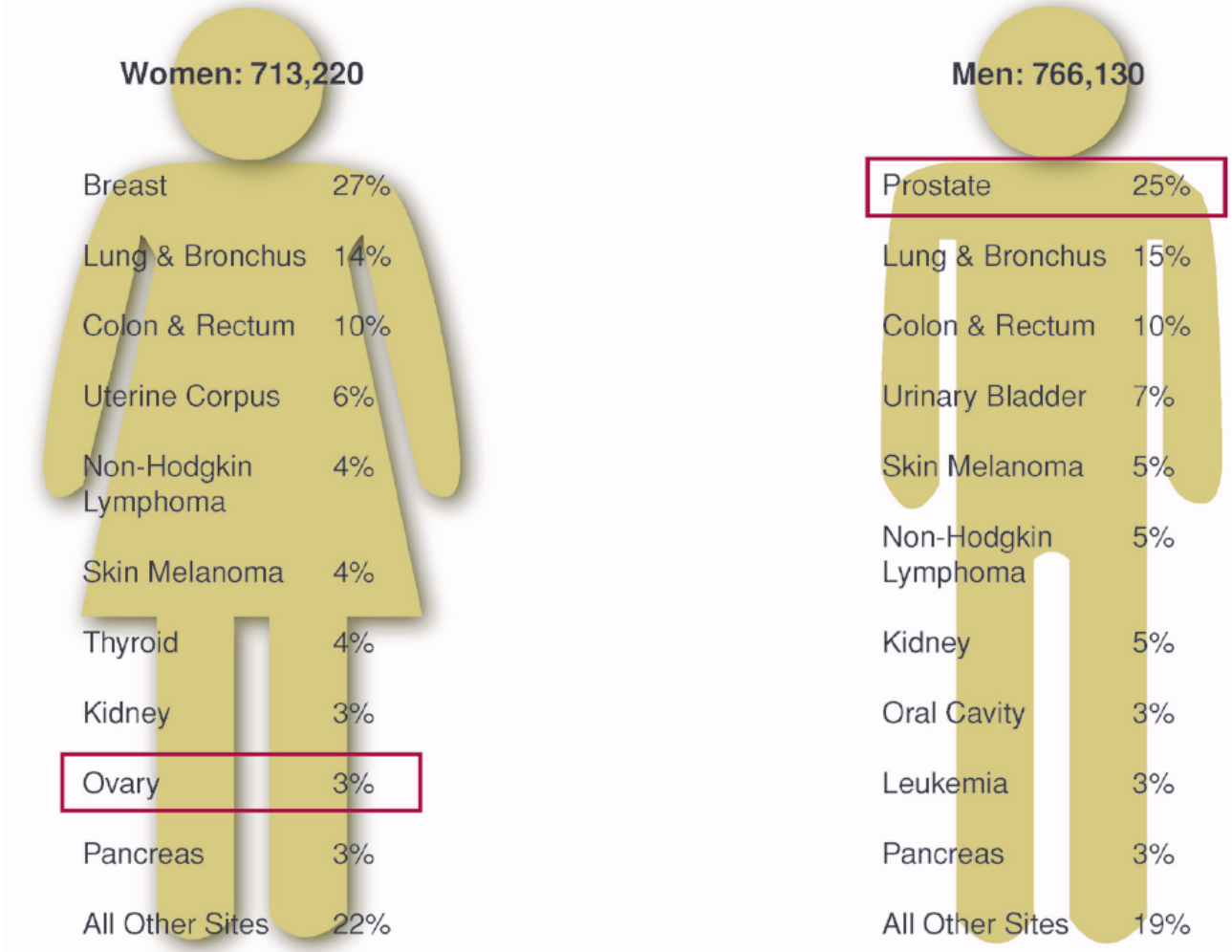
- Cancer:
  - 2nd leading cause of death in US
  - 1 of every 4 deaths is from cancer
- 5-year survival rate for all cancers:
  - 62%
- Annual costs for cancer:
  - $172 billion
    - $61 billion - direct medical costs
    - $16 billion - lost productivity to illness
    - $95 billion - lost productivity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

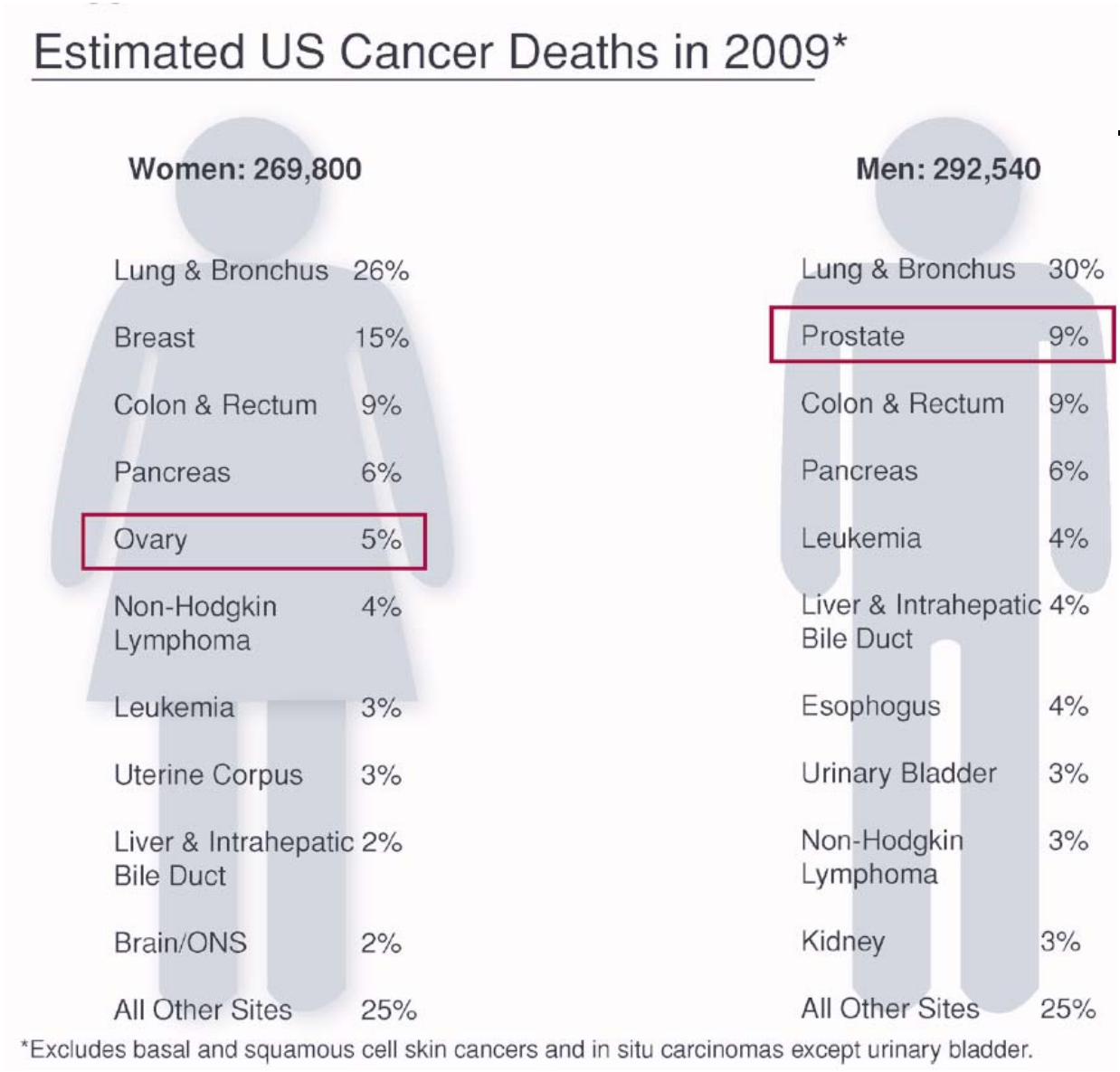
www.cancer.org, Cancer Facts & Figures

Estimated US Cancer Cases in 2009*



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

American Cancer Society



American Cancer Society

Worldwide Burden of Cancer

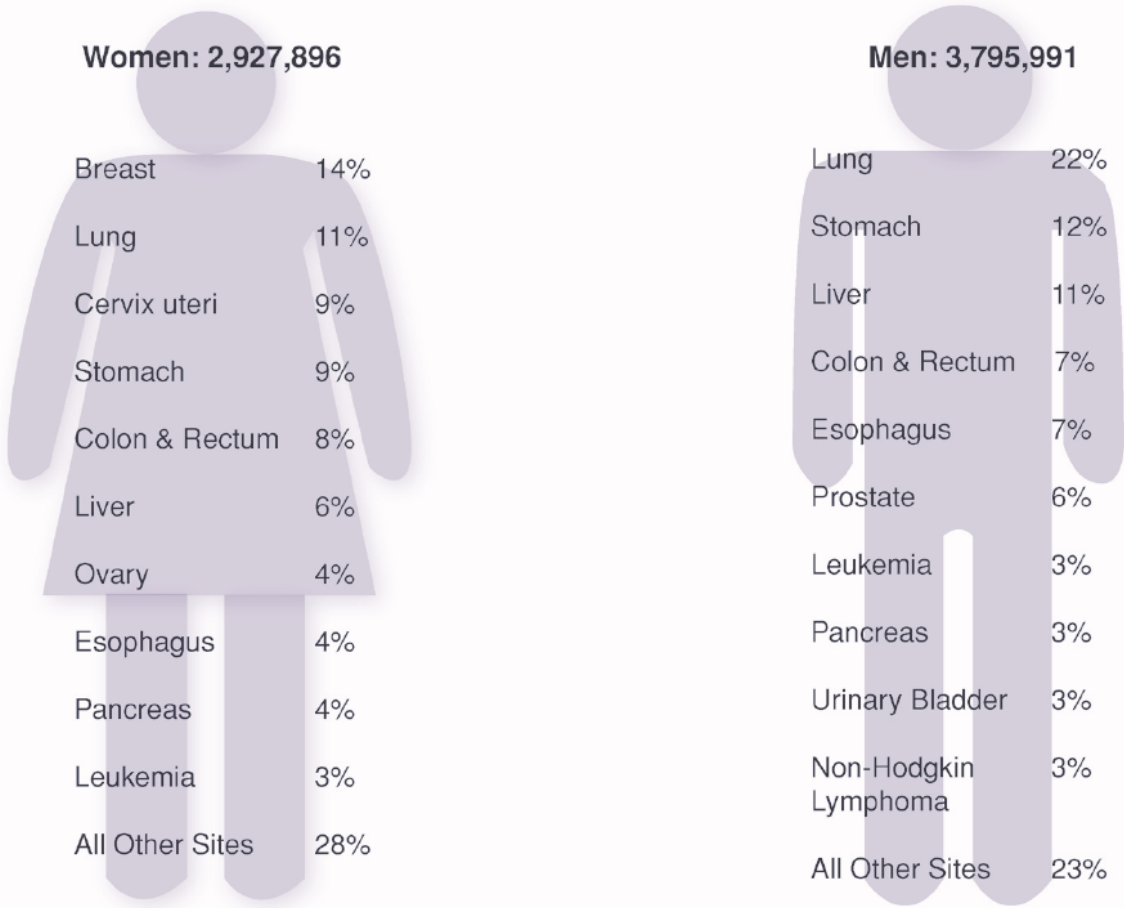
- Today:
  - 11 million new cases every year
  - 6.2 million deaths every year (12% of deaths)
- Can prevent 1/3 of these cases:
  - Reduce tobacco use
  - Implement existing screening techniques
  - Healthy lifestyle and diet
- In 2020:
  - 15 million new cases predicted in 2020
  - 10 million deaths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

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*



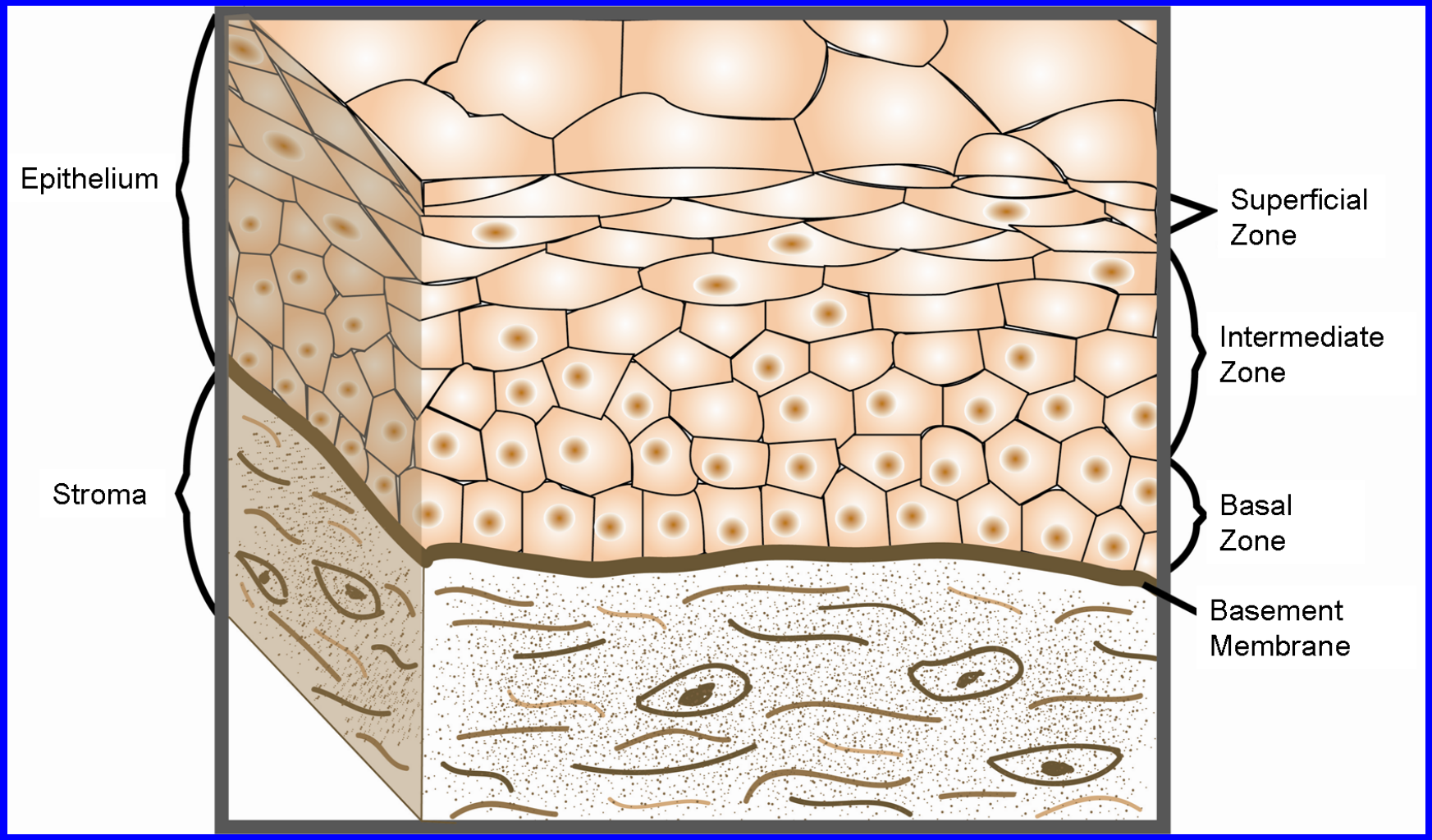
*Excludes basal and squamous cell skin cancers

American Cancer Society

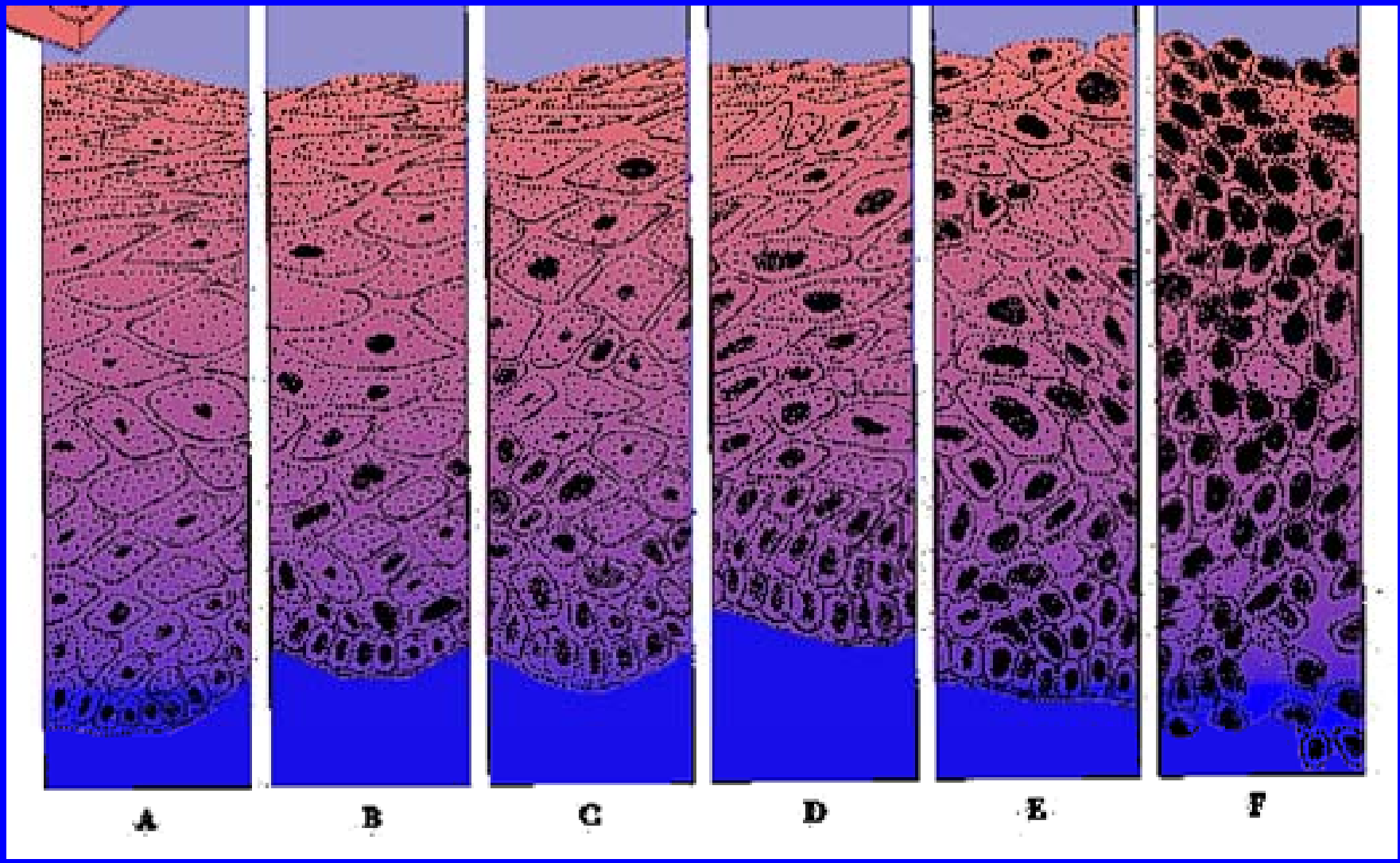
What is Cancer?

- 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



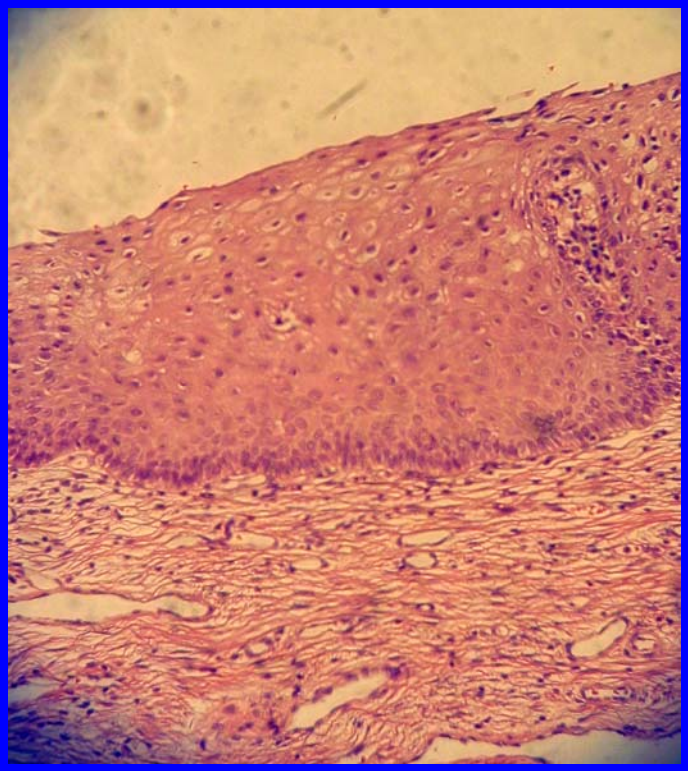
Precancer → Cancer Sequence



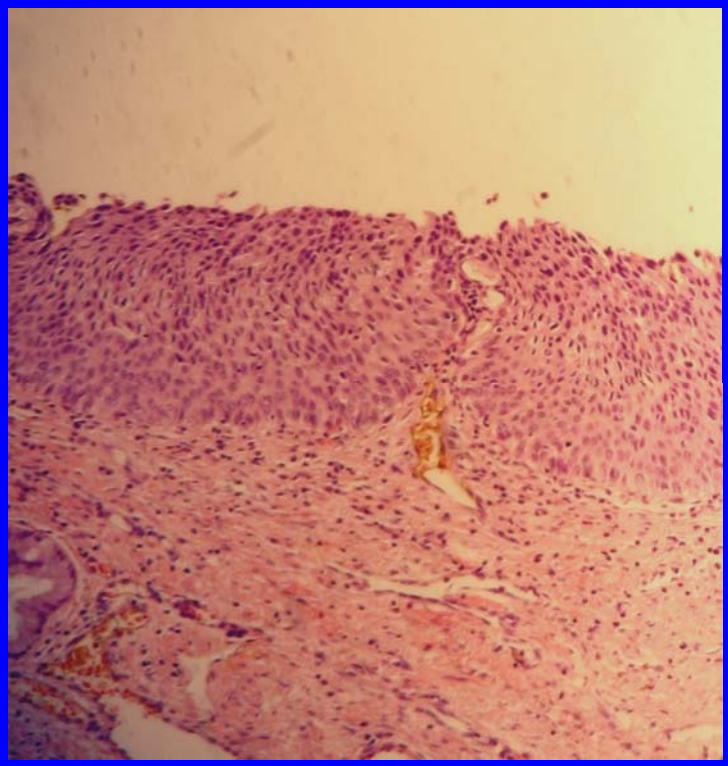
Journal of Nurse-Midwifery, **3b**(5), *McGraw R.K.,* Gynecology: A Clinical Atlas © *1991*

Histologic Images

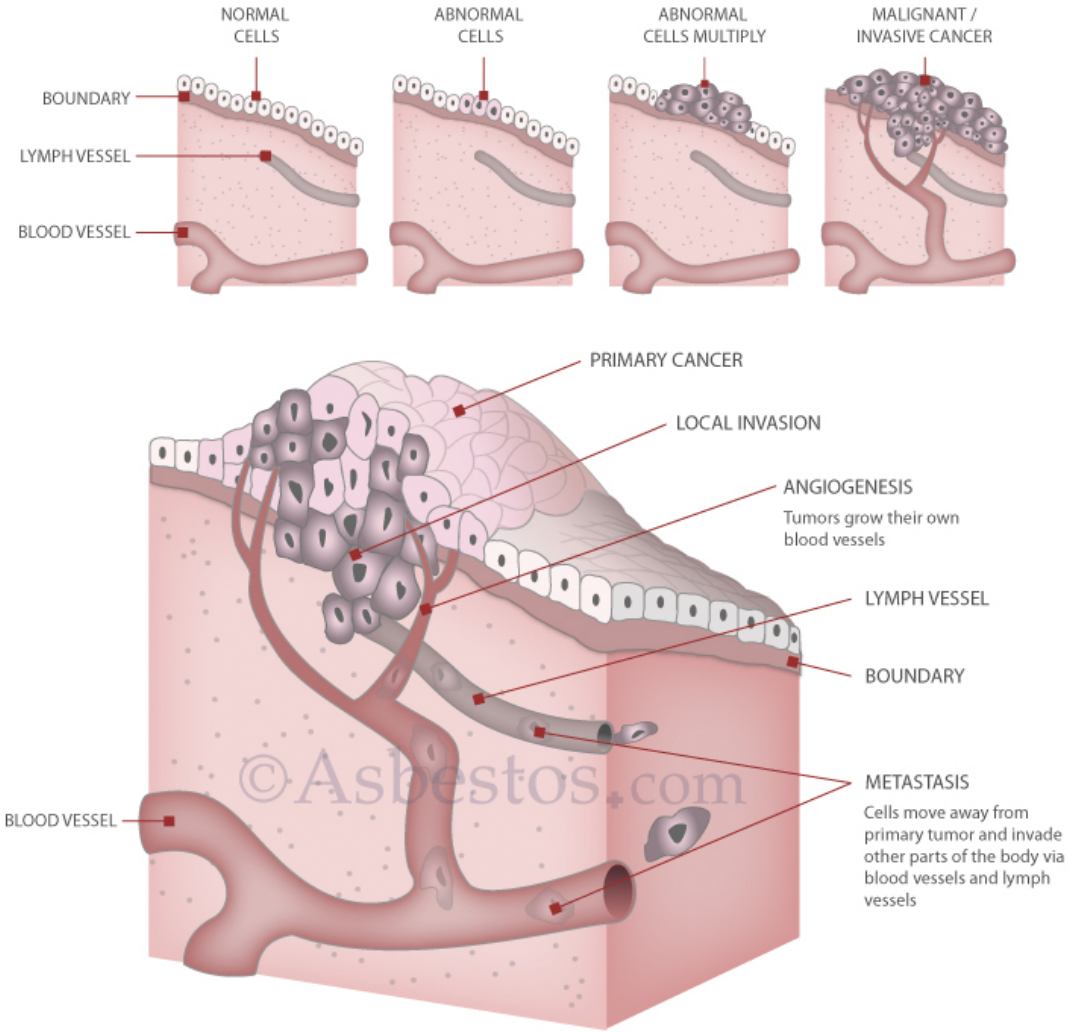
Normal



Cervical Pre-Cancer



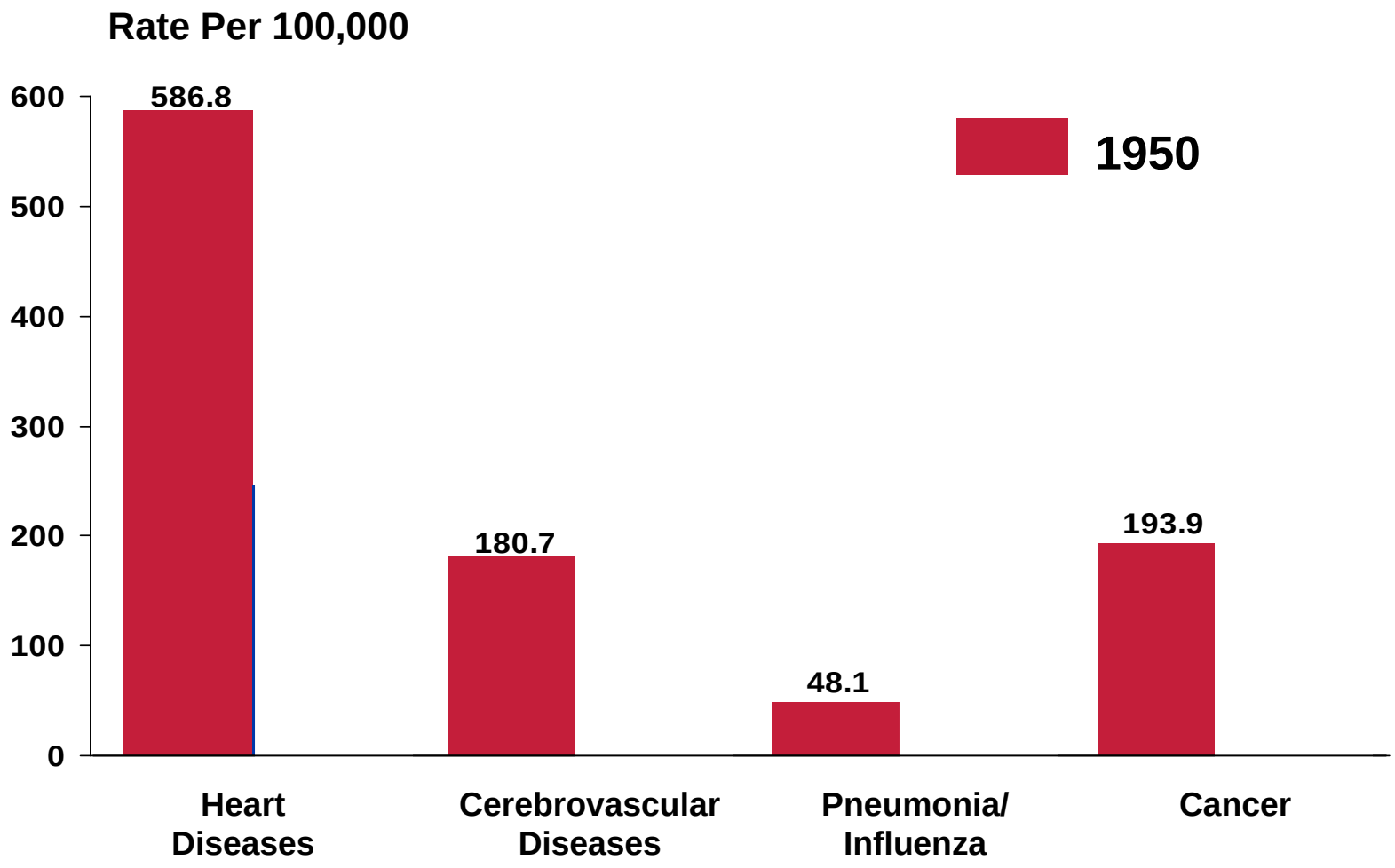
Progression of Malignant Cancer



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

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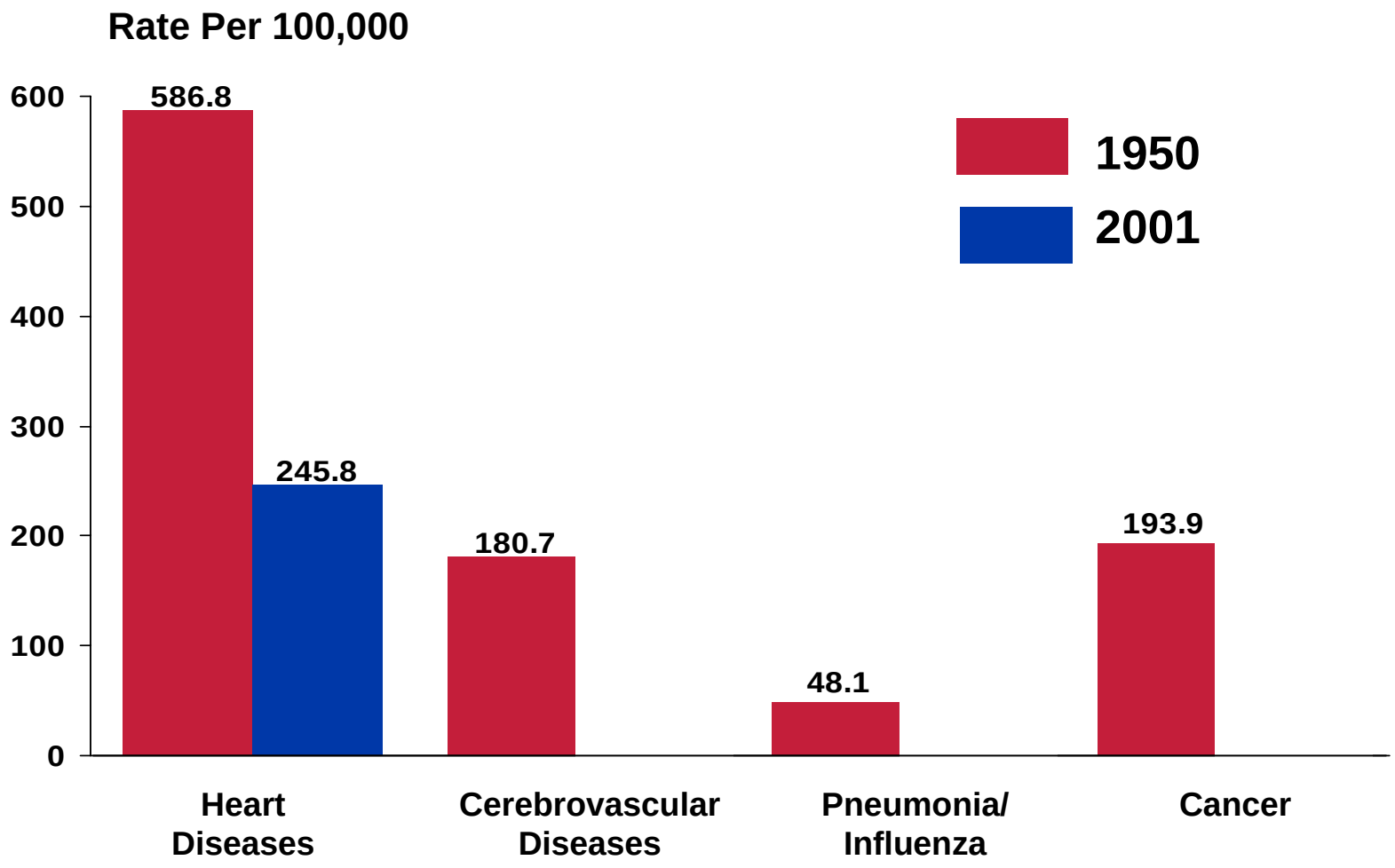

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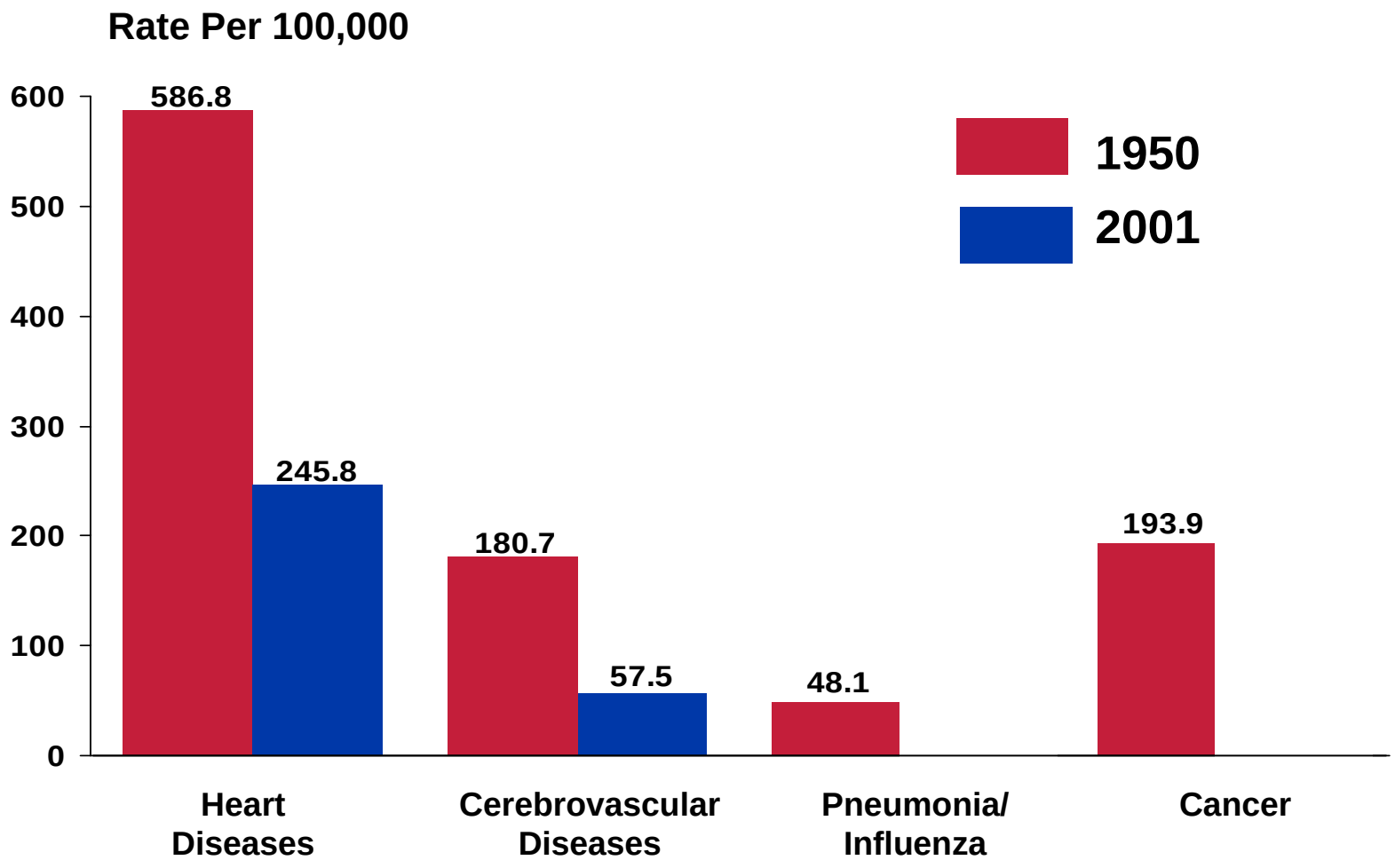

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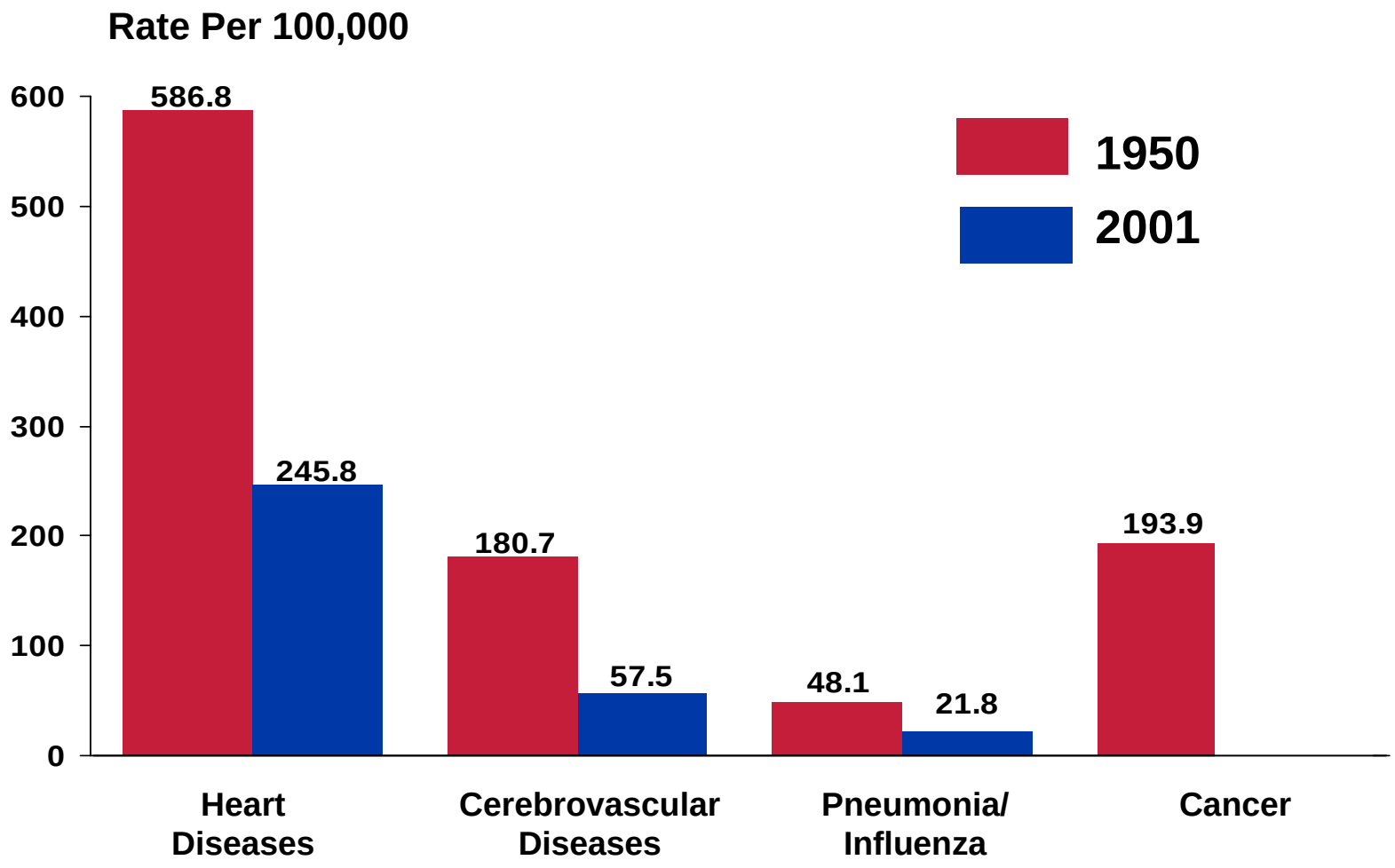

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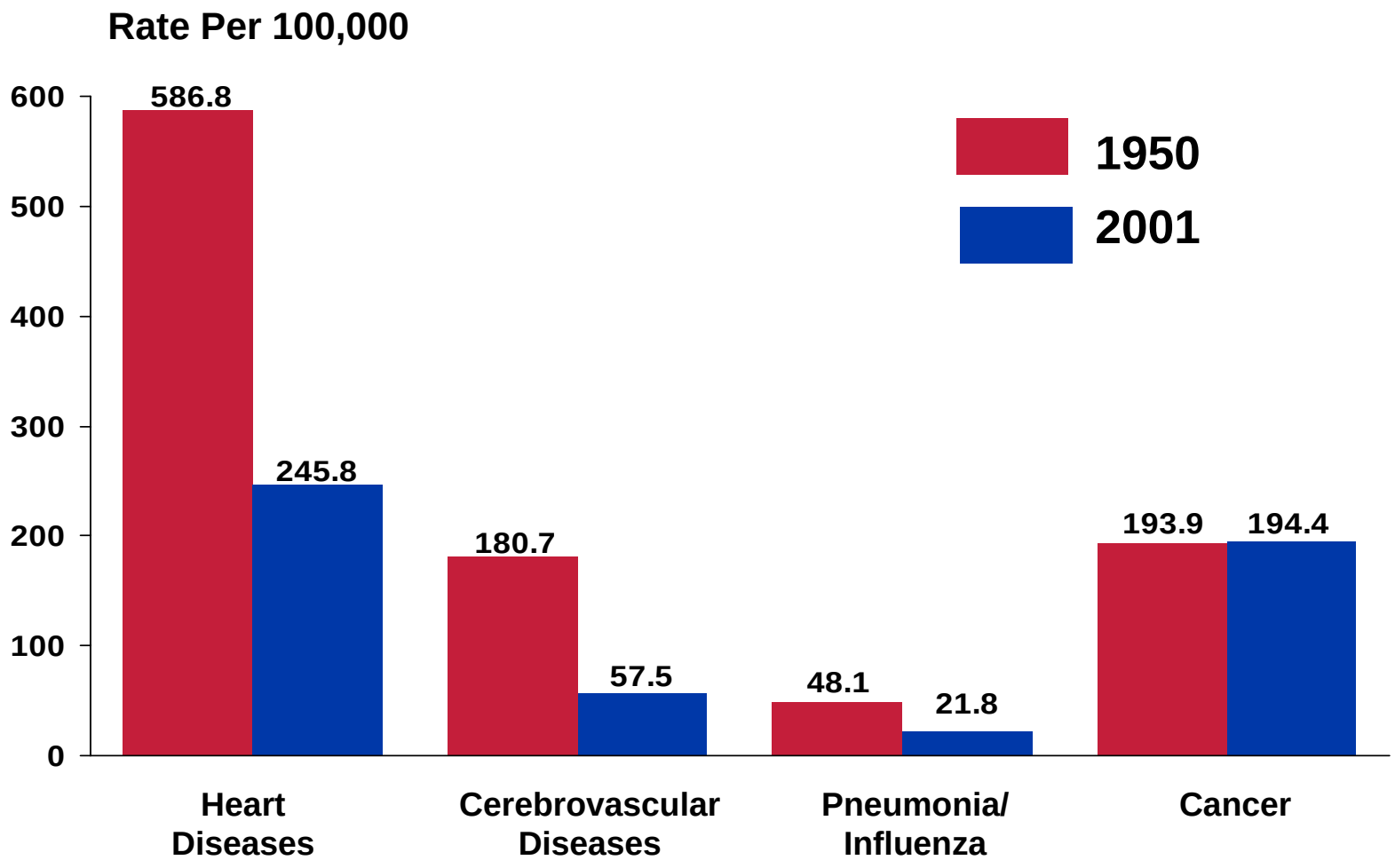

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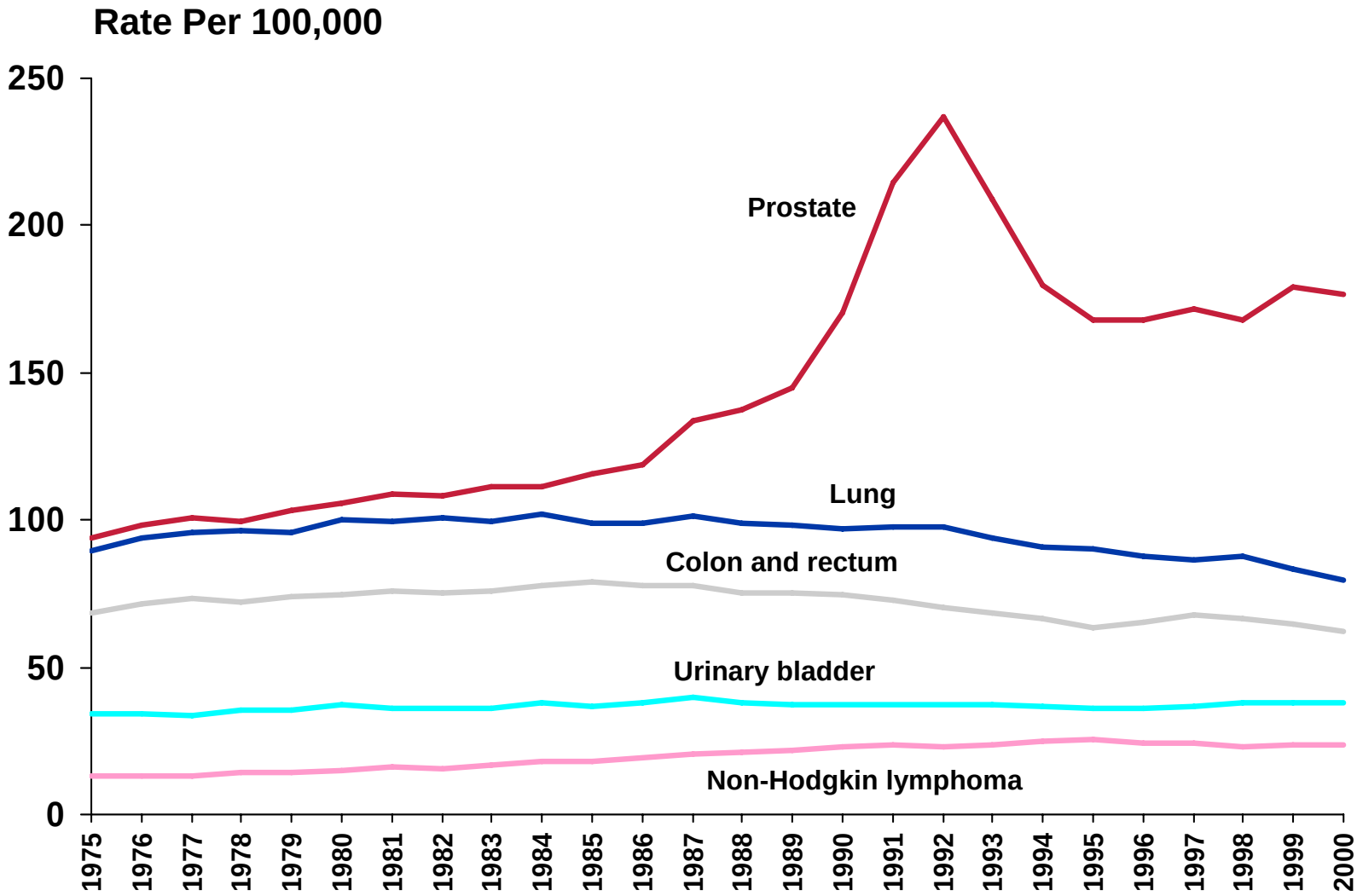
Cancer Incidence Rates* for Men, US, 1975-2000



*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.

Trends in 5-year Relative Survival Rates* (%) by Race and Year of Diagnosis, US, 1975-2004

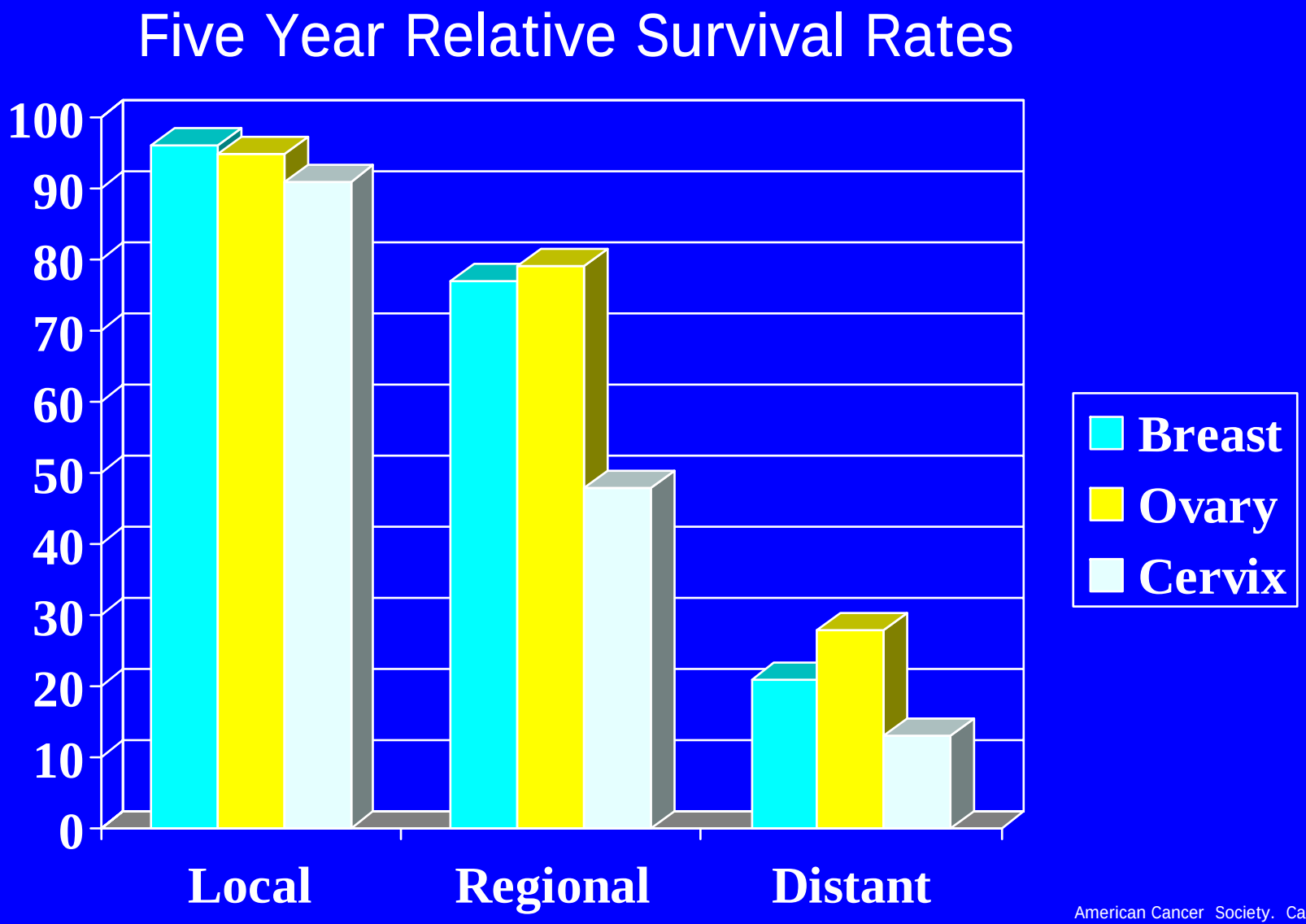
Site	All races			White			African American		
	1975-77	1984-86	1996-2004	1975-77	1984-86	1996-2004	1975-77	1984-86	1996-2004
All sites	50	54	66†	51	55	68†	40	41	58†
Brain	24	29	35†	23	28	34†	27	33	39†
Breast (female)	75	79	89†	76	80	91†	62	65	78†
Colon	52	59	65†	52	60	66†	46	50	55†
Esophagus	5	10	17†	6	11	18†	3	8	11†
Hodgkin lymphoma	74	79	86†	74	80	87†	71	75	80†
Kidney	51	56	67†	51	56	67†	50	54	66†
Larynx	67	66	64†	67	68	66	59	53	50
Leukemia	35	42	51†	36	43	52†	34	34	42
Liver#	4	6	11†	4	6	10†	2	5	8†
Lung & bronchus	13	13	16†	13	14	16†	11	11	13†
Melanoma of the skin	82	87	92†	82	87	92†	60‡	70§	78
Myeloma	26	29	35†	25	27	35†	31	32	33
Non-Hodgkin lymphoma	48	53	65†	48	54	66†	49	48	58
Oral cavity	53	55	60†	55	57	62†	36	36	42†
Ovary	37	40	46†	37	39	45†	43	41	38
Pancreas	3	3	5†	3	3	5†	2	5	5†
Prostate	69	76	99†	70	77	99†	61	66	96†
Rectum	49	57	67†	49	58	67†	45	46	59†
Stomach	16	18	25†	15	18	23†	16	20	25†
Testis	83	93	96†	83	93	96†	82‡	87‡	87
Thyroid	93	94	97†	93	94	97†	91	90	95
Urinary bladder	74	78	81†	75	79	82†	51	61	66†
Uterine cervix	70	68	73†	71	70	74†	65	58	65
Uterine corpus	88	84	84†	89	85	86†	61	58	61

* Survival rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 9 areas from 1975-1977, 1984-1986, and 1996-2004, and followed through 2005. † The difference in rates between 1975-1977 and 1996-2004 is statistically significant ($p < 0.05$). ‡ The standard error of the survival rate is between 5 and 10 percentage points. § The standard error of the survival rate is greater than 10 percentage points. # Includes intrahepatic bile duct.

Source: Ries LAG, Melbert D, Krapcho M, et al (eds.). *SEER Cancer Statistics Review, 1975-2005*, National Cancer Institute, Bethesda, MD, seer.cancer.gov/csr/1975_2005/, 2008.

American Cancer Society, Surveillance and Health Policy Research, 2009

Importance of Early Detection



American Cancer Society. Cancer Fact and Figures 2005

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.

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?

Cervical Cancer

Early Detection

Statistics on cervical cancer

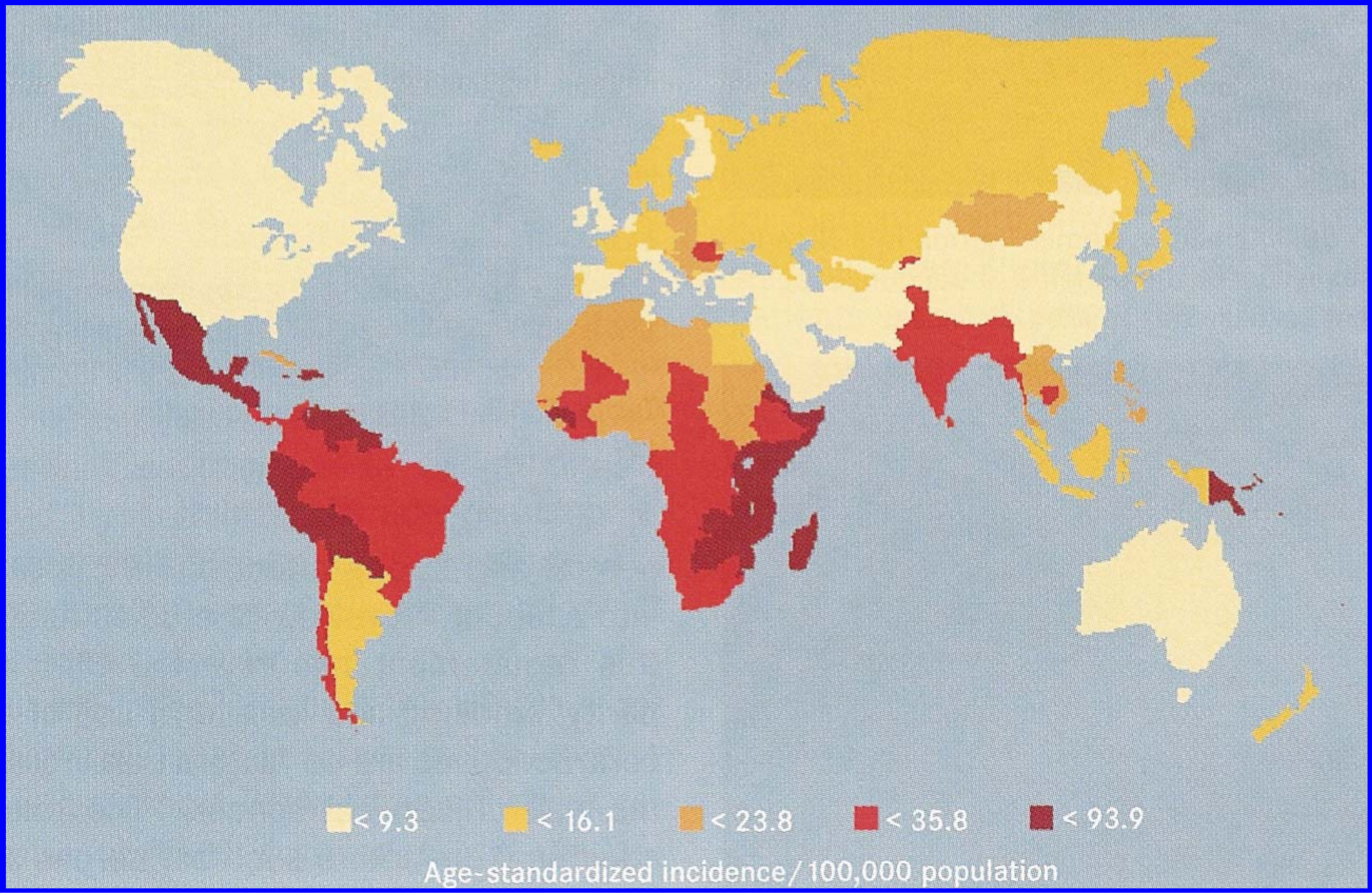
US data (2007)

- Incidence: 11,150
- Mortality: 3,670

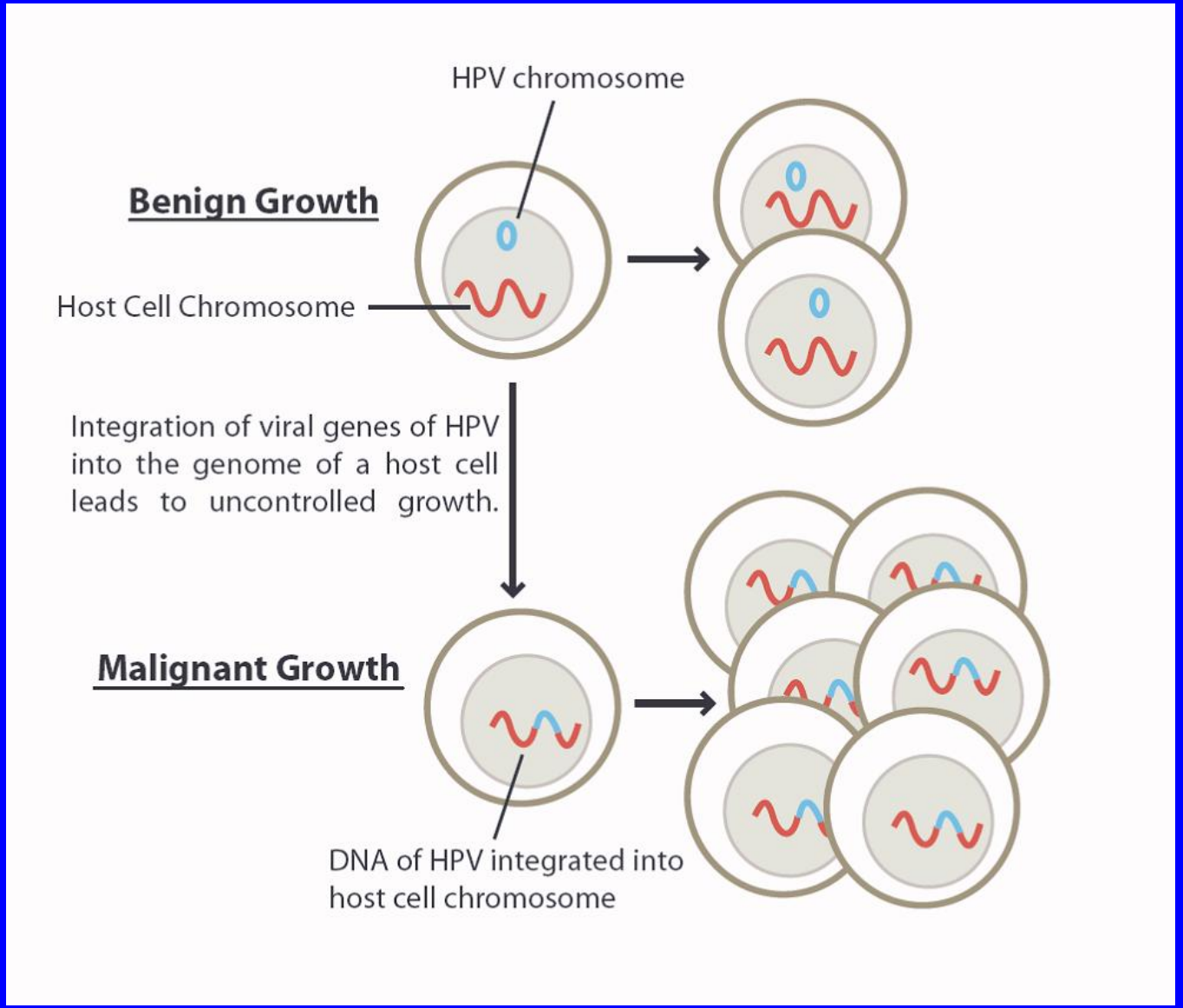
World data (2004)

- Incidence: 510,000 (80% developing world)
- Mortality
  - 288,000 deaths per year worldwide

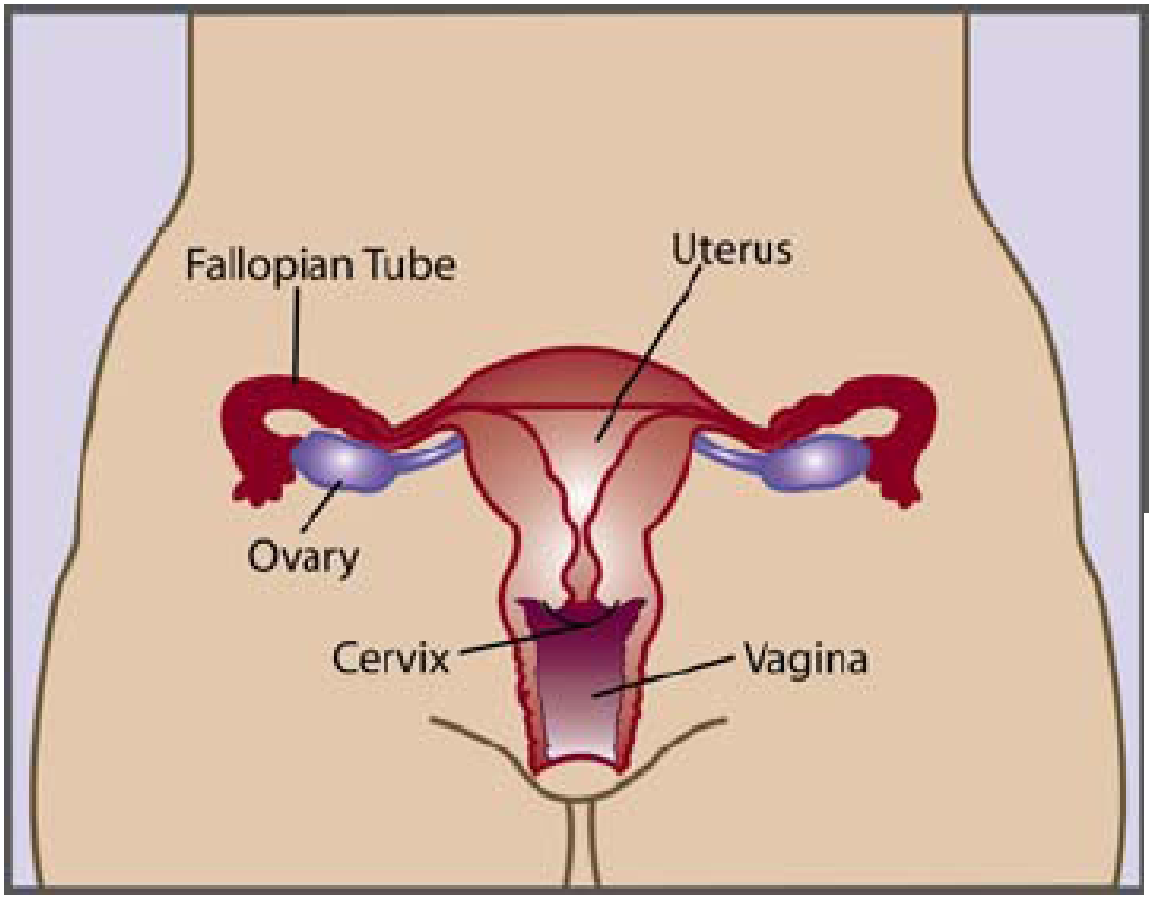
Global Burden of Cervical Cancer

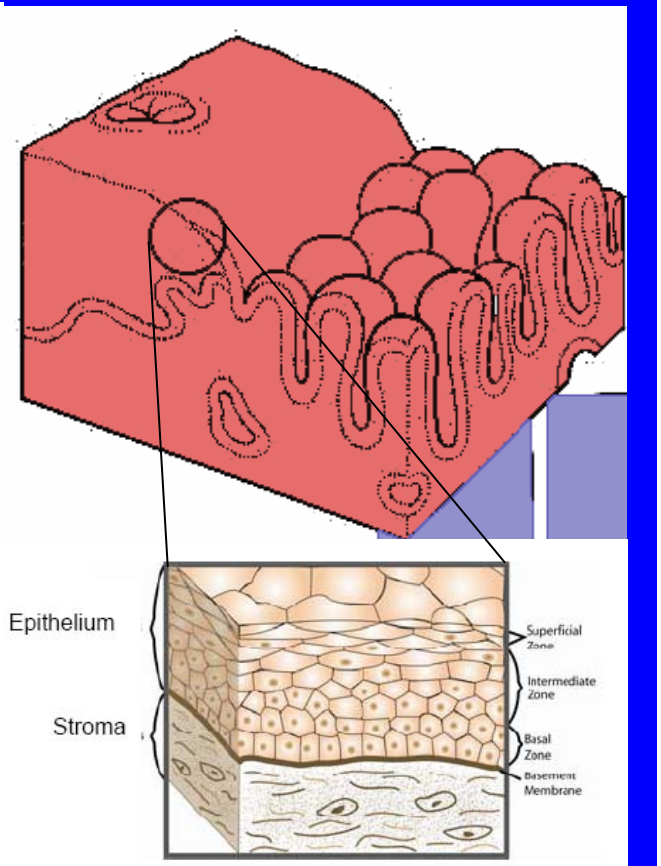


What Initiates Transformation?



Pathophysiology

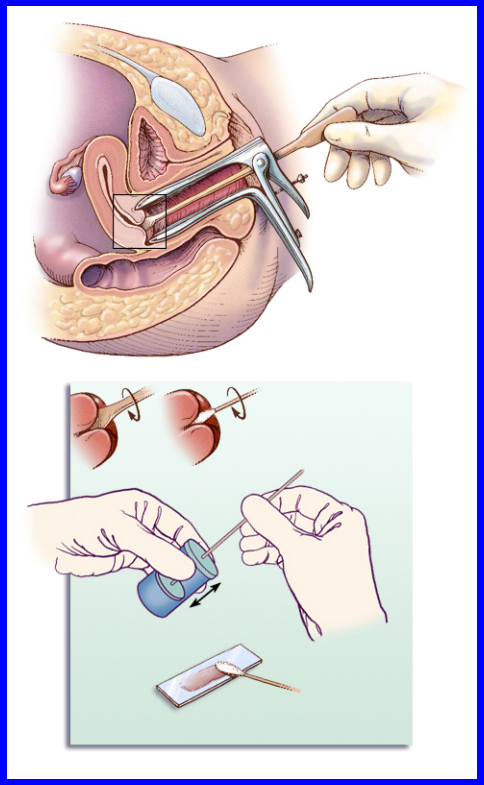




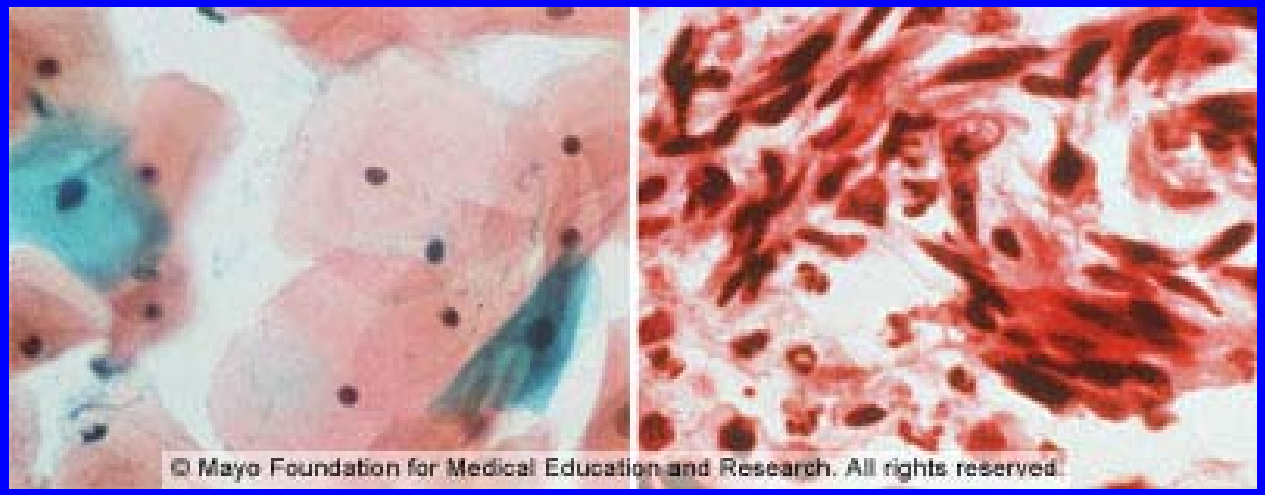
How Do We Detect Early Cervical Cancer?

- Pap Smear (The most successful cancer-screening test in medical history)
- Coposcopy + Biopsy

Pap Smear



Courtesy of Mayo Foundation



- 50,000-300,000 cells/per slide
- Cytotechnologists review slides (<100/day)
- Se = 62% → 3%
- Sp = 78% → $6B

Screening Guidelines for the Early Detection of Cervical Cancer, American Cancer Society 2006

All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.

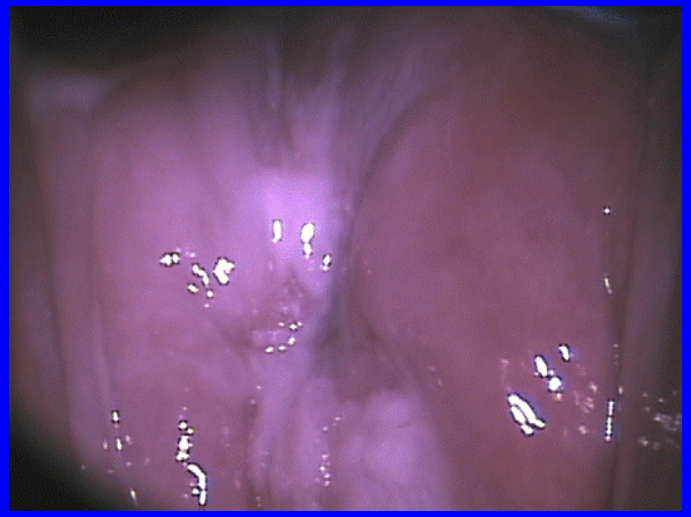
Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years with either the conventional (regular) or liquid-based Pap test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection,or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.

Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, *plus* the HPV DNA test.

Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or a weakened immune system should continue to have screening as long as they are in good health.

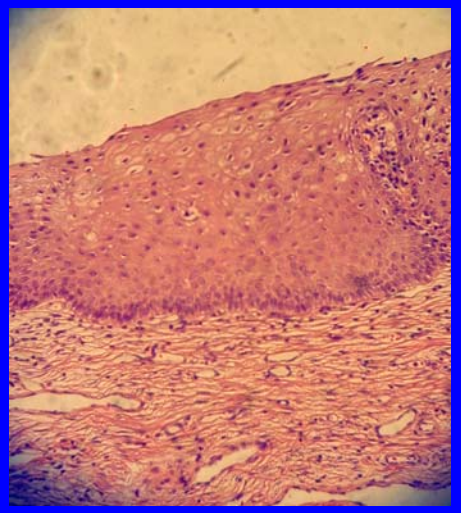
Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or precancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.

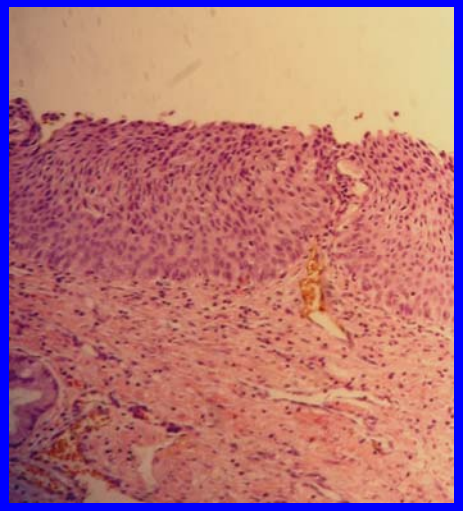
Colposcopy and Biopsy



Colposcope

Se = 95%
Sp = 44%





Biopsy sections

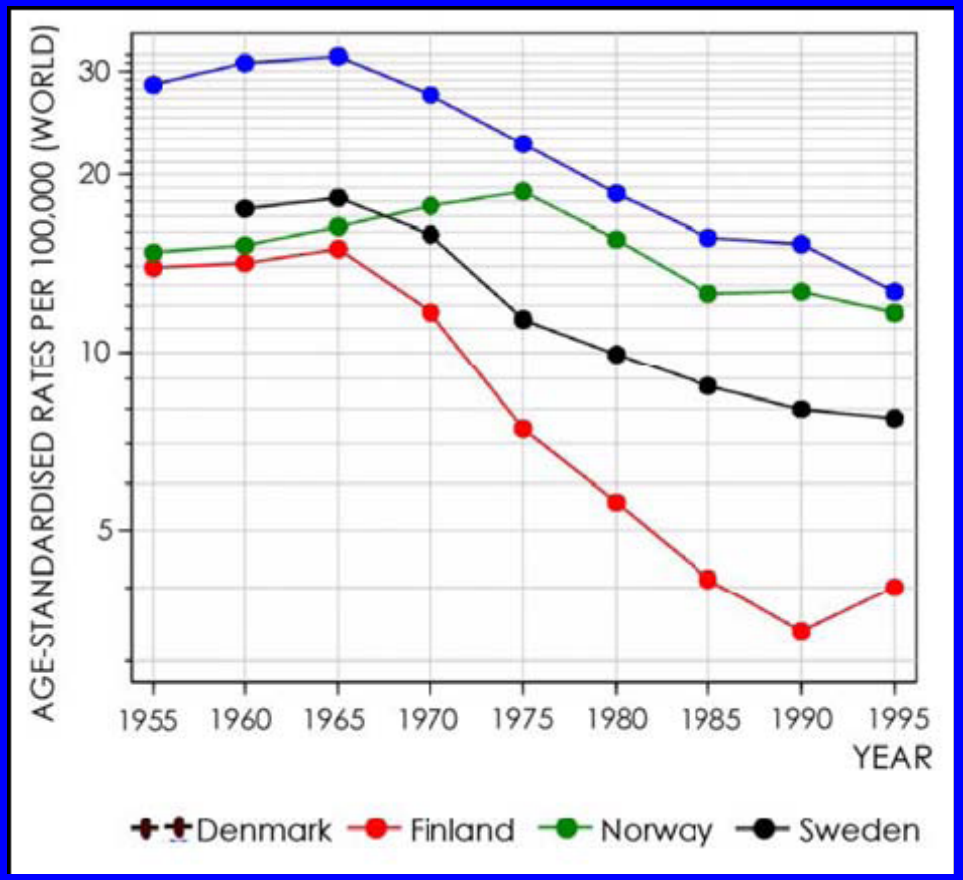
Detection and Treatment

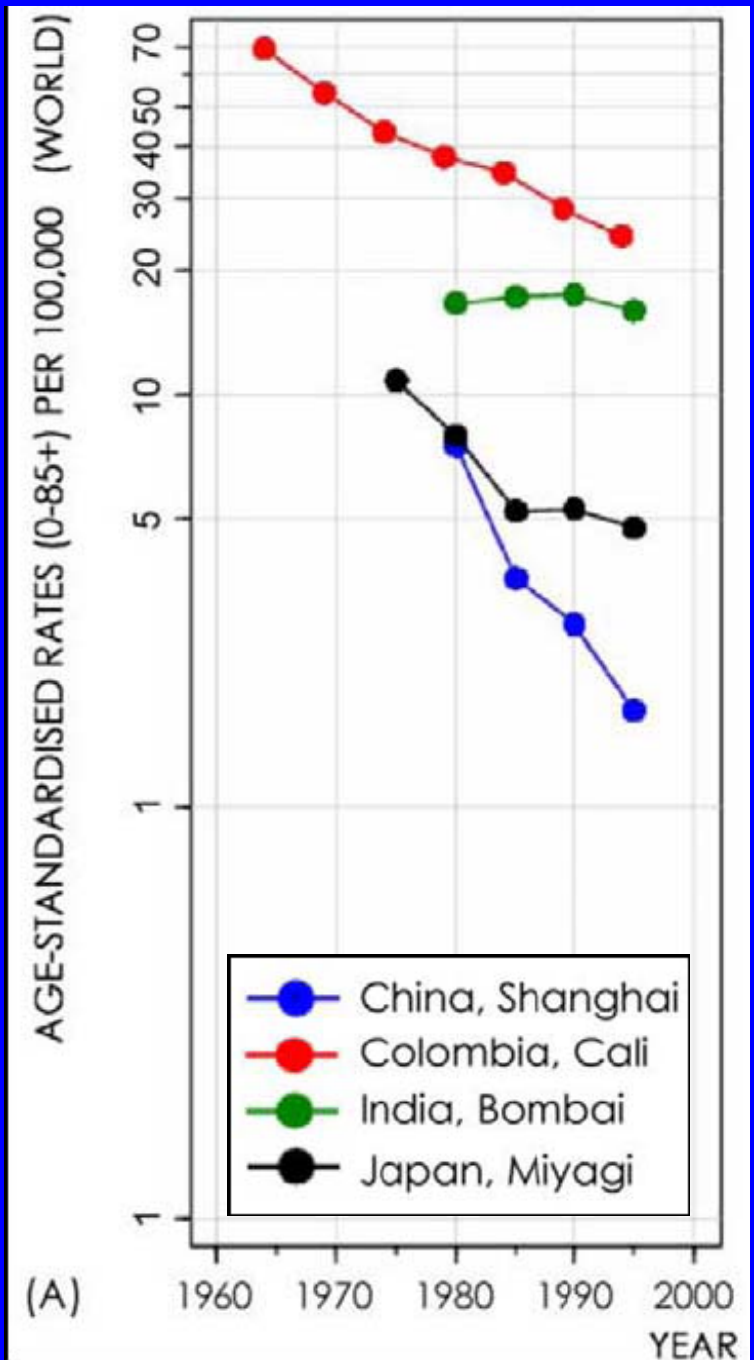
- Screening:
  - Pap smear
- Diagnosis:
  - Colposcopy + biopsy
- Treatment:
  - Surgery, radiotherapy, chemotherapy
- 5 year survival
  - Localized disease: 92% (56% diagnosed at this stage)

Screening Guidelines, ACS

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years with either the conventional (regular) or liquid-based Pap test.
- Option for women over 30 is to get screened every 3 years with either the conventional or liquid-based Pap test, *plus* the HPV DNA test.

Trends in Screening Cervical Cancer





Challenge

- Developed and developing world
- Cost and infrastructure requirements for screening
- Need for appropriate technologies

New Detection Technologies

Aims:

- Reduce the false positive and false negative rates
- Give instantaneous results
- Reduce the costs

New Technologies for Cervical Cancer

- Liquid Based Pap testing
- Automated Pap smear screening
- HPV Testing
- VIA
- HPV Vaccine

Liquid Based Pap Smear

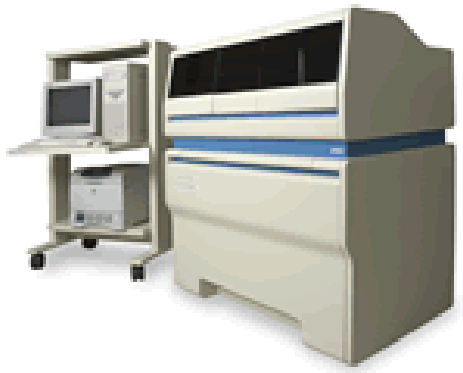
- Rinse collection device in preservative fluid
- Process suspension of cells to deposit a monolayer of cells on a microscope slide

Liquid Based Pap Smear

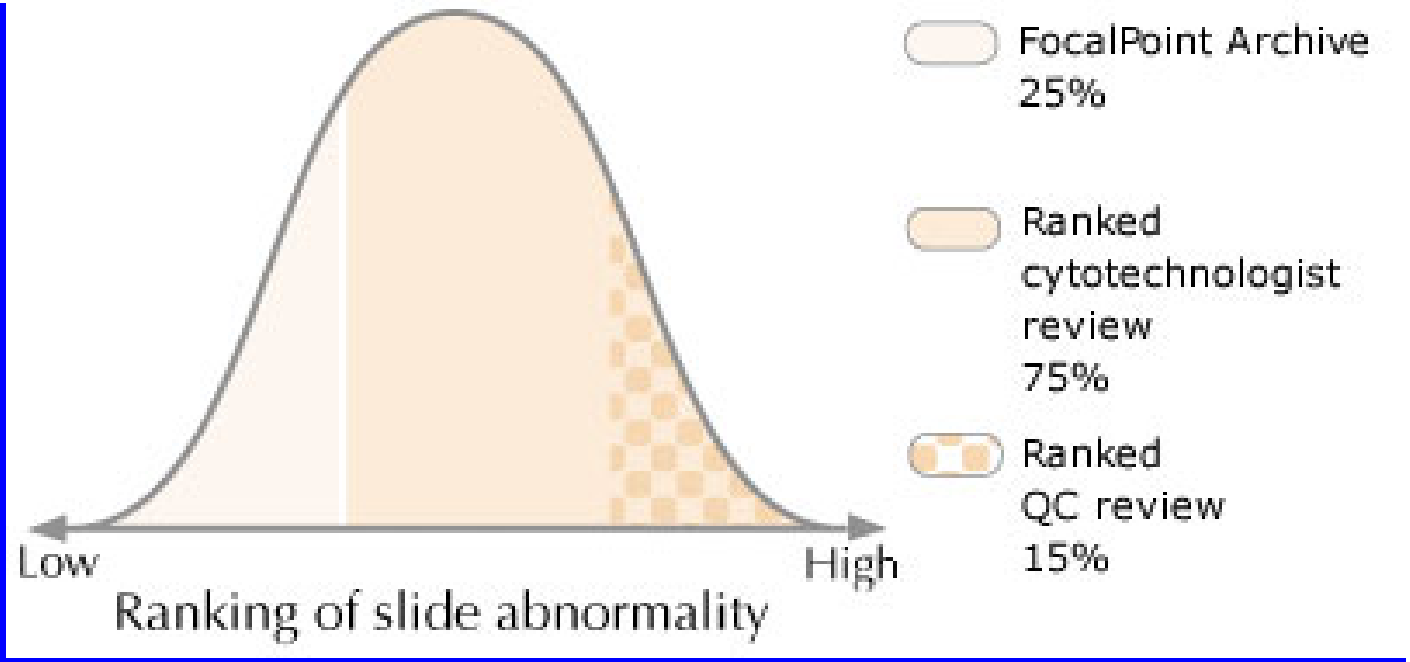
- Gentle dispersion breaks up blood, mucous, non-diagnostic debris, and mixes sample
- Negative pressure pulse draws fluid through filter to collect a thin, even layer of cells
- Monitor flow through filter during collection to prevent cells from being too scant or too dense
- Cells then transferred to a glass slide

Automated Pap Smear Screening

Courtesy of Becton, Dickinson, and Company



- TriPath Care Technologies
  - http://www.tripathimaging.com/usproducts/index.htm



The Lancet Oncology, *2001, Vol.* ***2*** *No. 1, pp. 27–32*

HPV Testing

- The DNAwithPap Test is FDA-approved for routine adjunctive screening with a Pap test for women age 30 and older.
- Digene
  - http://www.digene.com

1. Release Nucleic Acids

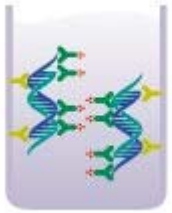
Clinical specimens are combined with a base solution which disrupts the virus or bacteria and releases target DNA. No special specimen preparation is necessary.

2. Hybridize RNA Probe with Target DNA

Target DNA combines with specific RNA probes creating RNA:DNA hybrids.

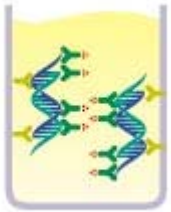
3. Capture Hybrids

Multiple RNA:DNA hybrids are captured onto a solid phase coated with universal capture anbtibodies specific for RNA:DNA hybrids.



4. Label for Detection

Captured RNA:DNA hybrids are detected with multiple antibodies conjugated to alkaline phosphatase. Resulting signal can be amplified to at least 3000-fold.



5. Detect, Read and Interpret Results

The bound alkaline phosphatase is detected with a chemiluminescent dioxetane substrate. Upon cleavage by alkaline phosphatase, the substrate produces light that is measured on a luminometer in Relative Light Units (RLUs).

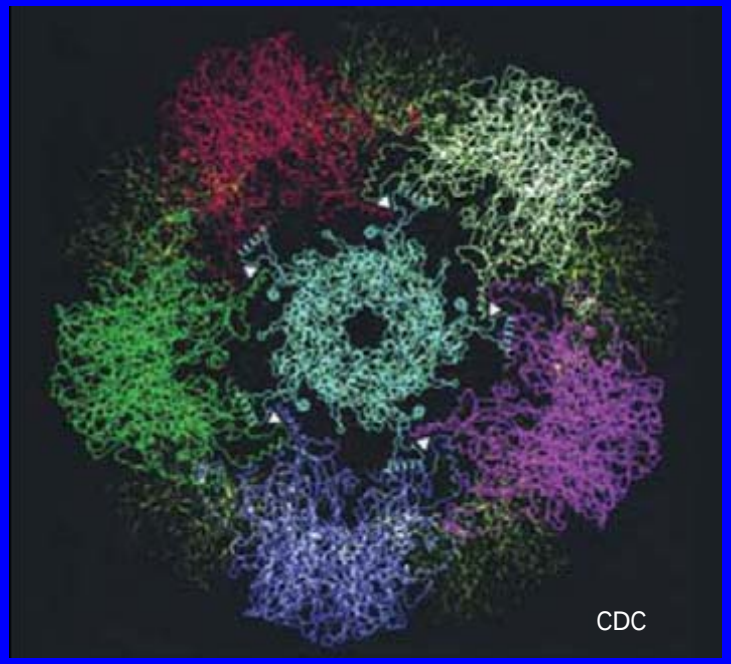
Comparison of Various Techniques

	Sensitivity	Specificity
Pap smear	60-80%	45-70%
Colposcopy	90-100%	20-50%
Digene HPV Test	80-90%	57-89%
VIA	67-79%	49-86%

Comparison of Various Techniques

Pap Test	$10-20
Liquid-based Pap	$50
Automated Pap Smear Screening	$20-60
HPV DNA test	$90
HPV vaccine	$360

HPV vaccine



Virus-like particles (VLP) made from the L1 protein of HPV 16

- approved for use in girls and women aged 9 to 26 years in the US
- not effective to women already exposed to HPV
- Effective on 4 HPV isotypes
- Recombinant technology
- Alternative prevention technique to screening?

Summary of Cancer

- 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

Summary of Cervical Cancer

- Cervical cancer
  - 2nd Leading cause of cancer death in women in world
  - Caused by infection with HPV
  - Precancer→cancer sequence
  - Precancer is very common
- Screening & Detection
  - Pap smear; colposcopy + biopsy
  - Reduces incidence and mortality of cervical cancer
  - Insufficient resources to screen in developing countries
- New technologies
  - Automated reading of Pap smears → reduce FN rate
  - HPV testing
  - VIA

Global Inequities in Cancer Prevention