Breakthroughs and Barriers in Cervical Cancer

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Learning Objectives

Summarize the risk factors for cervical cancer, with a focus on high risk HPV

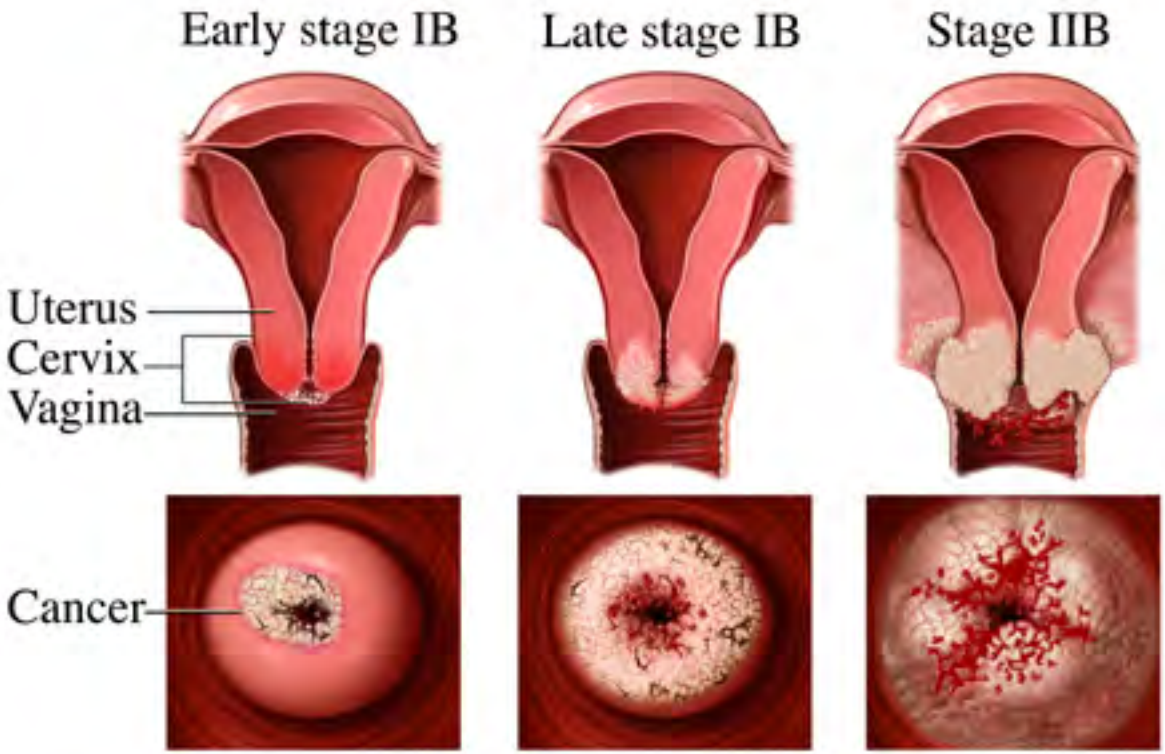
Review current screening guidelines

Understand the basic principles surrounding the HPV vaccine

Summarize key issues that contribute to racial disparities in cervical cancer

Background

Cervical Cancer



webmd.com

Epidemiology

- 10,370 new cases of cervical cancer
- Estimated 3,710 deaths from cervical cancer according to the ACS and based on mortality data from the National Center for Health Statistics
- 50 million women undergo Pap testing in the U.S./ year
- 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up or evaluation

- Approximately 500,000 new cases in the world, mainly in developing countries
- 273,500 deaths worldwide

Jemal, CA Cancer J Clin. 2006

Wright, JAMA. 2002

Risk Factors

•Persistent High risk human papilloma virus (HPV) in patient, partner, or partner's partners
•Three or more lifetime sexual partners.
•First sexual intercourse before age of 18
•Smoking
•Maternal DES (diethylstilbesterol) exposure during pregnancy

•A previous abnormal Pap smear
•Never having had a Pap or not having one in the previous 5-10 years

Human Papilloma Virus (HPV)

- Large group of more than 100 types of the virus
- The most common sexually acquired infection in the United States
- Almost all women who have had sex will have HPV at some time, but very few women will get cervical cancer
- Most HPV infections go away without causing changes in the cervix
- There is no cure for HPV infection, but the cellular changes, warts and lesions caused by the virus can be treated
- Persistent infection with High risk types of HPV can lead to cervical cancer, other genital cancers (anal, vulvar, vaginal and penile) and oral and pharyngeal cancers

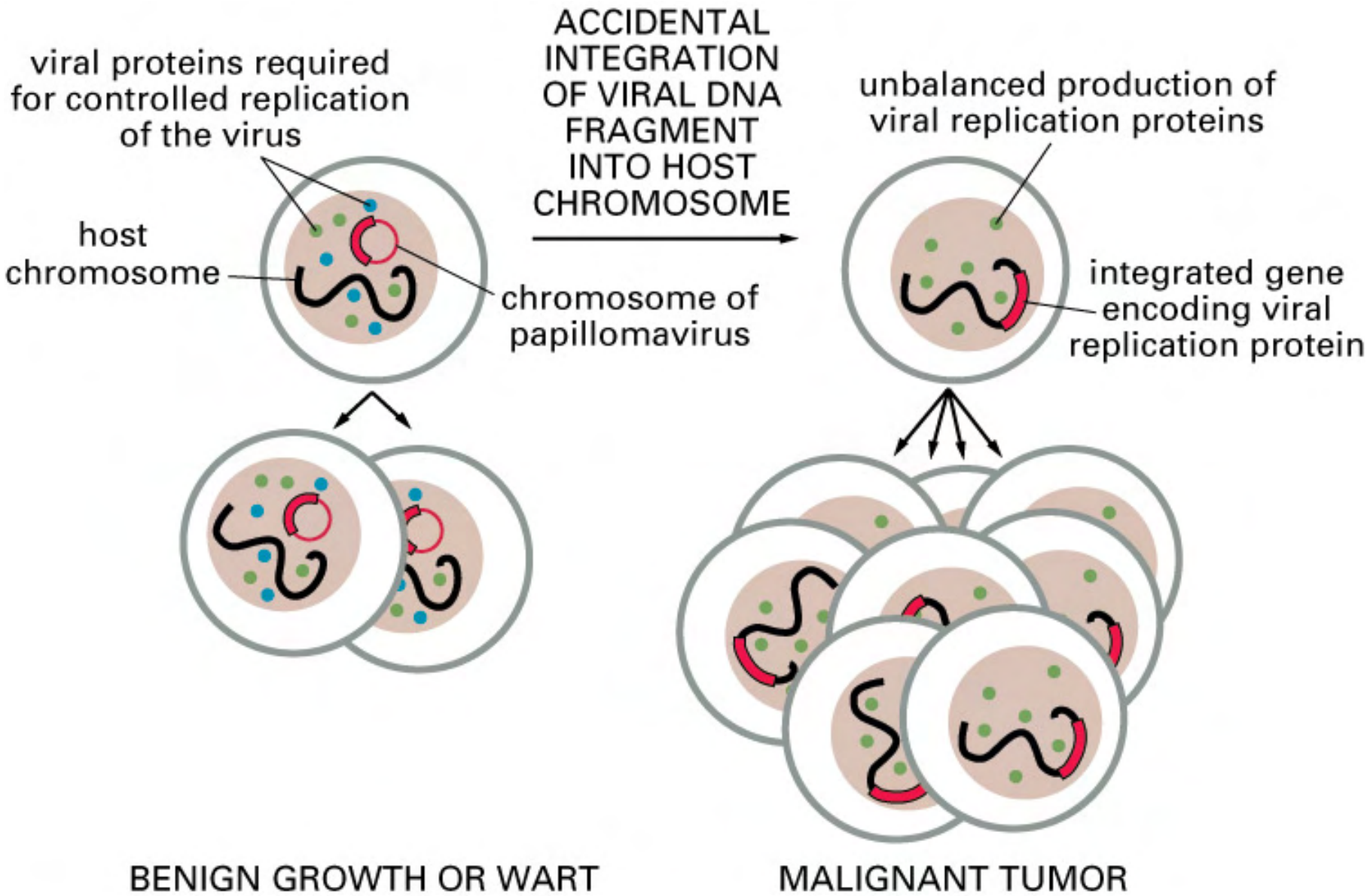


Figure 23–34. Molecular Biology of the Cell, 4th Edition.

Human papilloma Virus (HPV)

Risk	**HPV Subtype**	**Disease process**
Low risk	6, 11, 40, 42, 61, 72	Genital warts
High Risk	16	>50% of high grade dysplasias and both squamous and adenocarcinomas
	18	10% of squamous carcinomas, 50% of adenocarcinoma, 90% of small cell undifferentiated cancers

Munoz, N Engl J Med. 2003

Breakthroughs

1941 - Report of the Pap smear to detect abnormal cervical cells

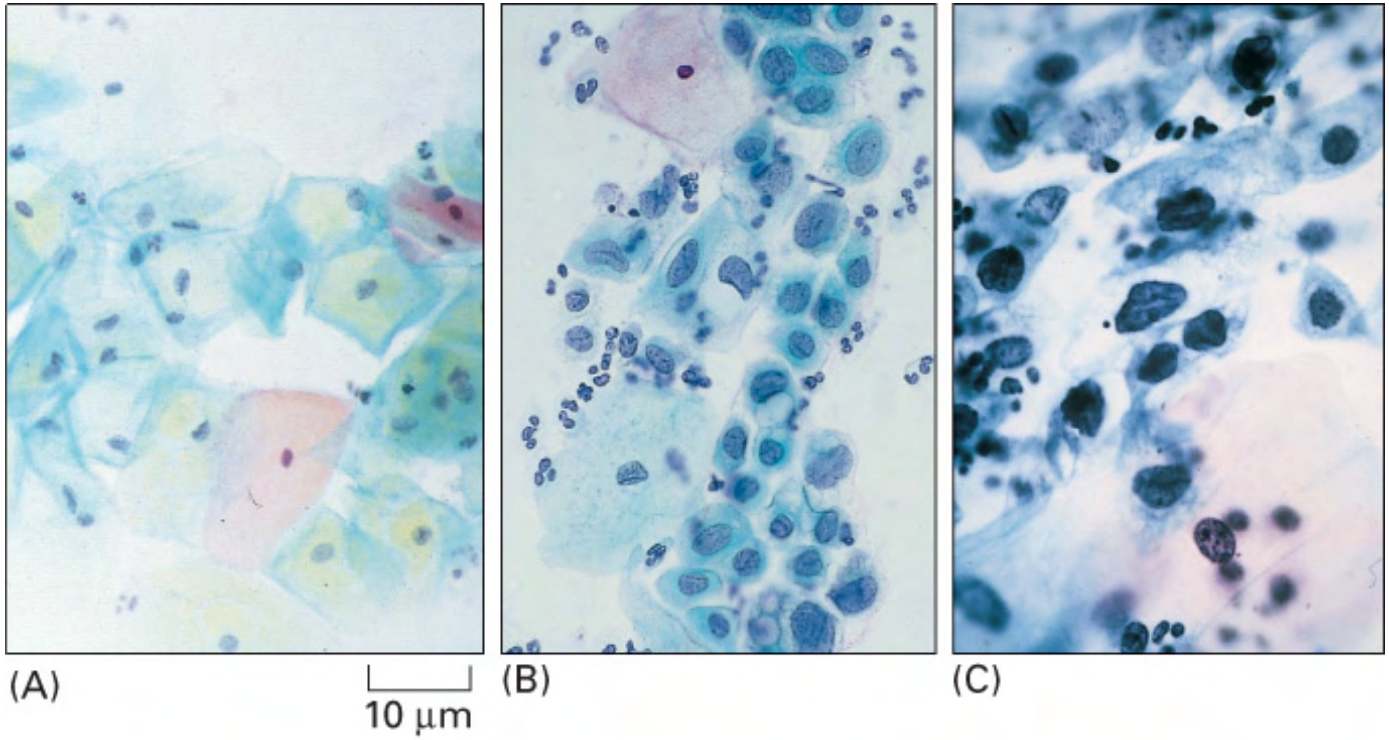
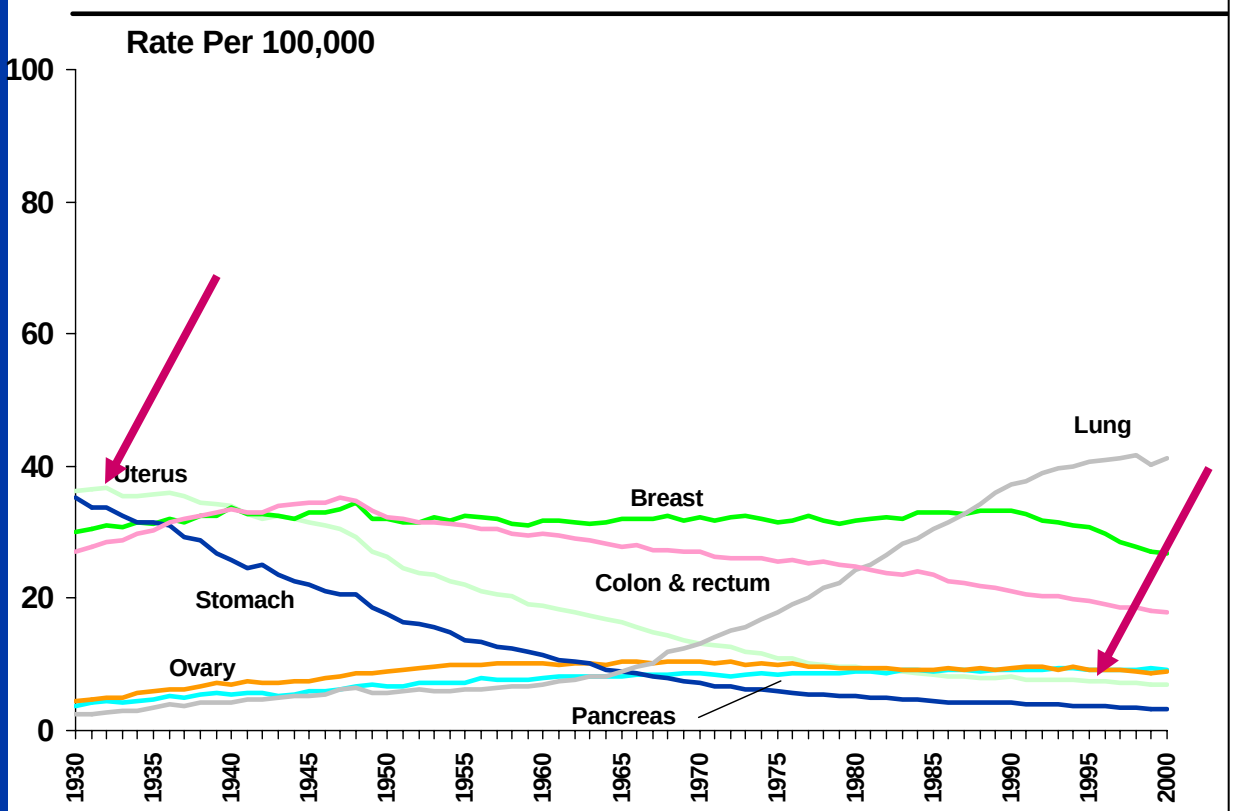


Figure 23–10. Molecular Biology of the Cell, 4th Edition.

Papanicolaou, GN, Traut, HF. Am J Obstet Gynecol, 1941
Alberts, B et al. Molecular Biology of the Cell, 4th ed., 2002

1950's-2000's – Marked decline in death rates from cervical cancer in the US



*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.

1996 - Liquid based cytology

- ThinPrep and SurePath, another liquid based system.
- Sensitivity for the diagnosis of high grade lesions was almost 95 – 100 %
- Reduces the false negative rate of a conventional Pap smear by 60 percent
- Decrease the number of ambiguous interpretations
- Seem to better predict adenocarcinoma in situ and adenocarcinoma
- A single specimen may be used to test for HPV, chlamydia, and gonorrhea infection, in addition to cervical cytology.
- Reflex HPV testing is an option for evaluation of women with cytology showing atypical squamous cells of undetermined significance (ASC-US).

- **Automated slide interpretation**

Cost advantage with new guidelines

- Triennial screening with liquid based cytology and reflex HPV testing for ASCUS cost $95,300 per year of life saved, which was less expensive than triennial combined screening with HPV and cytology for women age 30 ($228,700 per year of life saved) or annual combined screening with HPV and cytology ($2,215,100 per year of life saved).
- Routine HPV testing in women younger than age 30 was not cost-effective.
- Compared with annual conventional cytology, screening at three year intervals with either liquid based cytology with HPV for ASCUS, or combined testing in women age 30 provided improved cervical cancer screening, while reducing overall lifetime costs.

2001 - Bethesda Classification System

Pap Classes	Description	Bethesda 2001
I	Normal	Normal and variants
II	Reactive Changes	Reactive Changes
	Atypia	ASC, ASG
	Koilocytosis	Low Grade SIL
III CIN I	Mild dysplasia	Low Grade SIL
III CIN II	Moderate dysplasia	High Grade SIL
III CIN III	Severe dysplasia	High Grade SIL
IV	Ca in situ, suspicious	High Grade SIL
V	Invasive	Microinvasion (<3mm)
		Frankly invasive (>3mm)
CIN = cervical intraepithelial neoplasia, SIL = squamous intraepithelial lesion		

Progression from normal cervical epithelium to low-grade dysplasia

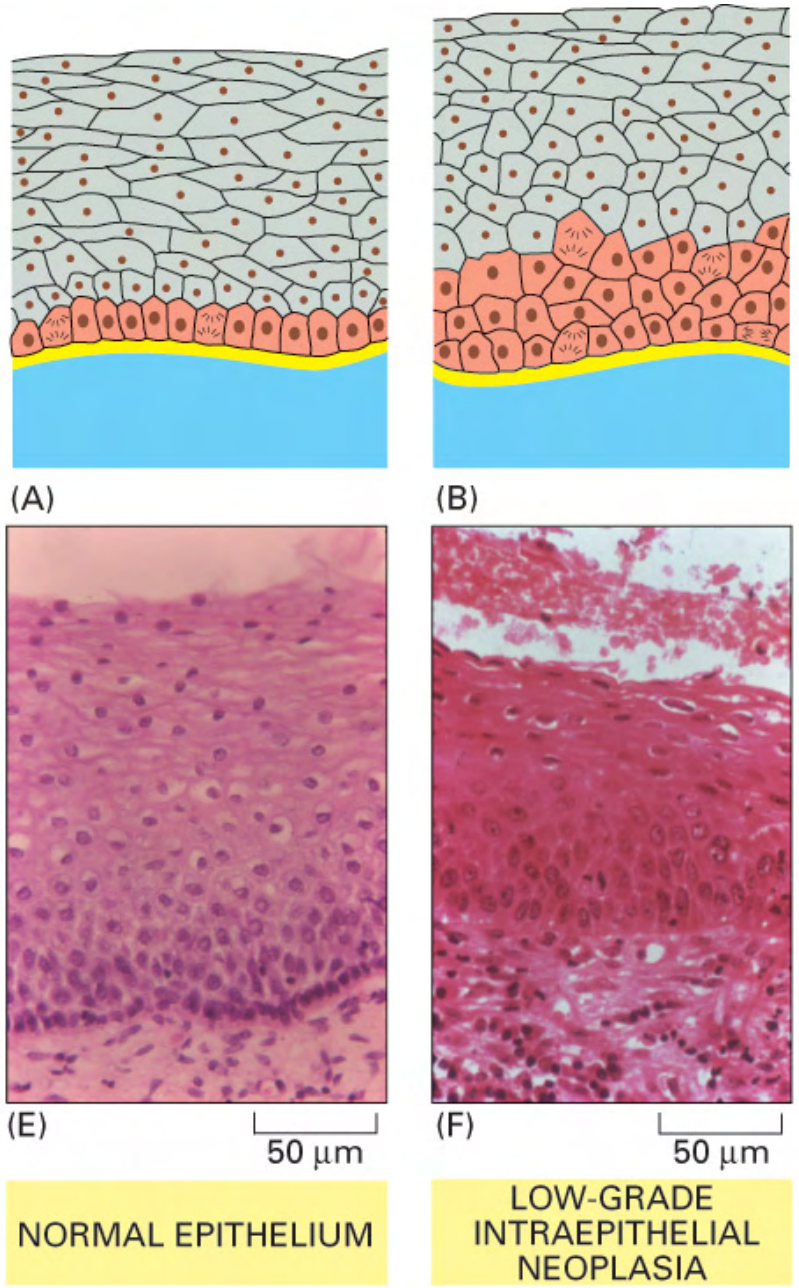


Figure 23–9 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Progression from high-grade dysplasia to cervical cancer

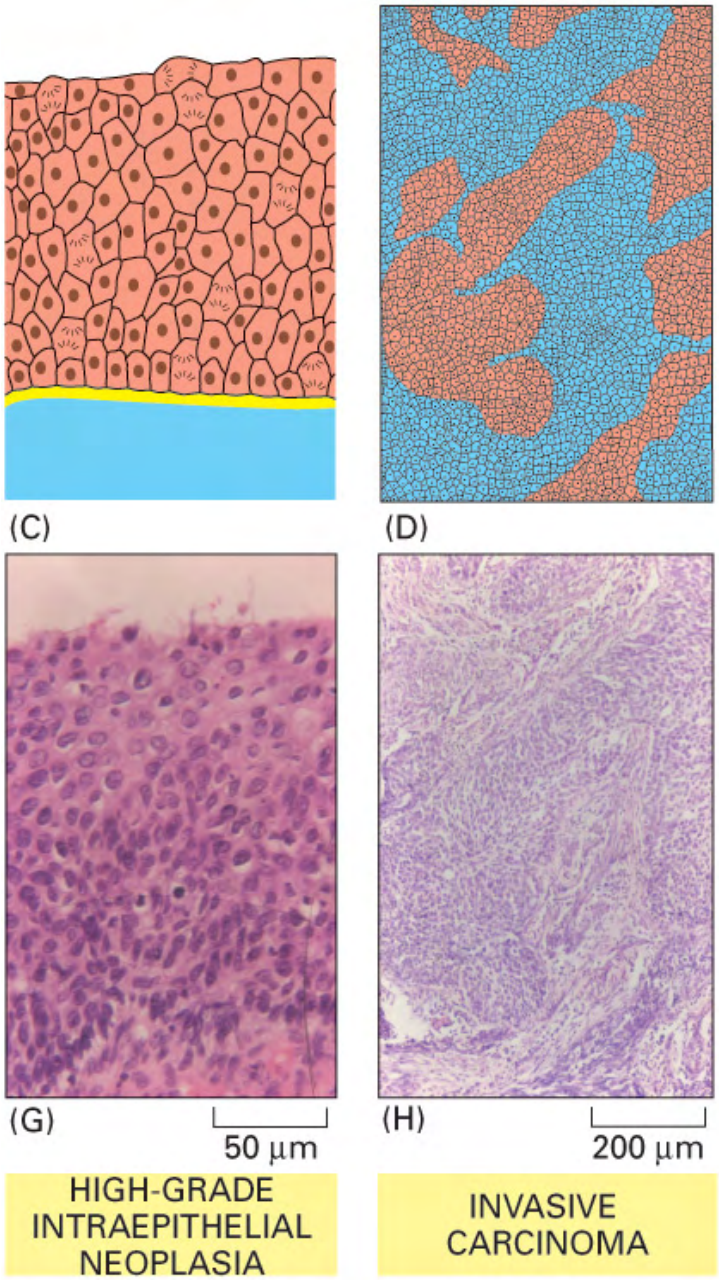


Figure 23–9 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

2002 - Hybrid capture (HC) HPV testing

- The only method for HPV testing of the cervix approved by the United States Food and Drug Administration (FDA)

- RNA probes specific for either high- or low-risk HPV types, both the phenotype and viral quantitation can be related to other investigational parameters such as HIV infection, immunosuppression, and partner number

- The detection method uses a chemiluminescent reaction to provide a semi-quantitative result

2002 – New ACOG and ACS Guidelines

TABLE 1: Comparison of ACS guidelines with the USPSTF Guidelines on Screening for Cervical Cancer

Criteria	***USPSTF guideline***	***ACS 2002 guideline***
Age to initiate screening	Optimum age unknown; within 3 years of onset of sexual activity or age 21	Three years after the onset of sexual activity; no later than age 21
Screening frequency	At least every 3 years	Annually with conventional cytology or every 2 years with liquid-based cytology. After age 30, women with 3 consecutive normal tests may be screened every 2-3 years.
Screening after hysterectomy	No cytologic testing after total hysterectomy for benign condition	No cytologic testing after total hysterectomy for benign condition
Discontinuation	After age 65 (see below)	After age 70 (see below)
Routine screening for HPV infection	Insufficient evidence	Not yet FDA approved. If approved, conventional or liquid-based cytology combined with test for DNA from high-risk HPV subtypes should be performed not more often than every 3 years

USPSTF = U.S. Preventive Services Task Force; ACS = American Cancer Society; HPV = human papillomavirus; FDA = U.S. Food and Drug Administration.

Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002;52:342-62.

U.S. Preventive Services Task Force. Screening for cervical cancer: recommendations and rationale. AHRQ Publication No. 03-515A. Rockville, Md.: Agency for Healthcare Research and Quality, 2003.

Management of Women with Combined Test Screening†

Results of cytology/HPV	Recommended follow-up
Negative / Negative	Routine screening in 3 years
Negative / Positive	Repeat combined test in 6 to 12 months*
ASCUS / Negative	Repeat cytology in 12 months**
ASCUS / Positive	Colposcopy
Greater than ASCUS / Positive or negative	Colposcopy

* If Negative / Negative then resume screening in 3 years
If ASCUS/ Negative then repeat combined test in 12 months
If greater than ASCUS / Negative then colposcopy
If any cytology result / Positive then colposcopy

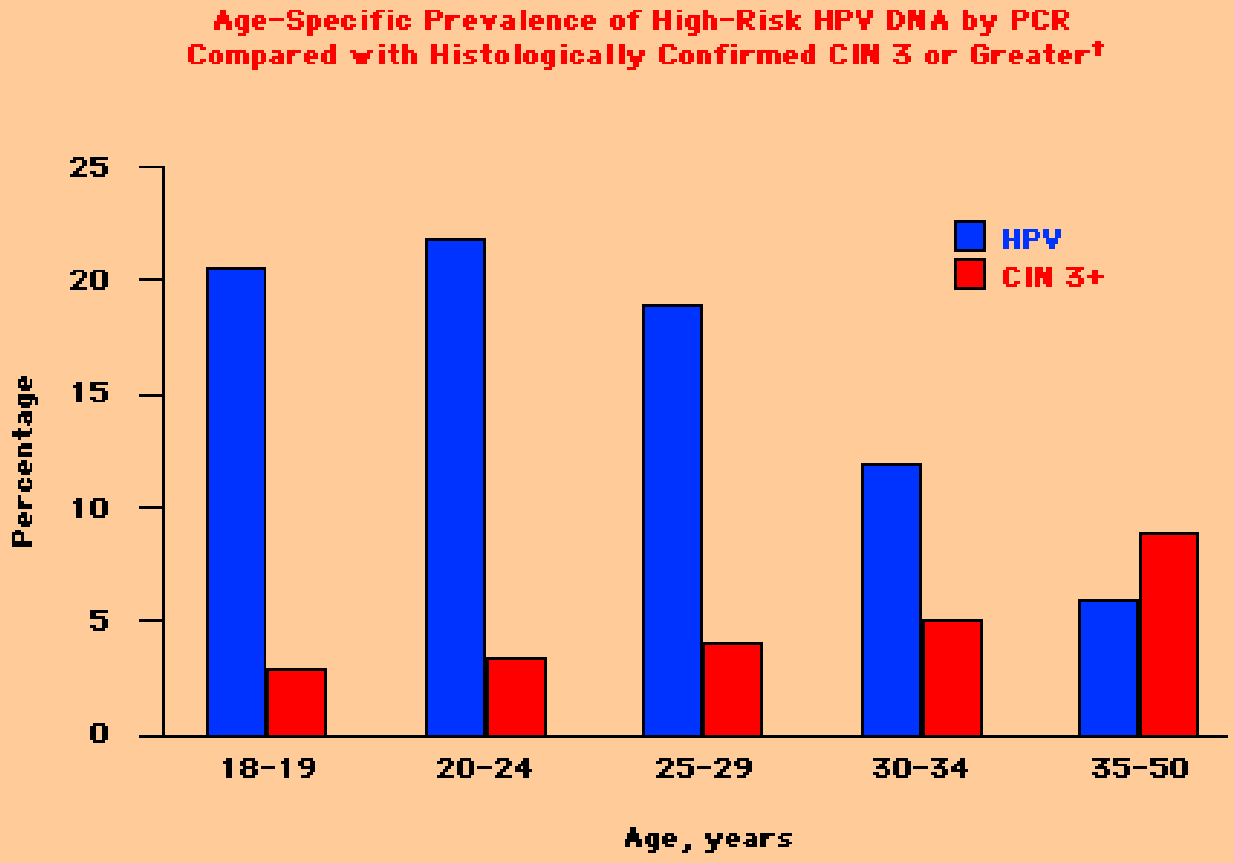
** Follow-up depends on cytology results

HPV = Human papillomavirus, Positive means high risk types are present, Negative means high risk types are not present

ASCUS = Atypical cells of underdetermined significance
Combined test refers to the combination of HPV DNA testing and cervical cytology

†Adapted from Wright, TC, Schiffman, M, Solomon, D, et al. Obstet Gynecol 2004; 103:304.

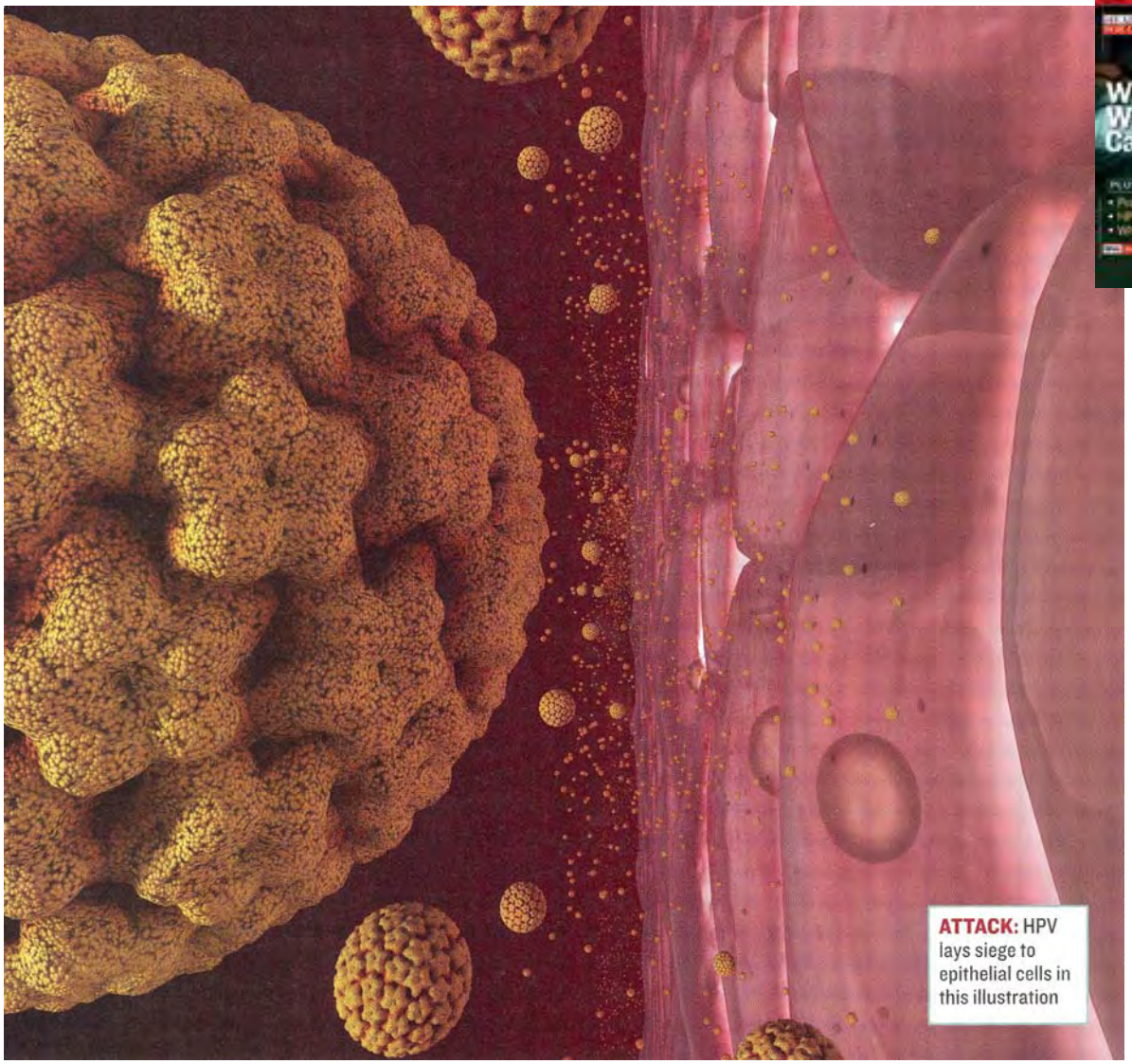
uptodate.com



HPV: human papillomavirus; PCR: polymerase chain reaction; CIN: cervical intraepithelial neoplasia.
† Modified from: Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, Koutsky LA. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA 2002; 288:1749.

uptodate.com

2006 – HPV Vaccine

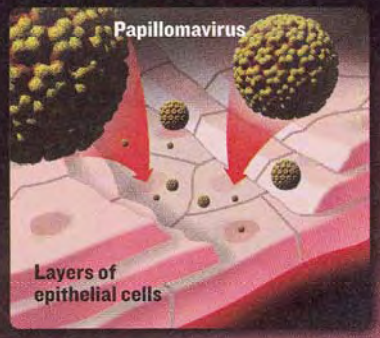


ATTACK: HPV lays siege to epithelial cells in this illustration

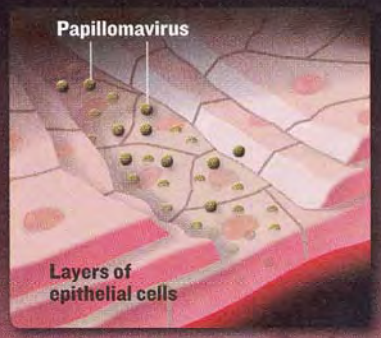
How the 'Cancer Shot' Works

More than 99 percent of cervical-cancer cases are the product of long-term infection with human papillomavirus, or HPV. How it happens—and how the vaccine prevents it:

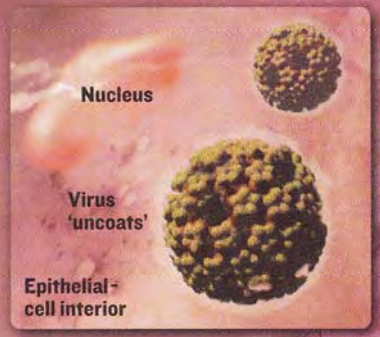
THE HPV INVASION



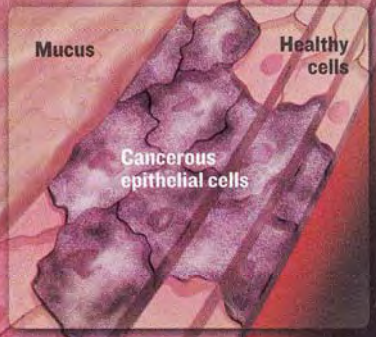
The virus, passed by skin-to-skin contact, needs to penetrate deeply into the lining of the cervix to establish a chronic infection. Sex, which abrades the lining, or a sore can provide a breach.



Once inside the cervical lining, the virus attaches to the epithelial cells. Mistaking it for a nutrient or other molecule that is normally in the environment, the cells take it in.



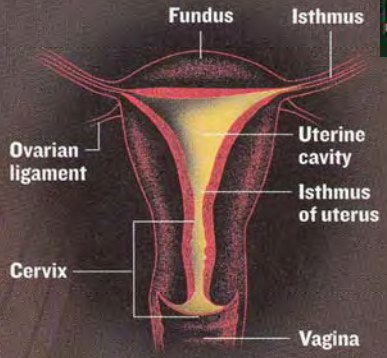
The HPV, which is housed in a protective shell made up of a viral protein called L1, "uncoats" and releases its genetic information into the host cell to infect it.



Viral genes E6 and E7 then disable the cell's tumor suppressors, allowing for abnormal cell division. It takes 12 to 15 years on average for the lesions to become cancerous.

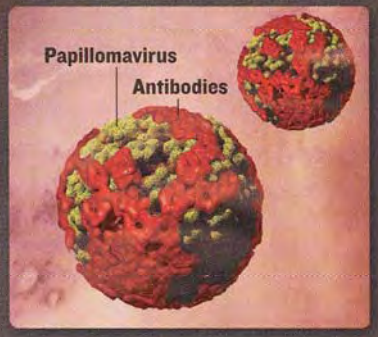
THE BATTLEFIELD

Cervical area: The HPV travels through the vagina to the cervix, which sits at the base of the uterus.



ANTIBODIES IN ACTION

The HPV vaccine, essentially an empty shell made of the L1 protein, works by triggering the production of



antibodies that neutralize the virus. If actual HPV appears in the body later, the antibodies cling to it, interfering with its ability both to bind to the cell and to release its genetic material.

SOURCES: DOUG LOWY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH. GRAPHIC BY STANFORD KAY—NEWSWEEK, TEXT BY MARC BAIN.

Barriers

The good news with the bad…

- The first decrease in the total number of cancer deaths since national mortality record keeping was instituted in 1930

- In analyses by race and ethnicity, African American men and women have 40% and 18% higher death rates from all cancers combined than White men and women, respectively

Jemal, CA Cancer J Clin. 2006

Cervical Cancer SEER Data Rates per 100,00, age-adjusted 2000 US population

All	White	African American	Asian American/ Pacific Islander	American Indian/ Alaskan Native	Hispanic/ Latino
2.8	2.5	5.3 (TN = 7.1)	2.7	2.6	3.5

Jemal, CA Cancer J Clin. 2006

Higher rates of cervical cancer deaths in certain populations

- Approximately to 9% of women who were diagnosed with cervical cancer went untreated
- Advanced stage of disease, older age, lower income, and single status were related factors
- Other issues that limit access to cancer care are comorbid conditions and the inability to pay for treatment, resulting in delays in care

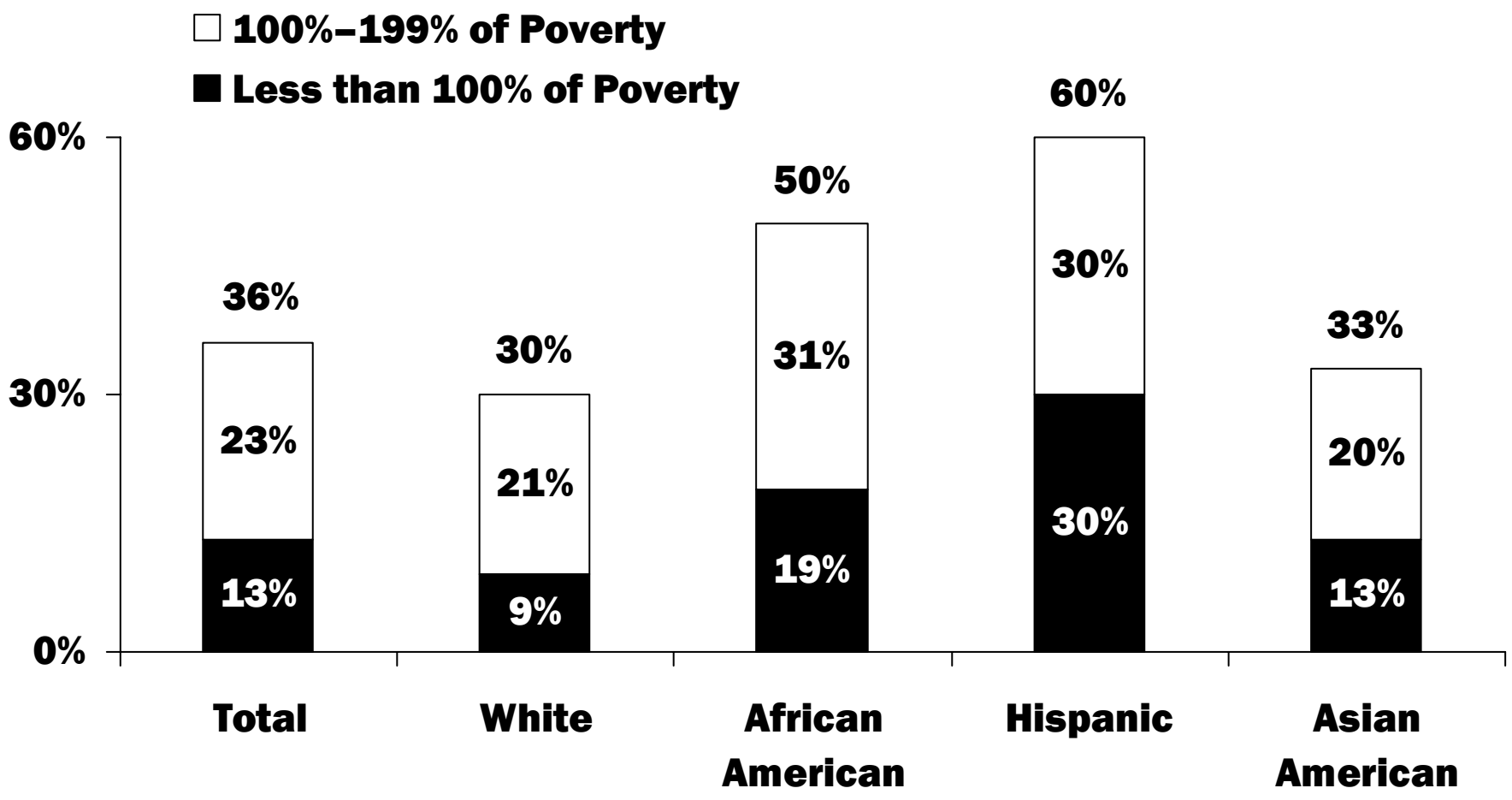
Trimble, Gynecol Oncol, 2005

The role of poverty and cervical cancer

- Poverty affects a woman's view towards providers, and her desire and ability to undergo conventional therapies
- Women who are poor seek care when they are symptomatic and more likely to be at advanced stages of disease.
- In addition, many poor women experience humiliation within some facilities that may be partly due to their inability to pay. A woman in poverty is more likely to have diminished self-esteem and fatalistic feelings about the diagnosis of cancer.

Parham, *Cancer. 1995*

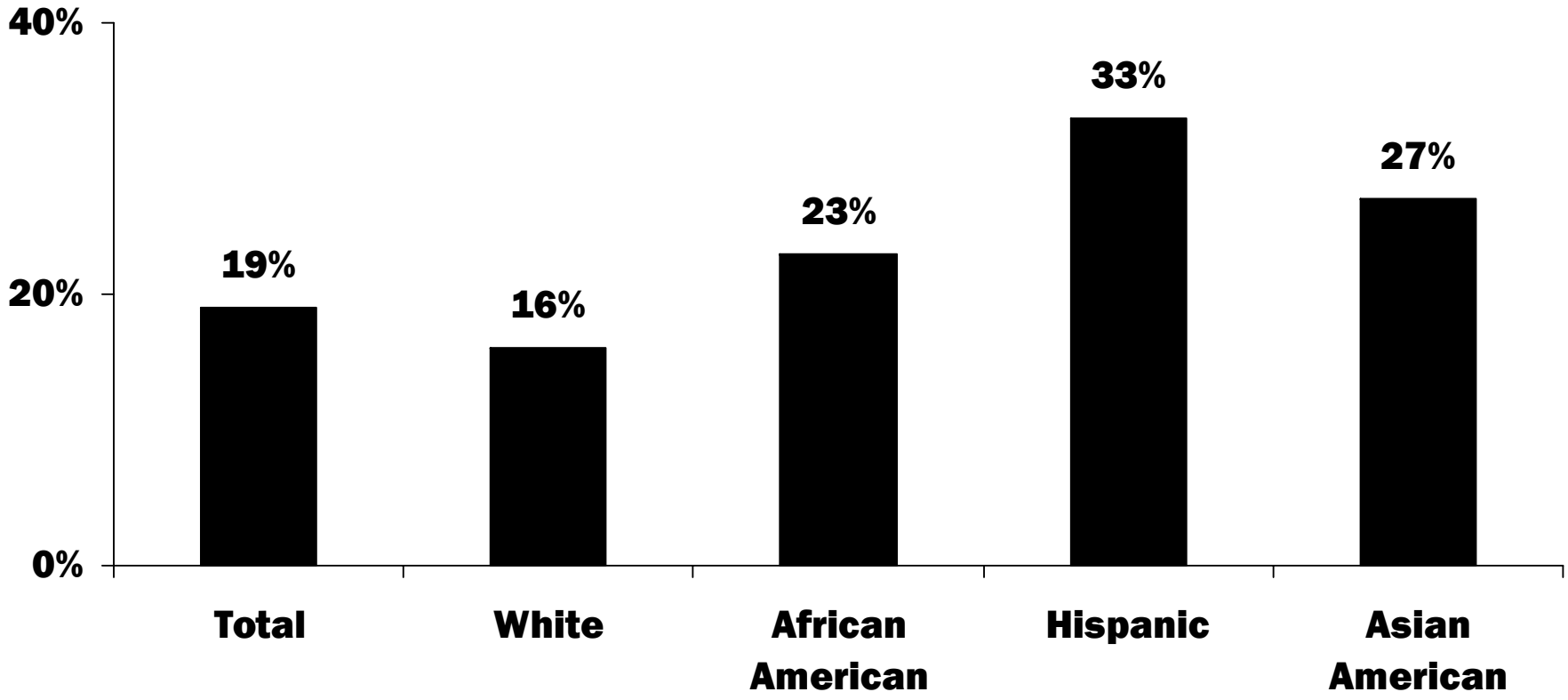
Poverty Status, by Race/Ethnicity



Source: The Commonwealth Fund 2001 Health Care Quality Survey.

Minorities Face Greater Difficulty in Communicating with Physicians

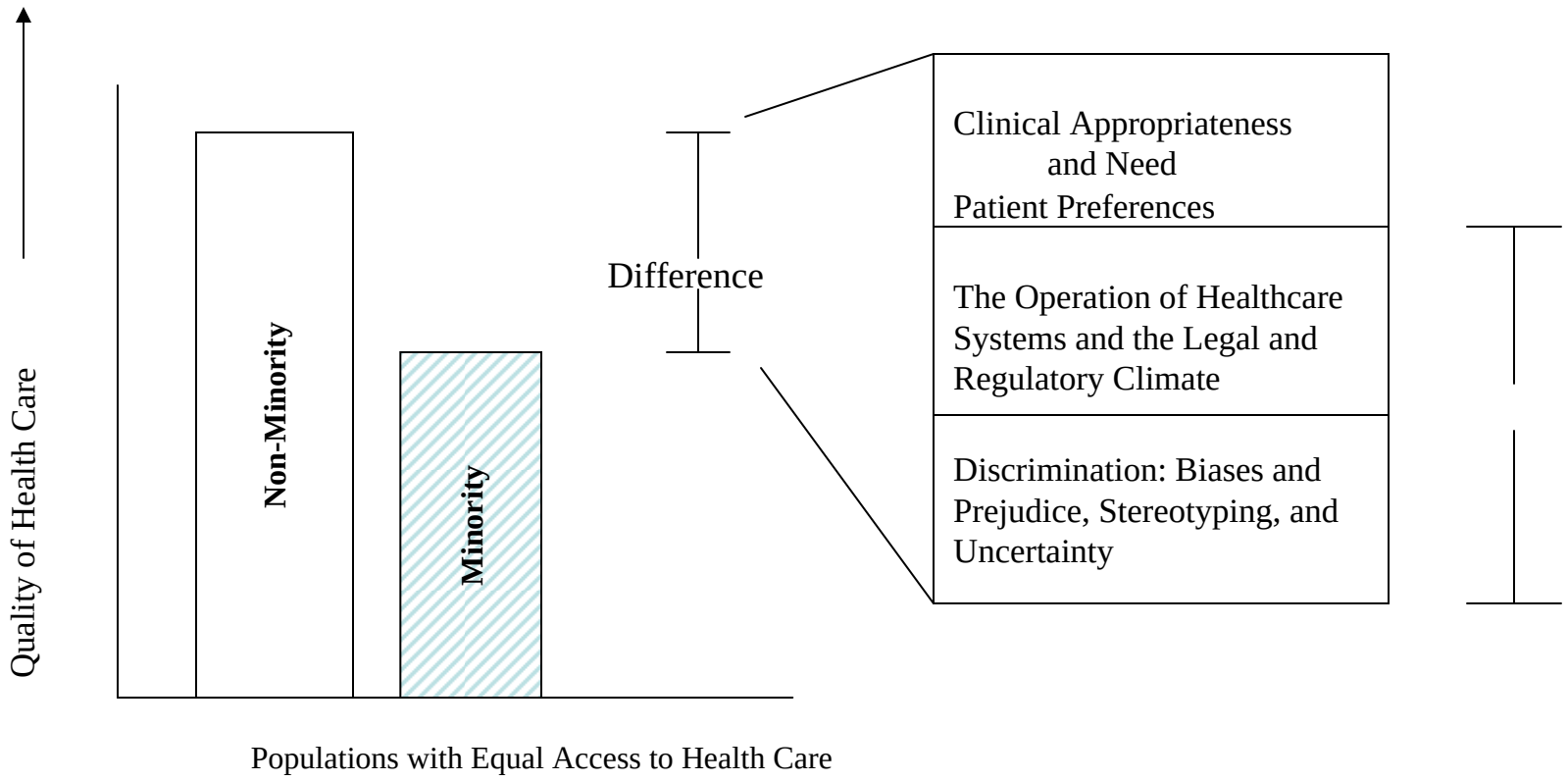
Percent of adults with one or more communication problems*



Base: Adults with health care visit in past two years.
* Problems include understanding doctor, feeling doctor listened, had questions but did not ask.

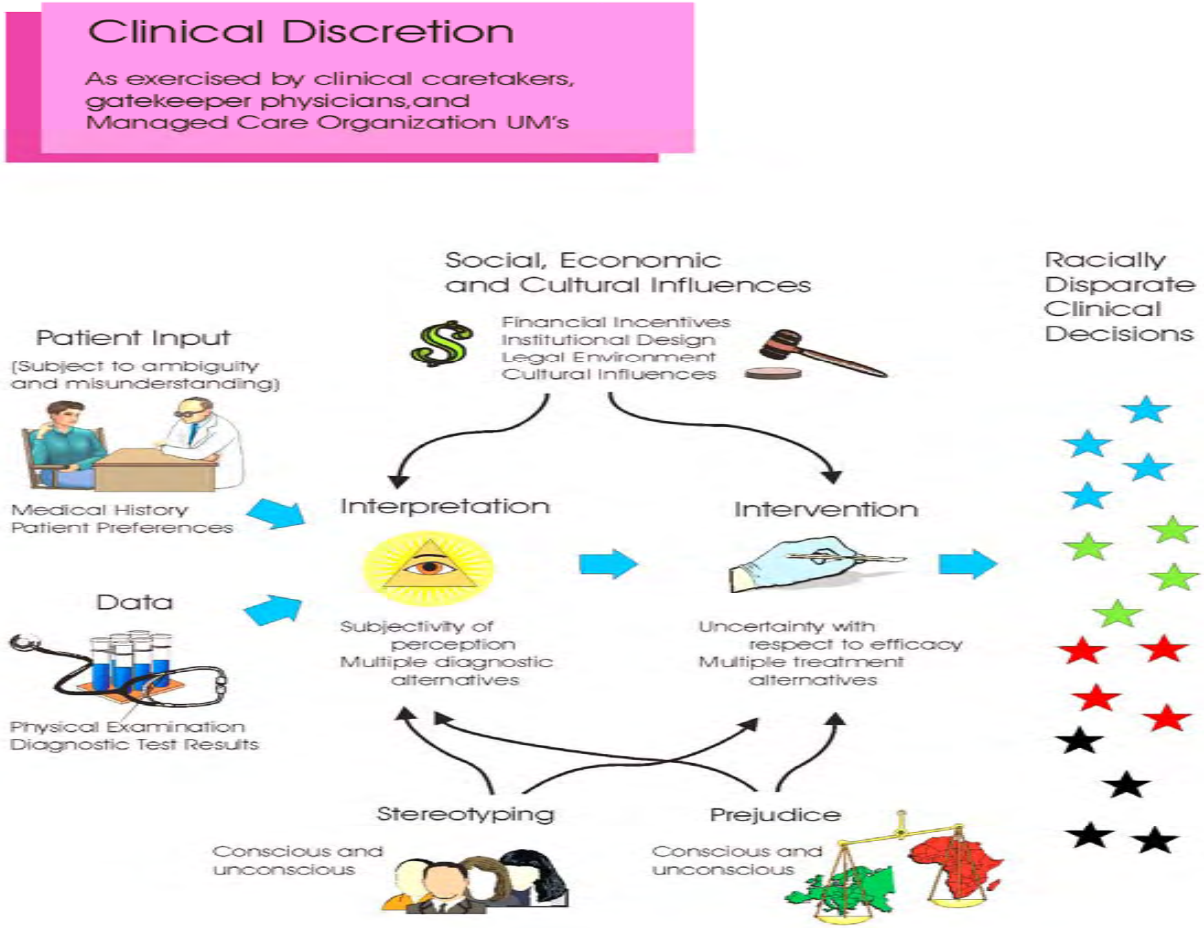
Source: The Commonwealth Fund 2001 Health Care Quality Survey.

Differences, Disparities, and Discrimination: Populations with Equal Access to Health Care



Source: Institute of Medicine: Unequal Treatment

Provider- Patient Interaction



Source: Institute of Medicine: Unequal Treatment

Models of Cultural Competency
Campinha-Bacote's Culturally Competent Model of Care:
1) Cultural awareness: cultural sensitivity and avoiding cultural bias
2) Cultural knowledge: understanding the cultural world view and the theoretical/conceptual framework of the patient
3) Cultural skill: skill-set to access an individual's background and formulate a culturally relevant treatment plan
4) Cultural encounters: cultural interaction with clients from culturally diverse backgrounds

Berlin Fowke's L-E-A-R-N model:	**Like's Ethnic Minority Patients and Families model:**
L: Listening to the patient's perspective	**E:** Explain symptoms
E: Explaining and sharing one's own perspective	**T:** Treatments
A: Acknowledging differences and similarities between these two perspectives	**H:** Helpers-healer, Family, Friends
R: Recommending a treatment plan	**N:** Negotiate options
N: Negotiating a mutually agreed-on treatment plan.	**I:** Intervention
	C: Collaborate on plan

Take home messages to the public

- Make regular appointments to see your provider
- Get your Pap tests!

11% of United States women report that they do not have regular cervical cancer screenings

In the United States, the Pap test saves the lives of 70% of the women who might have died from cervical cancer

Recent advances in screening and work on a vaccine could help the effort to wipe out cervical cancer.

Take home messages to providers

- Remember your basic medical training and keep up with medical advances
- Spend quality time with your patients
- Be culturally competent

Any visible lesion on the cervix should be biopsied, even in the presence of a normal PAP or other screening

Engage and educate your patients to ensure that cervical cancer rates continue to decline

Resources

- American Cancer Society www.cancer.org
- National Cancer Institutes www.cancer.gov
- American Society for Coloposcopy and Cervical Pathology www.asccp.org (online CME)
- Women's Cancer Netowrk and the Gynecologic Oncology Foundation www.wcn.org

Resources

- Centers for Disease Control and Prevention. REACH 2010. http://www.cdc.gov/reach2010/index.htm
- American Medical Association. Cultural Competence Compendium. : Chicago, IL (Product Number OP209199, 1-800-621-8335). 1999
- Department of Health and Human Services. Race and Health: How to Reach the Goals. http://www.raceandhealth.hhs.gov/3rdpgBlue/Cancer/3pgGoalsCancer.htm