

Biology of Cancer and AIDS



Lecture 16: HPV & Cancer

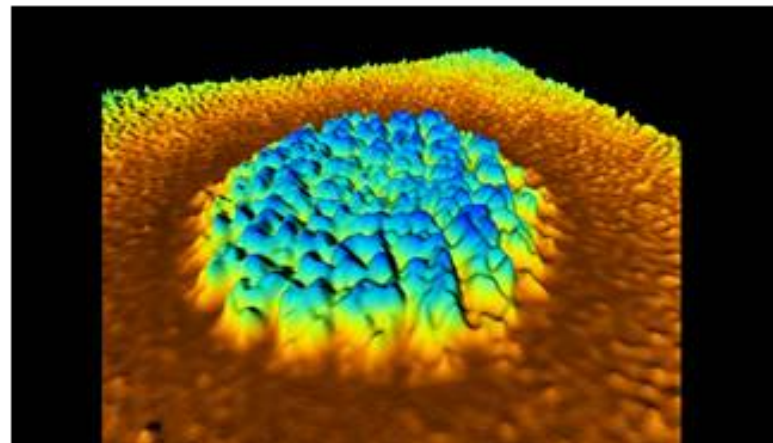
Human papillomavirus vaccination not linked to increase in sexually transmitted infections in adolescent females

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Level 2 (mid-level) evidence

Routine human papillomavirus (HPV) vaccination is recommended for all children 11-12 years old and is approved in adolescents and young adults up to 26 years old for the main purpose of preventing HPV associated cancers, particularly cervical cancer (*MMWR Recomm Rep.* 2014;63[RR-05]:1; *CACancer J Clin.* 2007;57[1]:7; *Obstet Gynecol.* 2014;123[3]:712; *Pediatrics.* 2012;129[3]:602). Though vaccination rates have been steadily increasing since the quadrivalent HPV vaccine first received FDA approval for girls and women in 2006, missed vaccination opportunities are common. In 2013 vaccine coverage for girls aged 13-17 years was 57.3% for ≥ 1 dose and only 37.6% received all three



Study results suggest that HPV vaccination is not associated with an increase in sexually transmitted infections in adolescent females.

Figure. HPV vaccine 3-dose coverage among girls in high-income countries²



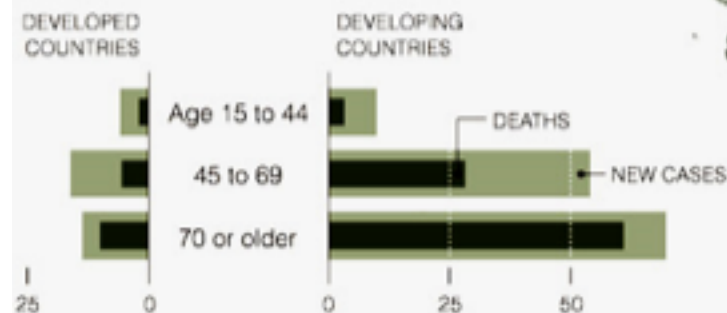
Source: CDC. Human Papillomavirus (HPV). For Clinicians. HPV: You Are the Key to Cancer Prevention. Page last updated September 30, 2015. cdc.gov/hpv/hcp/index.html

An Uneven Killer

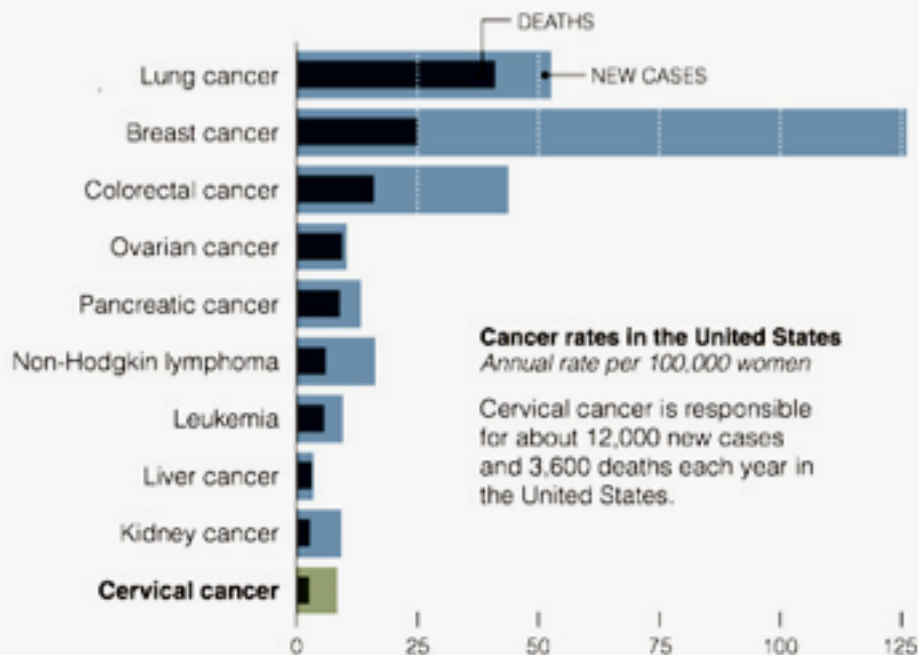
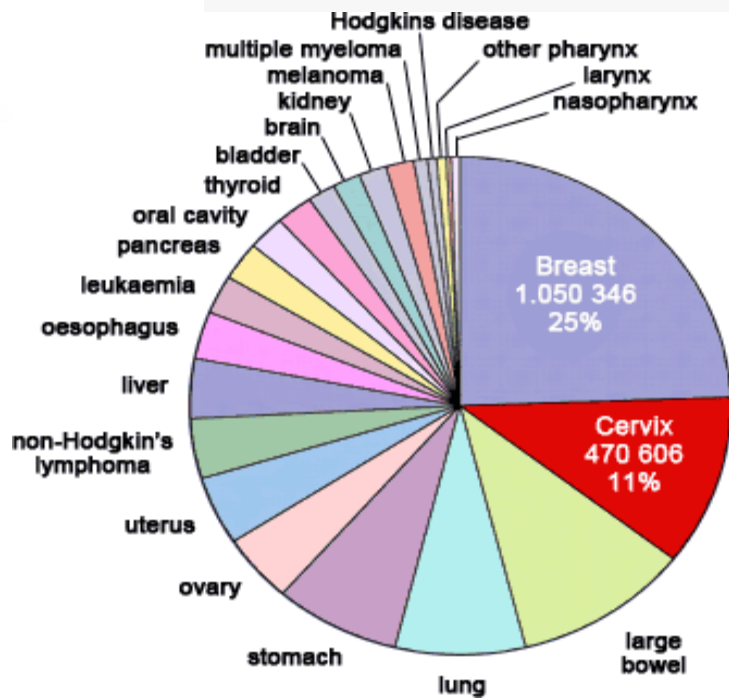
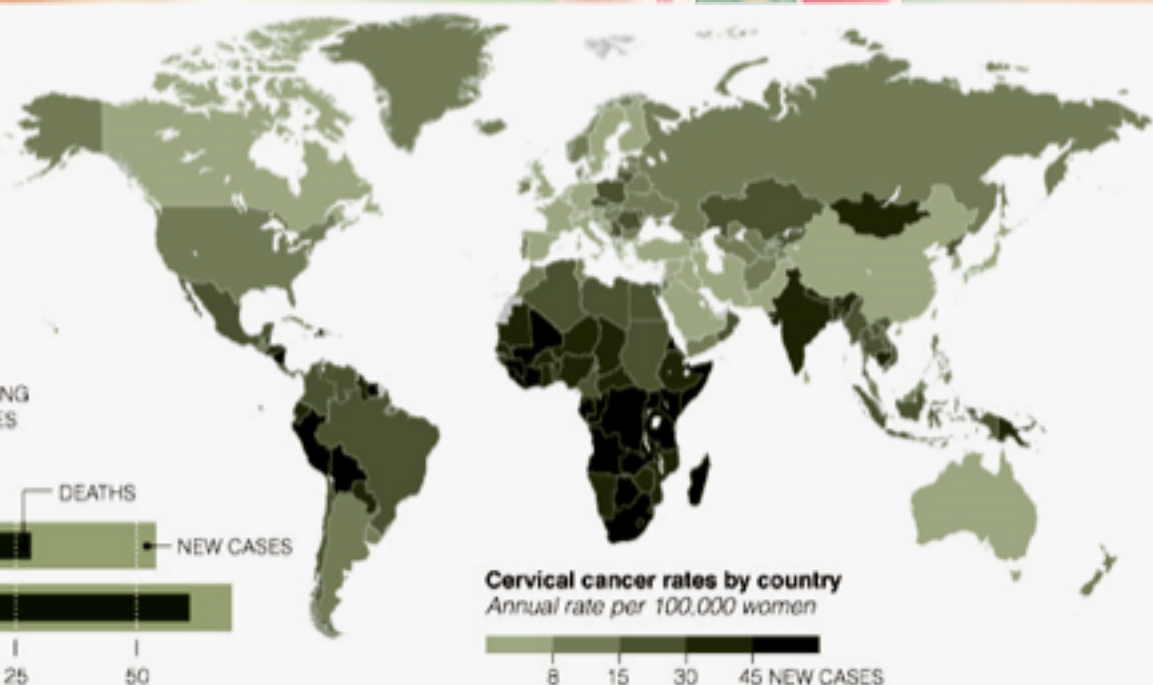
Cervical cancer is a major killer throughout the developing world, particularly Africa, but is rare in developed countries because it is almost always preventable through regular Pap smears, which detect precancerous cells.

Cervical cancer rates worldwide

Annual rate per 100,000 women



Sources: World Health Organization; National Cancer Institute



Cancer rates in the United States

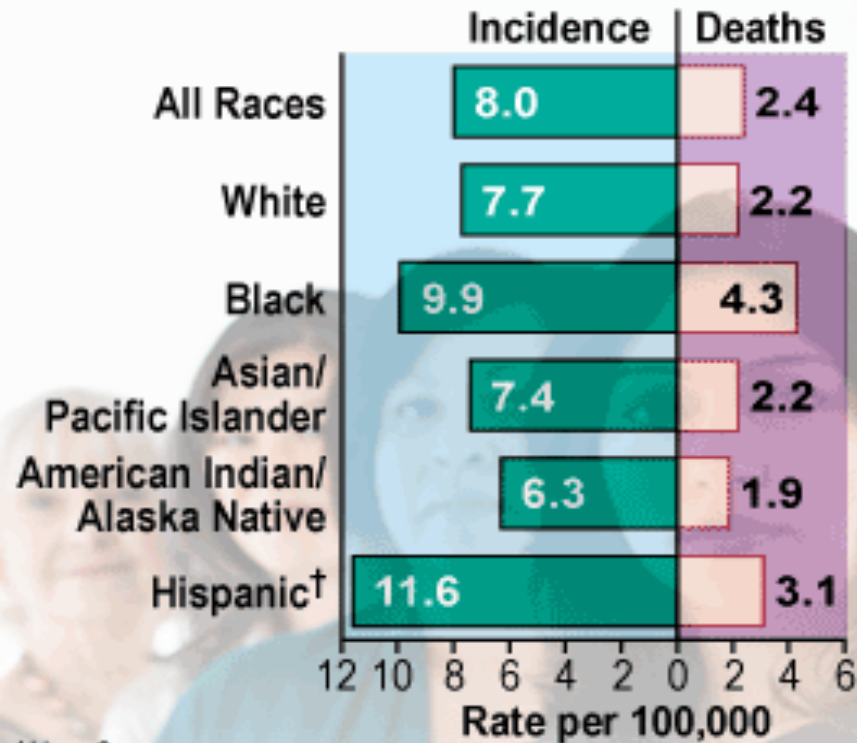
Annual rate per 100,000 women

Cervical cancer is responsible for about 12,000 new cases and 3,600 deaths each year in the United States.

Cervical Cancer

- ~ 510,000 cases of cervical cancer are reported each year with nearly 80% in developing countries
- 68,000 in Africa, 77,000 in Latin America, and 245,000 in Asia.
- Every year ~300,000 women die of this disease worldwide

Cervical Cancer Incidence[^] and Death Rates* by Race and Ethnicity, United States



[^]New Cases

*Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups— Census P25-1130).

[†]Hispanic origin is not mutually exclusive from race categories. Incidence counts cover approximately 96% of the U.S. population. Death counts cover 100% of the U.S. population. Use caution in comparing incidence and death counts.

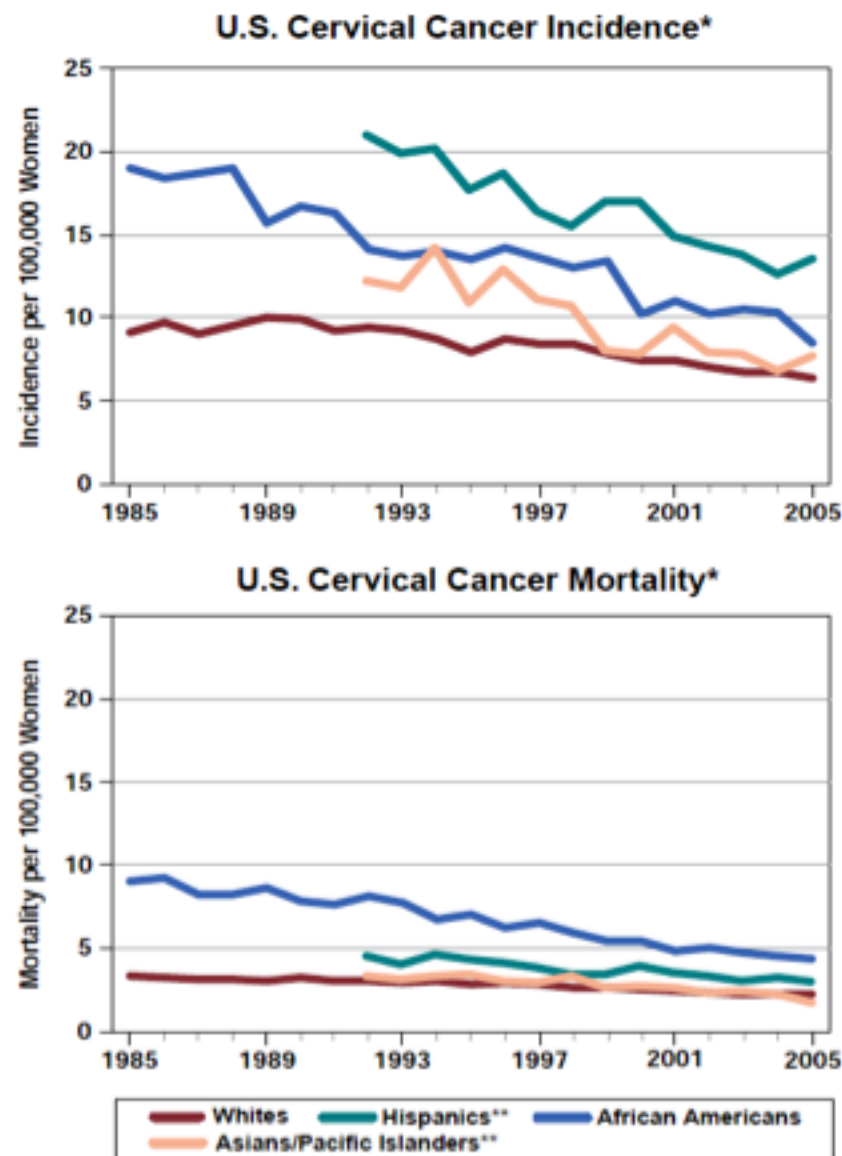
Source: United States Cancer Statistics: 1999–2006 Incidence and Mortality pre-release data.

Incidence and Mortality of Cervical Cancer

Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2010:

New cases: 12,200

Deaths: 4,210



*Significant data for American Indians/Alaskan Natives not available.

**Data for Hispanics and Asians/Pacific Islanders not available before 1992.

Uterine and Cervical Cancer Locations

Normal cervix



Normal cervical cells



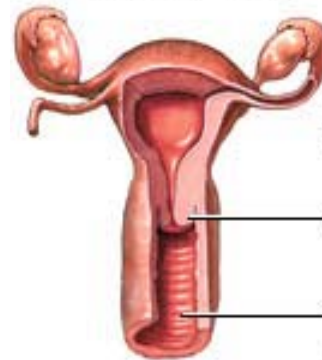
Cervical dysplasia



Cancerous or pre-cancerous cervical cells



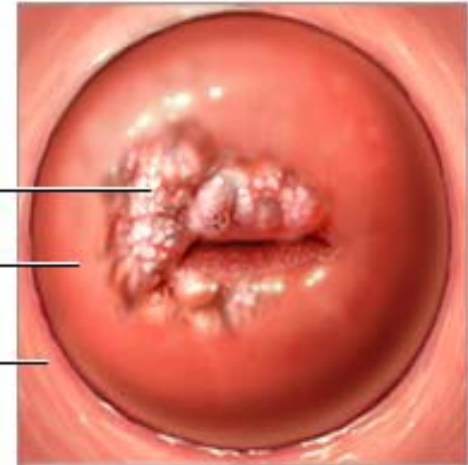
Anterior view



Cancer tissue

Cervix

Vaginal wall



Cervix viewed through speculum with patient in lithotomy position



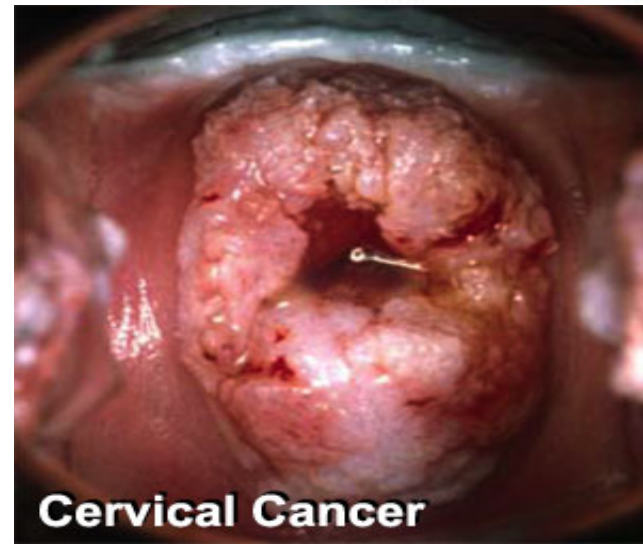
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Cervical cancer

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Cervical Cancer

Risk Factors of Cervical Cancer

- ☐ HPV infection (human papillomavirus)
- ☐ Multiple sex partners (high risk male partner)
- ☐ Started having sex before age 18
- ☐ Other STIs (HIV, syphilis, *Chlamydia*)
- ☐ Smoking
- ☐ Multiple pregnancies
- ☐ Oral contraceptives
- ☐ Diet
- ☐ Family history
- ☐ Low socioeconomic status
- ☐ Molecular genetic factors: p53, Rb mutations

Cervical Cancer History

Epidemiologists working in the early 20th century noted the following:

- ☐ Cervical cancer was common in female sex workers
- ☐ It was rare in nuns, except for those who had been sexually active before entering the convent
- ☐ It was more common in the second wives of men whose first wives had died from cervical cancer
- ☐ It was rare in Jewish women



Prevalence of HPV Infection

- ❑ **Currently, there are ~20 million people infected with the various types of HPV in the United States alone**
- ❑ **~6.2 million new cases of HPV infection occurring annually**
- ❑ **~75% to 80% of sexually active individuals will become infected with HPV within their lifetime**
- ❑ **Currently there are over 100 identified types of HPV, roughly 40 of which cause mucosal infection**
- ❑ **There are 18 different types of high-risk HPV which can be oncogenic**

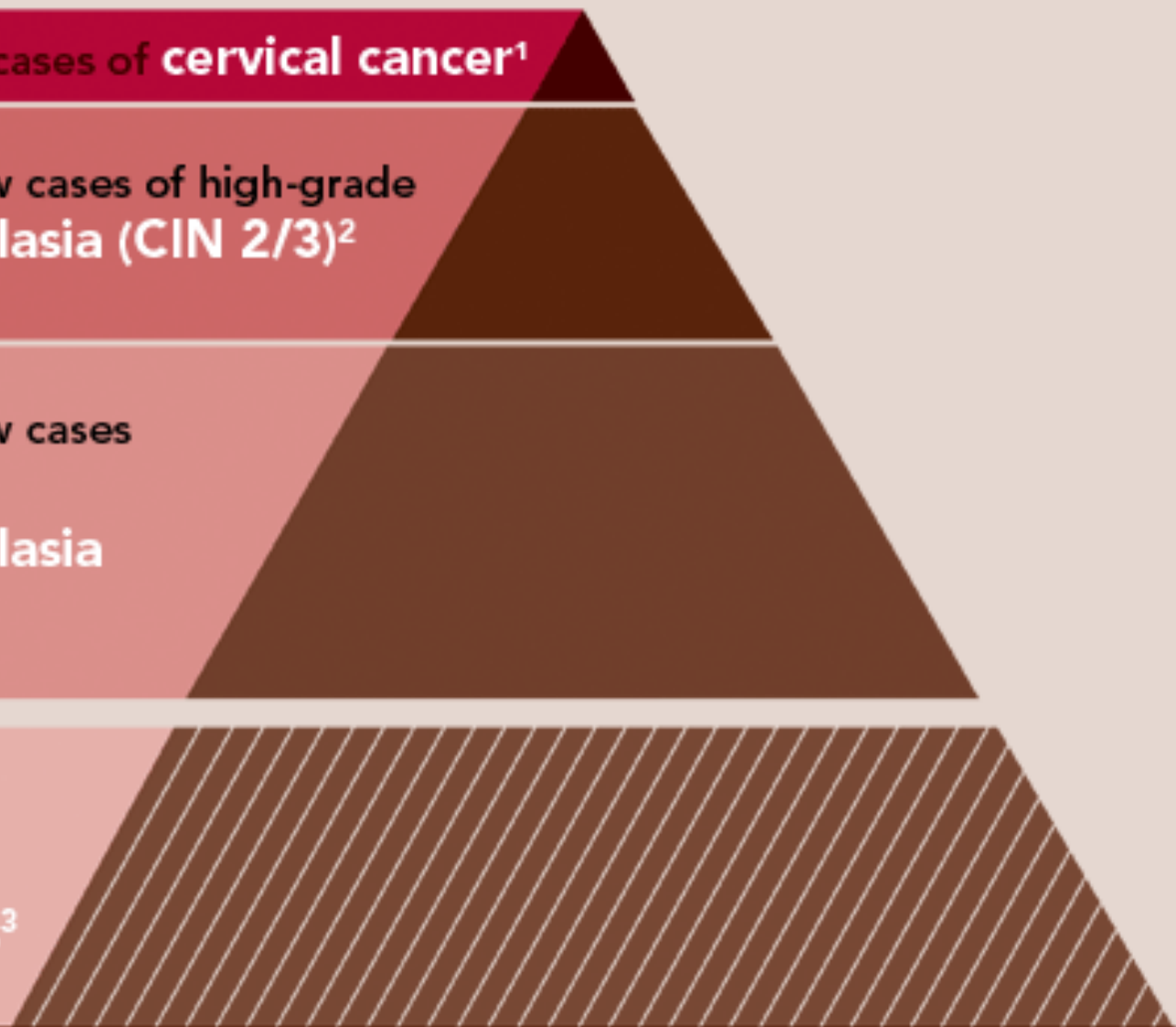
Prevalence & Consequence of HPV infection and Cervical Cancer Cases (Worldwide)

490,000 new cases of **cervical cancer**¹

10 million new cases of high-grade cervical dysplasia (CIN 2/3)²

30 million new cases of low-grade cervical dysplasia (CIN 1)²

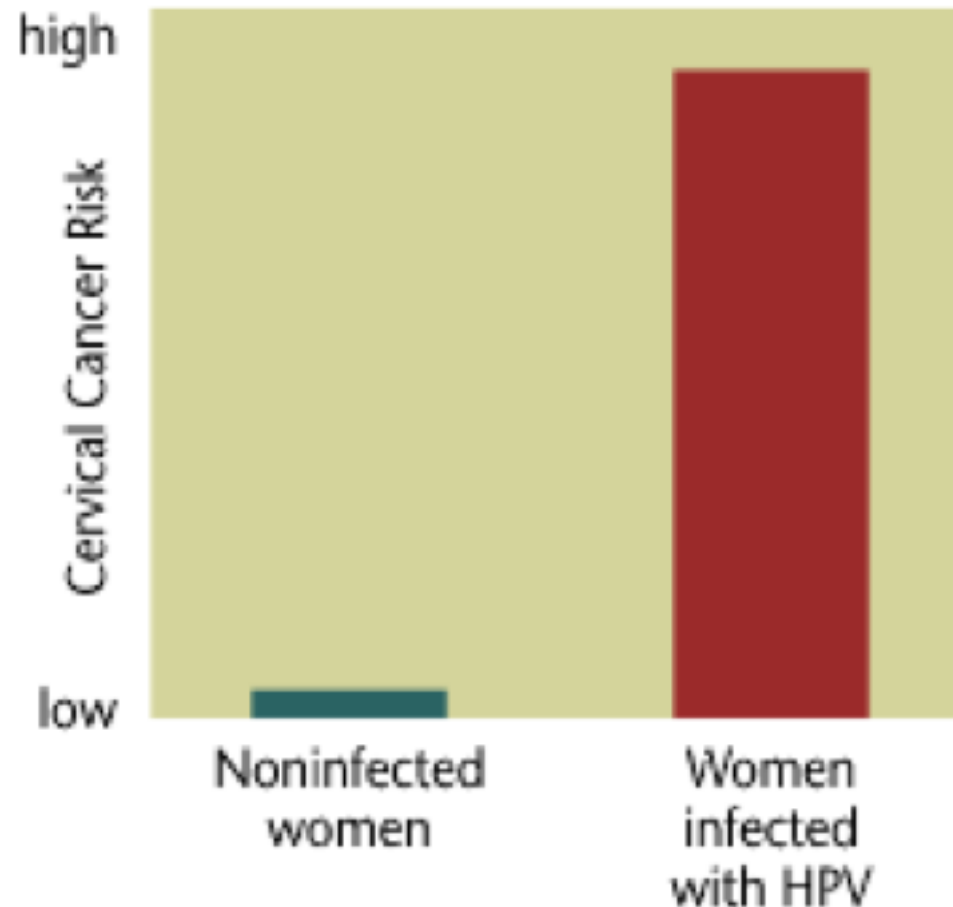
30 million new cases of genital warts³



The Cervix and HPV

Over 99% of all cervical cancer cases stem from infection with HPV, which is transmitted through sexual contact.

HPV Infection Increases Risk for Cervical Cancer

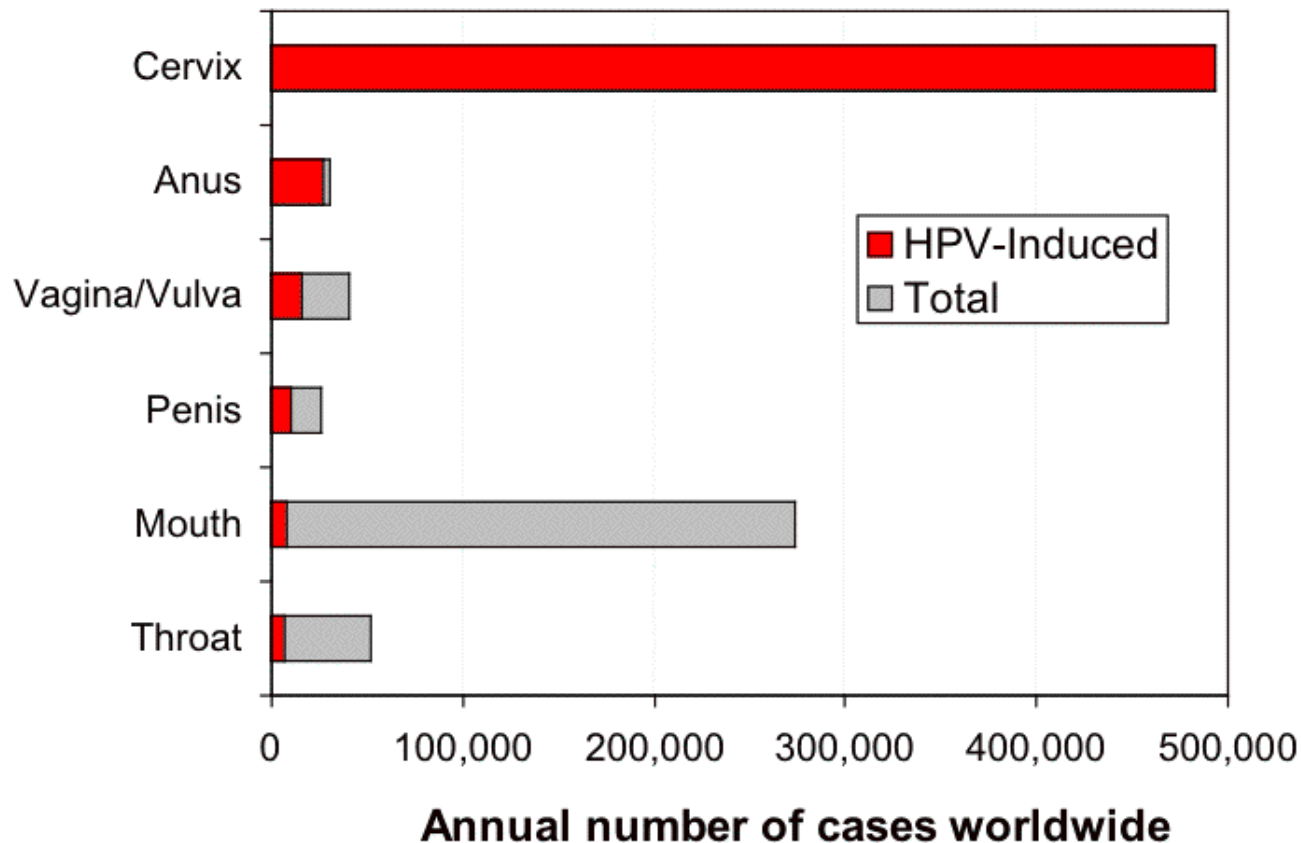


Facts about HPV and Various Cancers

Several types of cancers are associated with HPV:

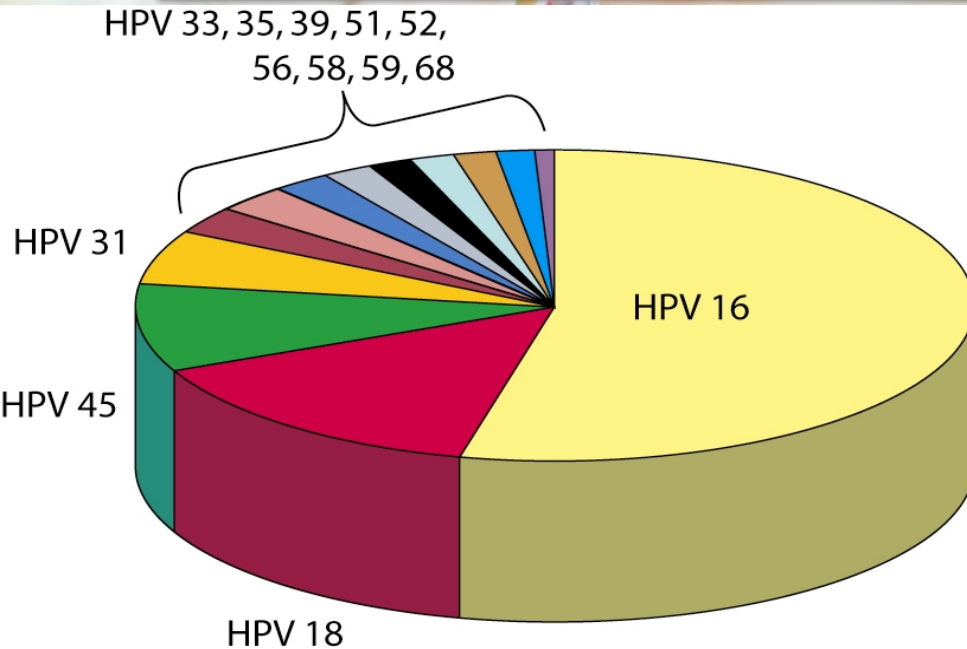
- ❑ Cervical cancer: The most common HPV-associated cancer. Almost all cervical cancer is caused by HPV.
- ❑ Vulvar cancer: About 40% are linked to HPV.
- ❑ Vaginal cancer: About 70% are linked to HPV.
- ❑ Penile cancer: About 40% are linked to HPV.
- ❑ Anal cancer: About 85% are linked to HPV.
- ❑ Cancers of the head and neck are mostly caused by tobacco and alcohol, but recent studies show that ~25% of mouth and 35% of throat cancers may be linked to HPV.

Cases of HPV Cancers



HPV is a virus that is very common. In fact, most men and women are infected with HPV at sometime in their lives. A recent study showed that women who have had at least three sexual partners, 81% of them had HPV.

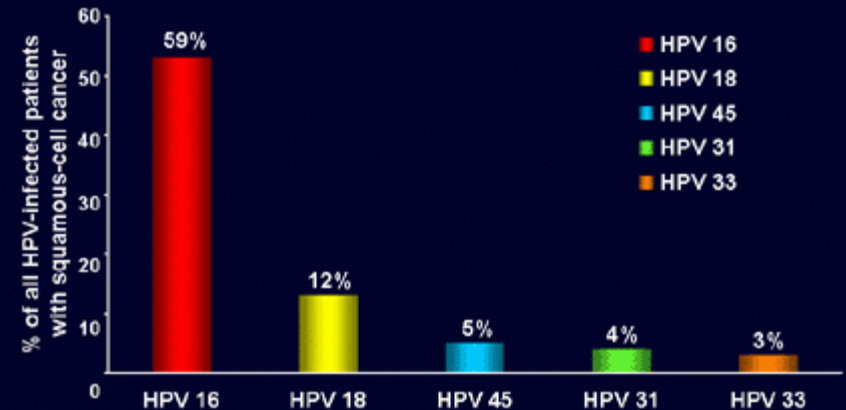
Common HPV Types



High-risk types of HPV cause growths that are usually flat and nearly invisible, as compared with the warts caused by HPV-6 and HPV-11.

From L. J. Kleinsmith, *Principles of Cancer Biology*. Copyright (c) 2006 Pearson Benjamin Cummings.

Most Prevalent HPV Types That Cause Cervical Cancer



HPV DNA was detected in 1739 (90%) of the 1918 patients with cervical cancer. Based on a worldwide survey
 Munoz N et al. *N Engl J Med* 2003;348:518-527.



Genital warts:
 Found on shaft of penis (male),
 vagina, vulva, cervix (female),
 and around anus

Infection & Progression to Cervical Cancer

Time after HPV infection

3-6 months

4-5 years

9-15 years

Initial
HPV
Infection

Persistent
Infection

CIN
2/3

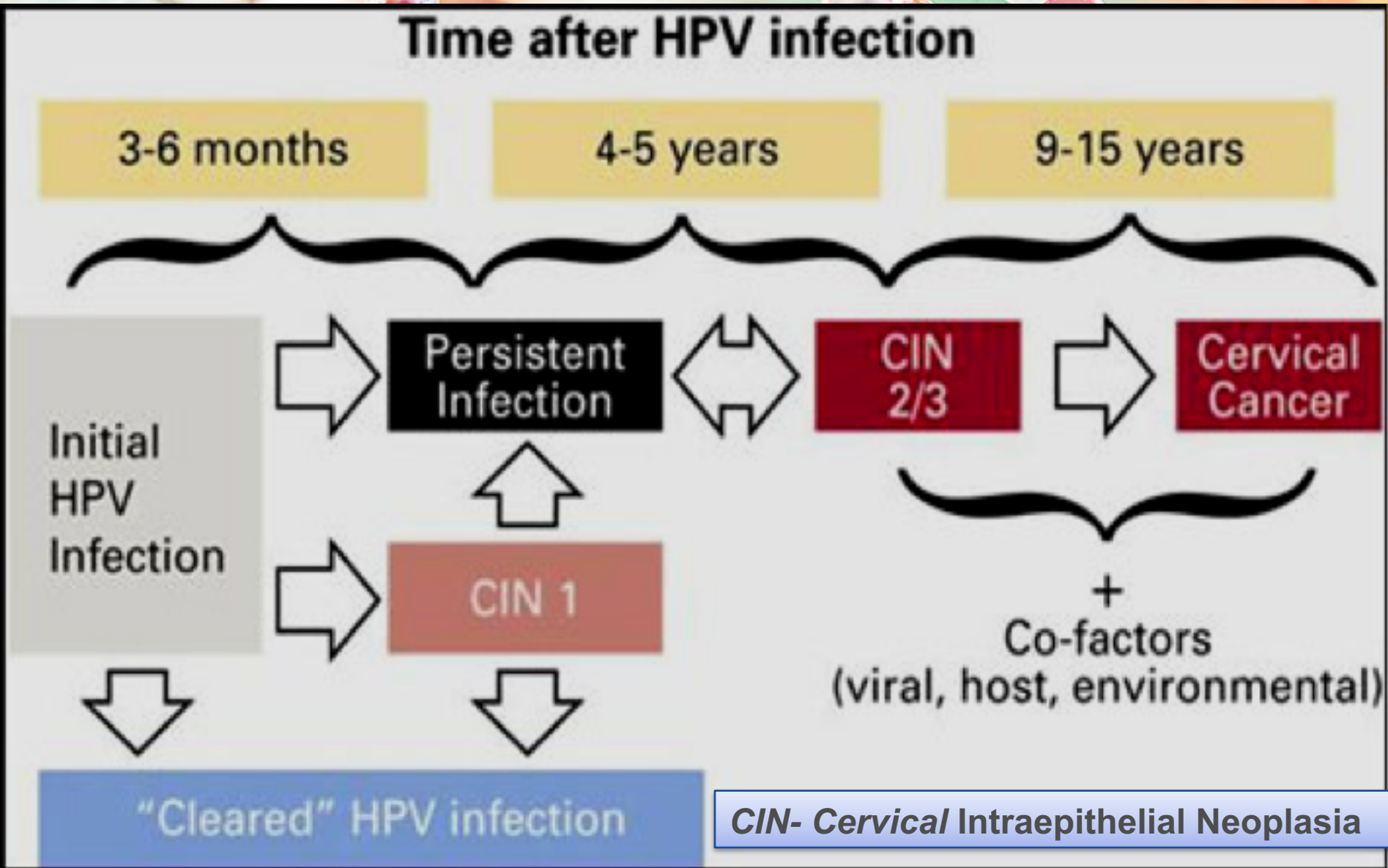
Cervical
Cancer

CIN 1

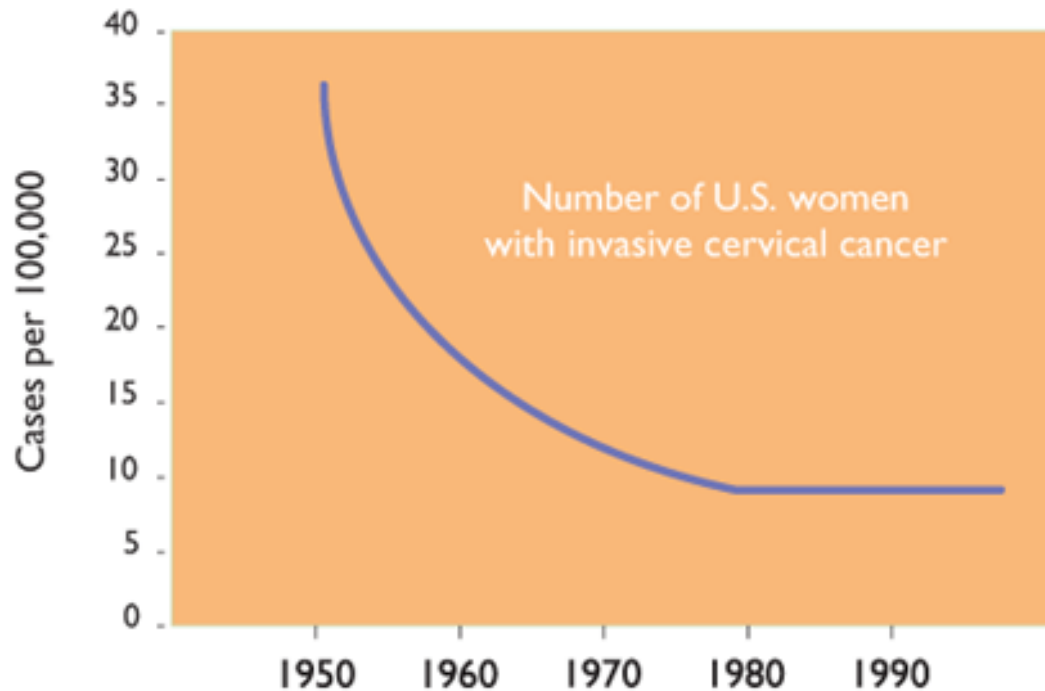
+
Co-factors
(viral, host, environmental)

"Cleared" HPV infection

CIN- Cervical Intraepithelial Neoplasia



Pap Test and Cervical Cancer



New guidelines suggest that women begin Pap test screening at age 21, be screened every 2 years through age 30, and then be screened every 3 years as long as their last three test results have been normal.

☐ The Pap test was developed in 1943 by Dr. George Papanicolaou. Since then, early detection of cervical cancer has greatly improved. As a result, cervical cancer dropped from the second-leading cause of cancer deaths among American women to the 13th in the US.

☐ This is the most successful screening test, reducing cervical cancer mortality by 70% in the United States

PAP and HPV Test

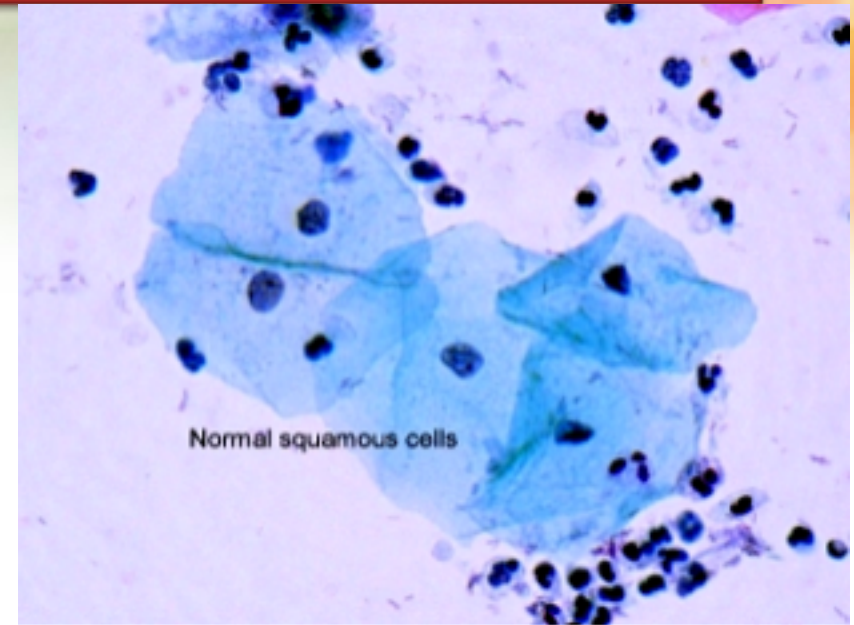
Normal and Abnormal Pap Test Result	What it Means
Normal	Your cervical cells appear to be healthy.
Abnormal	There appear to be changes in your cervical cells that are not normal and need to be tested further.
Borderline, or inconclusive (officially called "ASC-US", which stands for atypical squamous cells of undetermined significance)	Your cervical cells are not obviously normal, but they are not clearly abnormal either.

	Looks For:	How it Works
Pap Test	Signs of abnormal cell changes	Lab professional looks at a sample of cervical cells through a microscope
HPV Test	The virus that <i>causes</i> the abnormal cell changes that can lead to cervical cancer	A test is done on the sample of cervical cells by an automated system

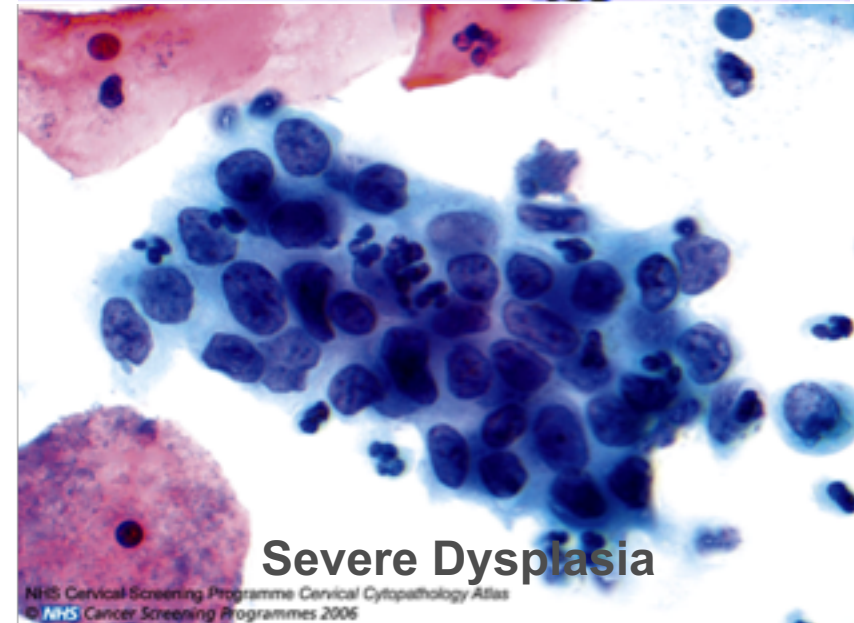
A Pap test usually can detect 90% of cervical cancers

Pap Smear Morphology

- ❑ **Dysplasia:** a higher nuclear to cytoplasmic ratio. This means the nucleus is larger than it should be for the size of the cell.
- ❑ **Mild Dysplasia:** the nucleus is about 3-4 times larger than it should be.
- ❑ **Moderate Dysplasia:** the nucleus is 5-6 times larger than it should be.
- ❑ **Severe Dysplasia:** the nucleus is taking up most of the cell.

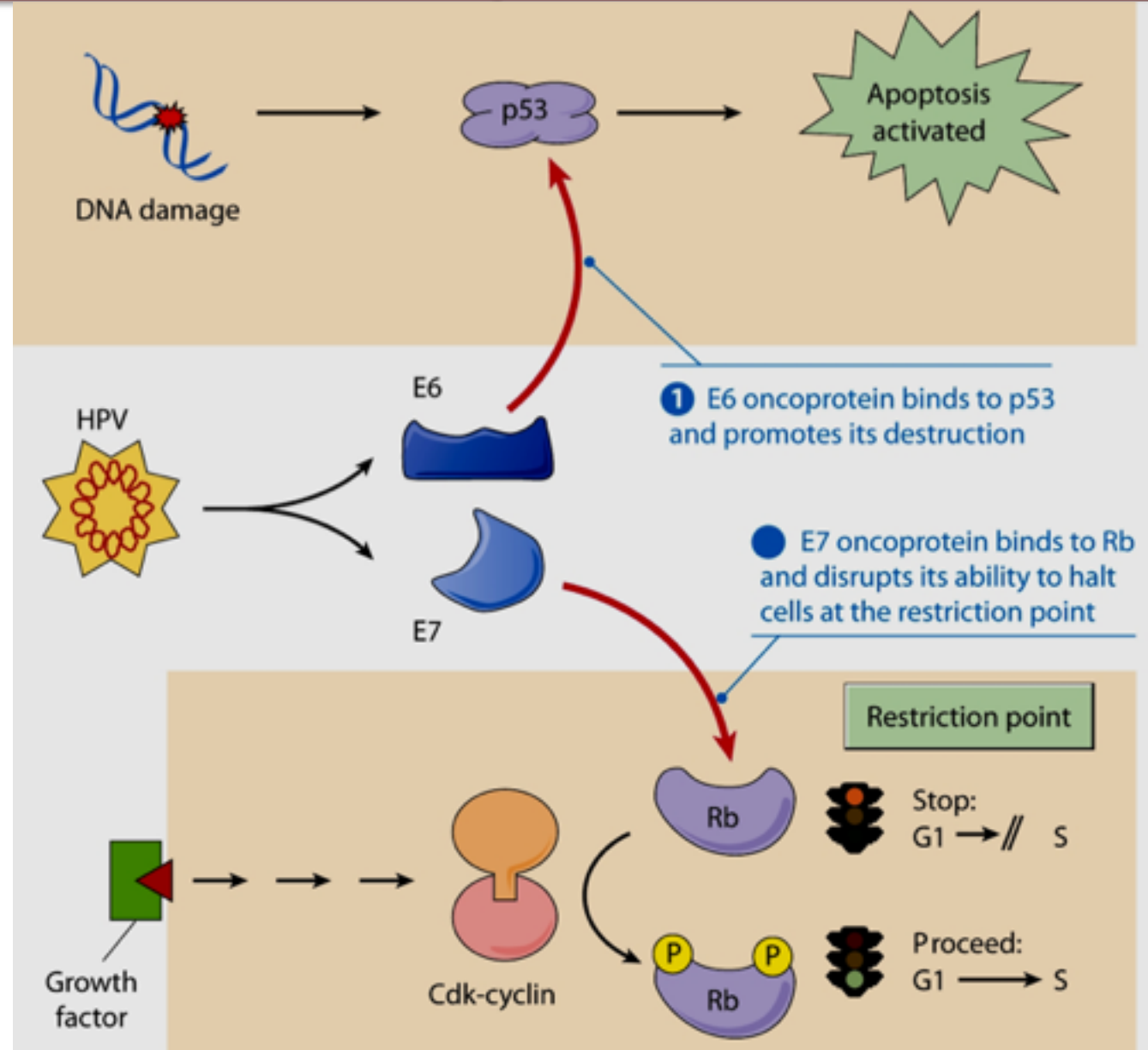


Normal squamous cells



Severe Dysplasia

Mechanism of Action of HPV E6 and E7 Oncoproteins

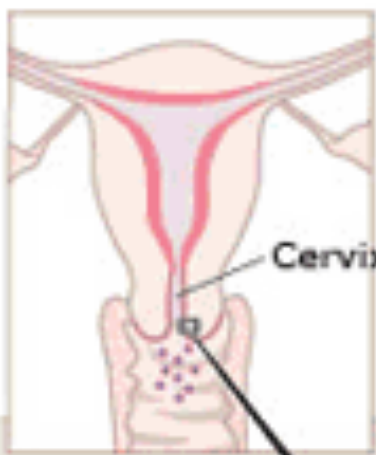
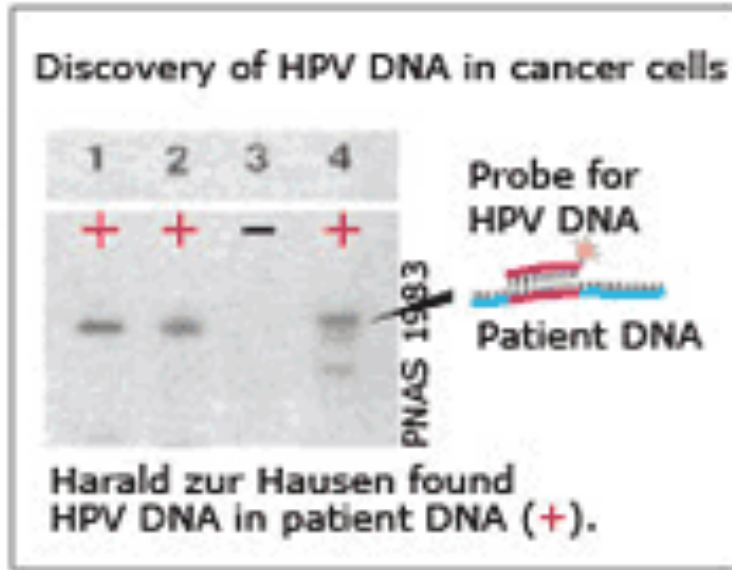
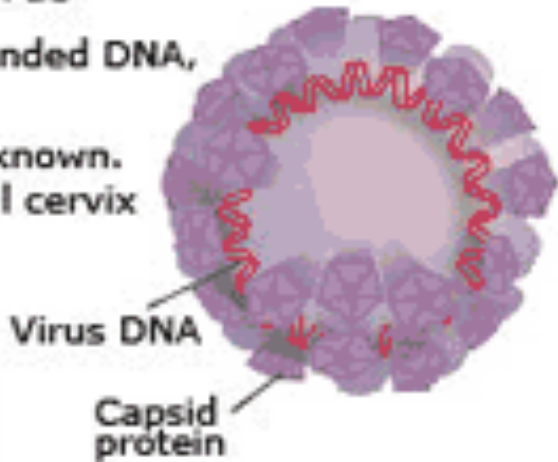


HPV DNA Integration and PCR Test for Virus

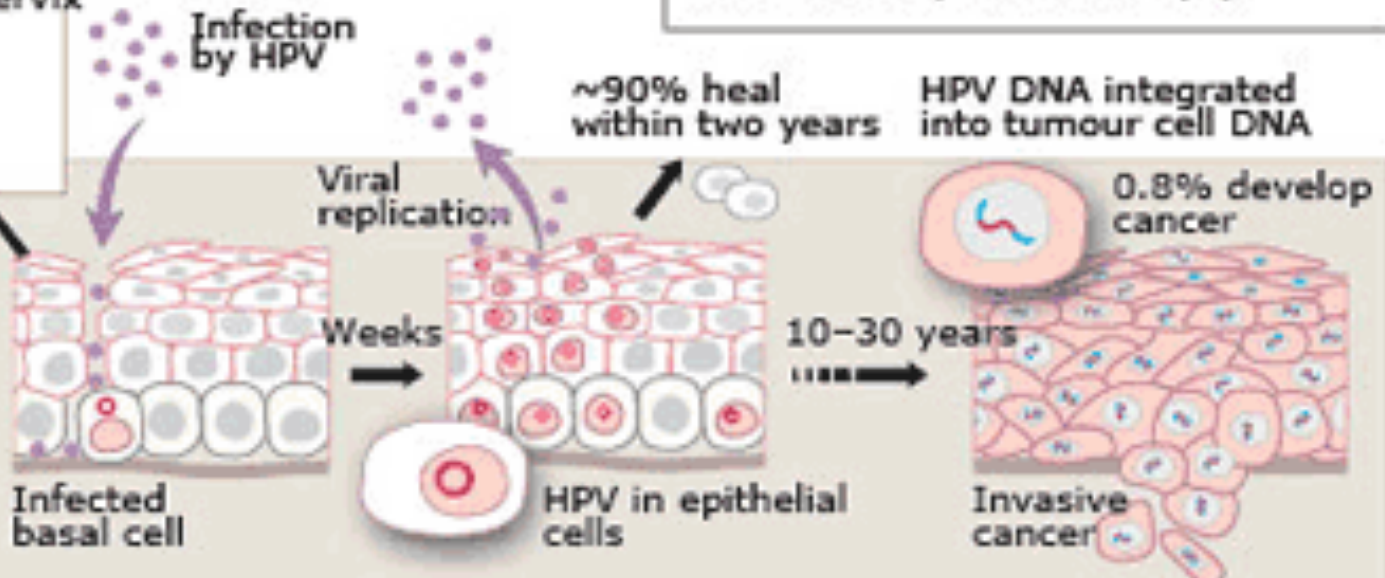
HPV – human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

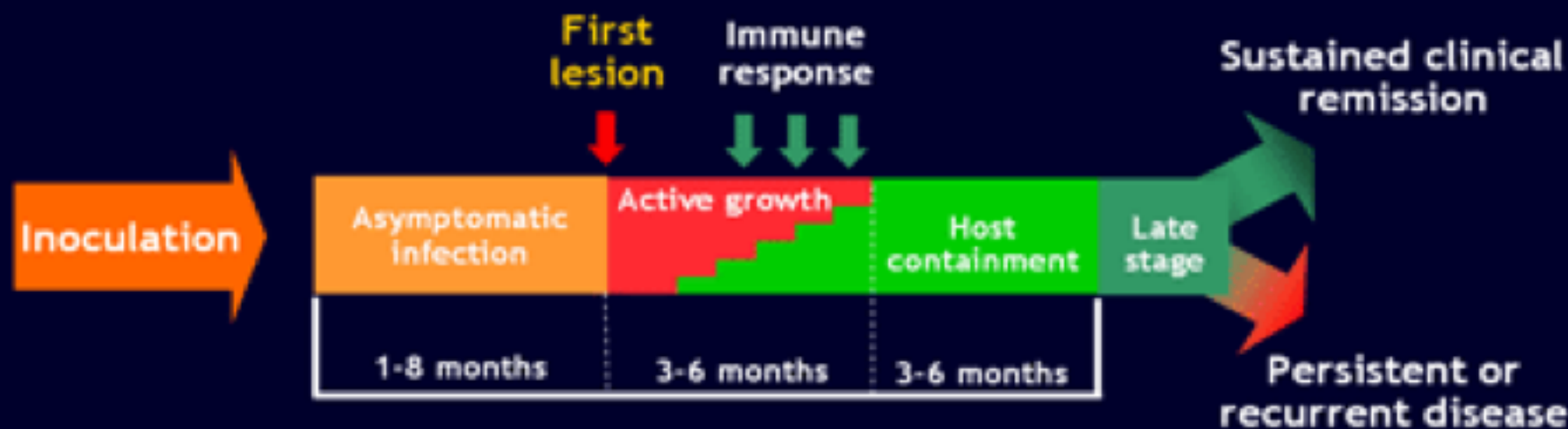
More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.



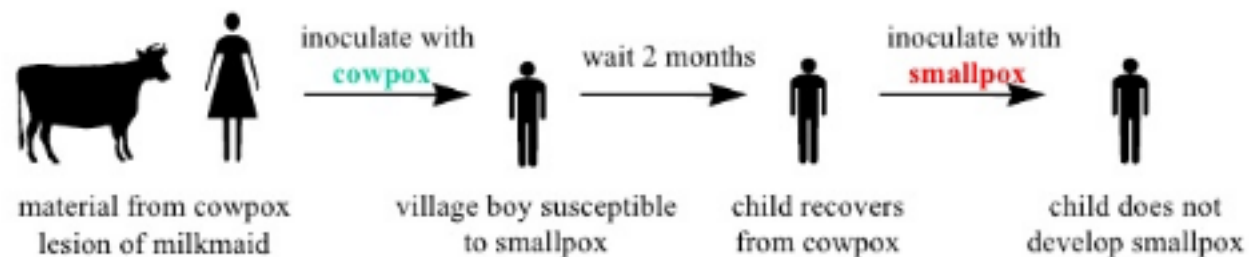
Infection by HPV
HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.



Natural History of HPV Infection



Edward Jenner's experiment (1796)



Gardasil Cervical Cancer Vaccine

**OF THE APPROXIMATELY 6 MILLION
NEW CASES OF GENITAL HPV⁺ IN THE
UNITED STATES EVERY YEAR, IT IS
ESTIMATED 74% OF THEM OCCUR IN
15 - 24 - YEAR - OLDS .**


GARDASIL.
[Human Papillomavirus Quadrivalent
(Types 6, 11, 16, and 18) Vaccine, Recombinant]

Your **SON** or **DAUGHTER** could be



oneless
person affected by HPV disease.

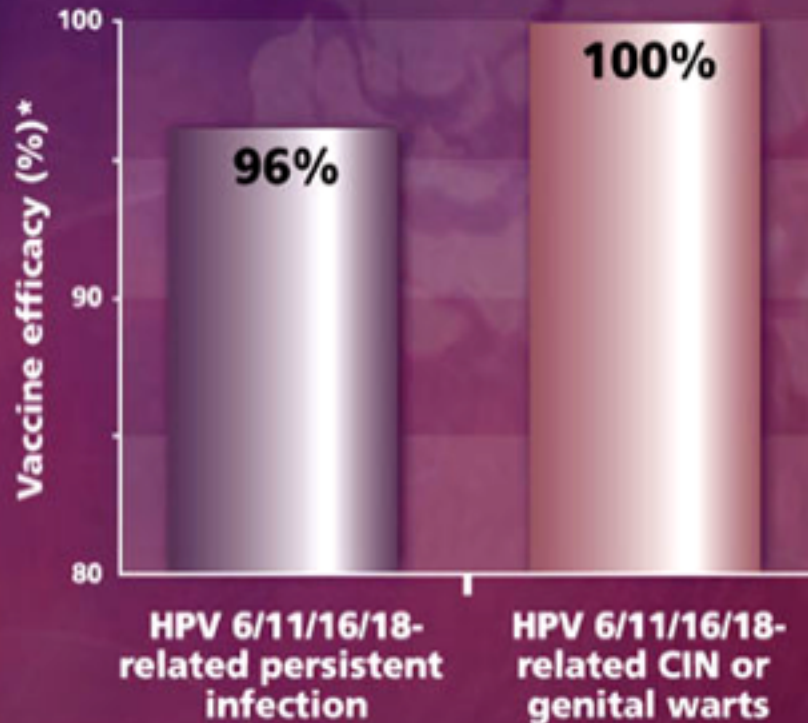
➤ **PARENTS:**
Why GARDASIL for your son or daughter?
[Find Out](#)



©2006 Publications International, Ltd. **Gardasil is injected three times over six months.**

HPV Vaccine and Cervical Cancer

Quadrivalent HPV vaccine: maintenance of efficacy for up to 5 years.



Vaccine type-specific anti-HPV geometric mean titers remained at or above those following natural infection for up to 5 years.

*Per-protocol data analysis; N=241 16- to 23-year-old women.

Source: Adapted from: Villa LL, et al. Presented at: EUROGIN; April 23-26, 2006; Paris, France.

ACIP recommendations for the quadrivalent HPV vaccine.

- **Routine vaccination of girls 11-12 years of age with 3 doses of quadrivalent HPV vaccine**
- **Vaccination series can be started in girls as young as 9 years of age at discretion of provider**
- **Catch-up vaccination for adolescent and young women 13-26 years of age who have not been previously vaccinated**

Source: ACIP. Recommendations for the Quadrivalent HPV Vaccine. Available at: www.cdc.gov/od/oc/media/pressrel/n060629.htm. Accessed July 31, 2006.

How common are HPV problems in men?



Corbis

❑ On October 16, 2009, the FDA licensed Gardasil (Merck & Co. Inc.) for use in males aged 9 through 26 years for prevention of genital warts caused by human papillomavirus (HPV) types 6 and 11.

- ❑ ~1% of sexually active men in the U.S. have genital warts
- ❑ Each year in the U.S. there are about:

800 men who get HPV-related penile cancer

1100 men who get HPV-related anal cancer

5700 men who get HPV-related head and neck cancers. [Note:

although HPV is associated with some of head and neck cancers, most of these cancers are related to smoking and heavy drinking.]

Safety of The Cervical Cancer Vaccines

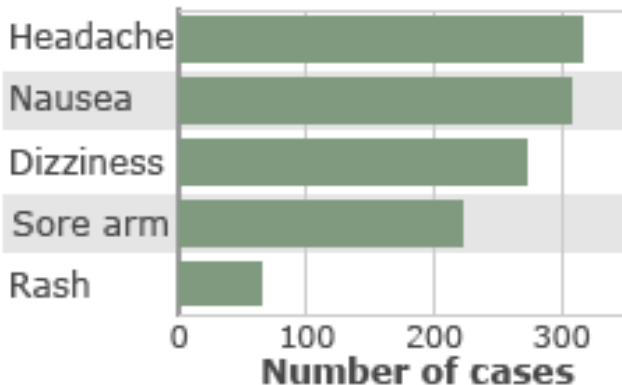
Gardasil and Cervarix

UK

1.4million
vaccinations

4,657
adverse reactions

Some key reactions



US

25million
vaccinations

14,072
adverse reactions

of which

7%
Serious

including
26
confirmed
deaths



Source: MRHA/CDC

4,567 represents the total number of reactions reported in the UK between 14 April 2008-23 September 2009. In the US figures represent reactions between June 2006 and June 2009.

HPV Causes Oral and Throat Cancer

Last Updated: Thursday, 10 May 2007, 07:40 GMT 08:40 UK

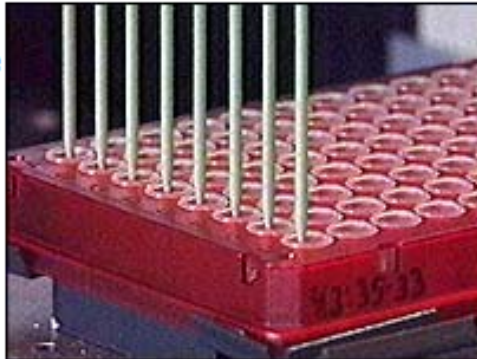
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 Printable version

Oral sex linked to throat cancer

A virus contracted through oral sex is the cause of some throat cancers, say US scientists.

HPV infection was found to be a much stronger risk factor than tobacco or alcohol use, the Johns Hopkins University study of 300 people found.

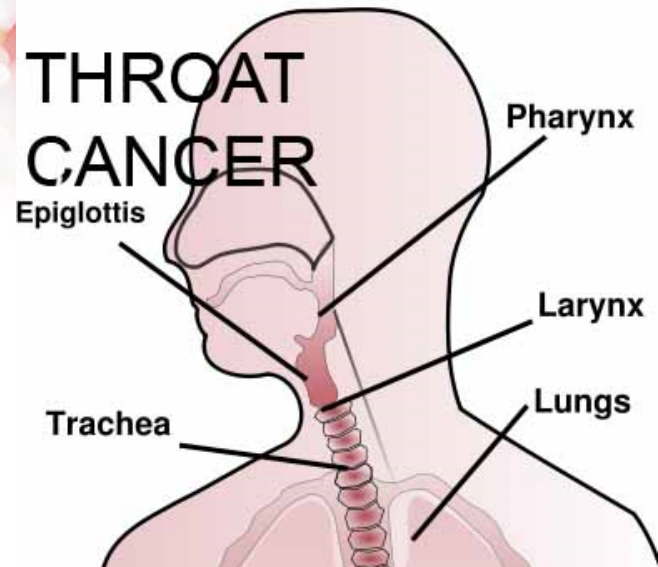


Scientists looked at tissue samples from patients

The New England Journal of Medicine study said the risk was almost nine times higher for people who reported oral sex with more than six partners.

But experts said a larger study was needed to confirm the findings.

HPV infection is the cause of the majority of cervical cancers, and 80% of sexually active women can expect to have an HPV infection at some point in their lives.



Throat Cancer Tipping Scales Toward HPV Vaccination of Boys

At yesterday's meeting, the ACIP heard a disturbing report from Aimee Kreimer, PhD, an expert in head and neck cancer at the National Cancer Institute.

"At some point ... it is projected that there will be the same incidence of OP cancer in men as cervical cancer in women," Kreimer said. "If current trends continue, OP cancer in men will pass cervical cancer in 2025."

And HPV is to blame. Only a few decades ago, the major risk factors for throat cancer were [smoking](#) and alcohol. Not any more. In the five-year period of 1984-1989, only 16% of OP cancers were linked to HPV. By 2000-2004, HPV was behind 75% of OP cancers.

What are the risk factors? Not all are known, but HPV-related throat cancer risk goes up with increased oral sex and kissing, Kreimer said. Current tobacco use and [HIV](#) infection also are risks.

Fortunately, oral HPV infection appears to be much less common than genital HPV infection. Among healthy individuals infected with HPV, fewer than one in 20 has detectable HPV in the oral cavity.

- 
- 10/25/12 US Vaccine Advisory Board recommends Gardasil for Boys.
 - Throat cancer then and now.
 - Until recently throat cancer was associated with age, smoking and alcohol consumption.
 - Studies have now shown that throat cancers in younger (30-40) are often due to HPV infection. (~2% 1974 – 2000 76%)
 - Currently no swab test for throat HPV (Throat PAP smear)
 - **Herd immunity.** Immunization of boys would prevent/protect individuals **AND** would often greater protection for all sexually active individuals.

Future HPV Cancers

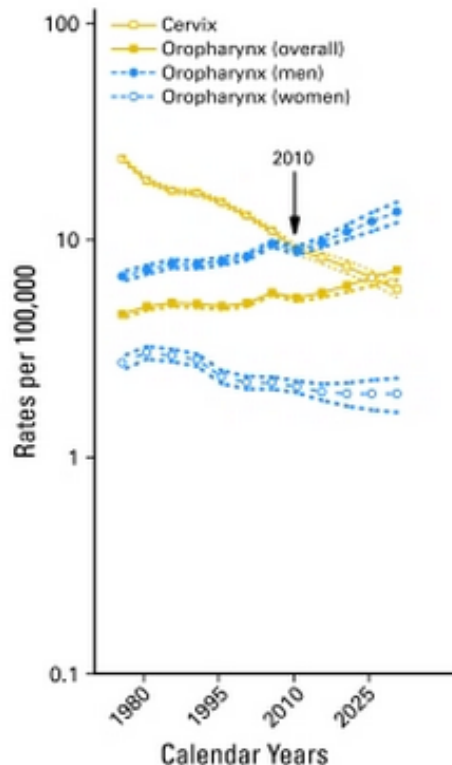
J Clin Oncol. 2011 November 10; 29(32): 4294–4301.

PMCID: PMC3221528

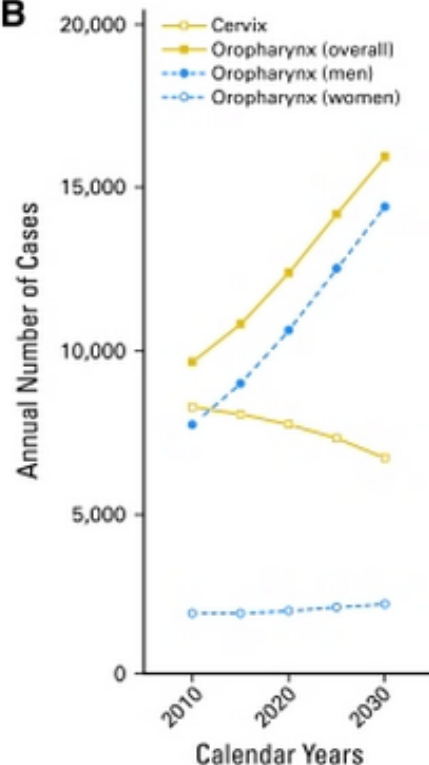
Published online 2011 October 3. doi: [10.1200/JCO.2011.36.4596](https://doi.org/10.1200/JCO.2011.36.4596)

Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States

A



B



HPV- down less smoking
HPV+ better treatment

Science, Society, Internet, lies

- Cervical dysplasia and warts down since Gardasil
- Gardasil in India

Herd immunity vaccinate all protect all
including *UN*vaccinated



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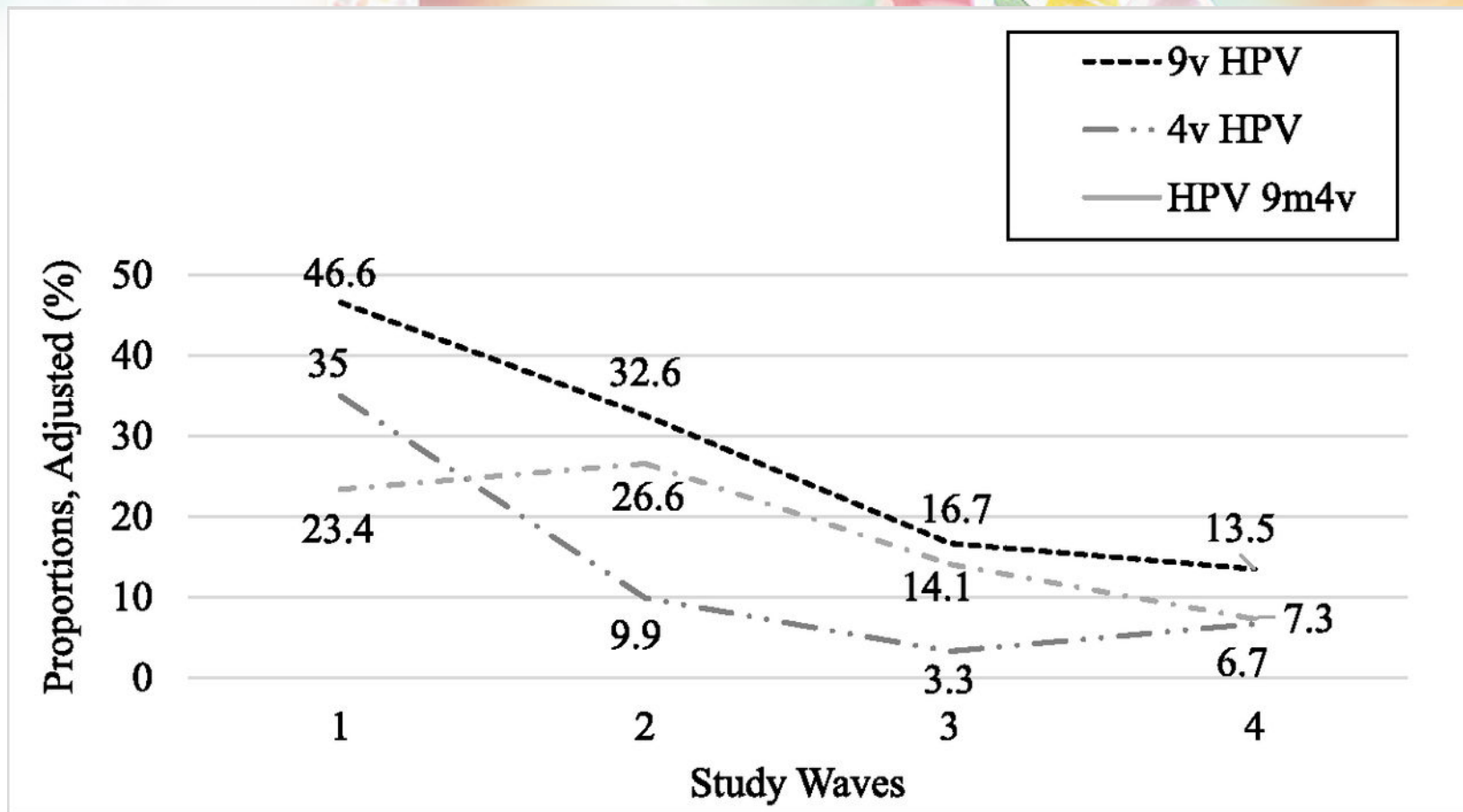
Calls in India for legal action against US charity

Study organizers firmly refute alleged misconduct in cervical cancer vaccination project.

[Sanjay Kumar](#) & [Declan Butler](#)

09 September 2013

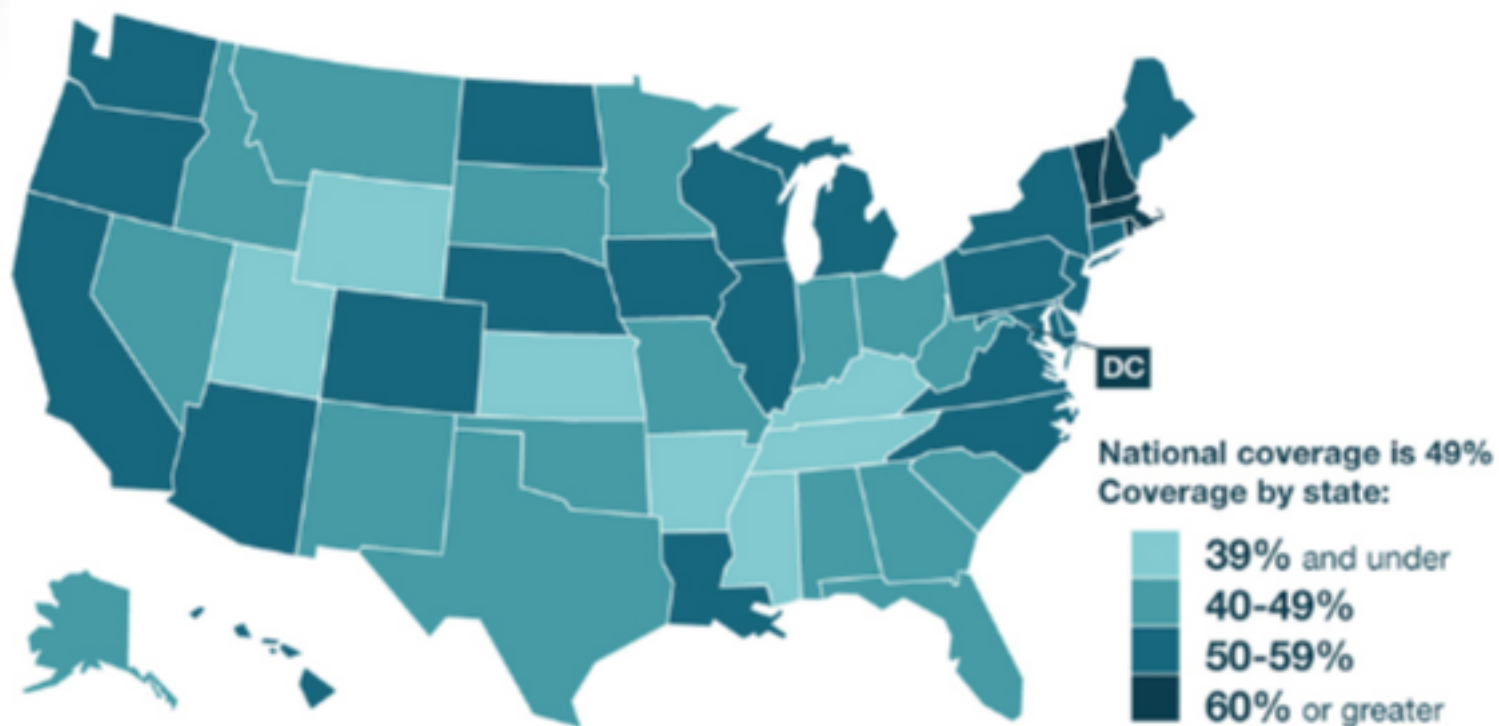
Proportions of women who were vaccinated across the 4 study waves infected with any vaccine-type HPV, adjusted for propensity scores.



Chelse Spinner et al. Pediatrics 2019;143:e20181902

PEDIATRICS

Percentage of adolescents who are up to date on HPV vaccination



Source: MMWR August 24, 2018

www.cdc.gov/hpv



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Tobacco Use Tied to Oral Cancer–Causing HPV

News | October 09, 2014 | Head & Neck Cancer

By Anna Azvolinsky, PhD

Using any form of tobacco is linked to an increased risk of infection with oral human papillomavirus (HPV) type 16, a sexually transmitted virus that is known to cause cancers of the mouth and throat. The study shows HPV-16 infection is more common among those who have recently used tobacco or been exposed to tobacco, independent of sexual behavior. The study was published in *JAMA*.

Test your
knowledge
of breast
cancer

PLAY
NOW

HPV 16 is thought to be the cause of the increase in oropharyngeal squamous cell cancers in the United States. According to the American Cancer Society (ACS), about 37,000 Americans will be diagnosed with an oropharyngeal or oral cavity cancer in 2014, and about 7,300 will die of the disease. While cancer rates in general are on the decline, having decreased by about 20% in the last 20 years, the rate of oral cancers in the United States has increased 225%.

Tobacco and alcohol are two of the strongest known risk factors for oral cancers and HPV 16 has also been previously linked to these cancers, according to the ACS. Men are more likely to be infected with HPV 16. Most people infected have no symptoms, and only a small fraction of those infected will go on to develop oropharyngeal cancer. HPV 16 is found in about 80% of all cancers of the throat and is typically transmitted through oral sex.

The current study found that the chance of being infected with HPV 16 increases with increased tobacco use. According to the study authors, three cigarettes a day can increase the risk of HPV infection by almost 30%.

"It appears that tobacco exposure increases the likelihood of having oral HPV-16 infection, and although we do not yet know why, we suspect that the virus may not be cleared from the body as easily in people who use tobacco," said study author Gypsyamber D'Souza, PhD, MPH, MS, an associate professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health and Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, in a statement.



Leukoplakia on buccal mucosa; biopsy showed early squamous cell carcinoma.



HPV vaccine hesitancy: findings from a statewide survey of health care providers.

McRee AL, Gilkey MB, Dempsey AF.

Abstract

INTRODUCTION: Health care provider recommendations are critical for human papillomavirus (HPV) vaccine uptake. We sought to describe providers' HPV vaccine recommendation practices and explore their perceptions of parental hesitancy.

METHOD: A statewide sample ($n = 575$) of Minnesota health care providers (20% pediatricians, 47% family medicine physicians, and 33% nurse practitioners) completed our online survey in April 2013.

RESULTS: Only 76% of health care providers reported routinely recommending HPV vaccine for girls ages 11 to 12 years, and far fewer (46%) did so for boys ($p < .001$). A majority of providers reported asking questions about parents' concerns (74%), but many lacked time to probe reasons (47%) or believed that they could not change parents' minds (55%). Higher levels of self-efficacy and outcome expectations were associated with routine recommendations ($p < .05$).

DISCUSSION: Findings suggest that providers' perceptions of hesitancy may discourage them from routinely recommending the HPV vaccine. Improving providers' self-efficacy to address hesitancy may be important for improving vaccination rates.

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KEYWORDS: HPV vaccine; health care provider communication; vaccine hesitancy

HPV vaccination rates still low for boys



By Christopher Wanjek · Published October 03, 2014



"While vaccinating males may benefit female partners, it is critical for physicians and parents to recognize the positive health impacts for males and females," said Susan Vadaparampil, a researcher at Moffitt Cancer Center in Tampa, Florida, and senior author on the report, which will be published in an upcoming issue of the journal Cancer Epidemiology, Biomarkers & Prevention. [[5 Dangerous Vaccine Myths](#)]

Vadaparampil said HPV can significantly raise men's risk of penile and anal cancers and that the virus also raises the risk of [head and neck cancers in men](#) more than it does in women. This is why it is important to vaccinate both boys and girls before they become sexually active, she said.

The Centers for Disease Control and Prevention recommends a three-dose series starting as early as age 11.

According to the CDC, 34.6 percent of boys ages 13 to 17 received at least the first dose of the HPV vaccine in 2013, up from 20.8 percent in 2012 and 8.3 percent in 2011. The rate for girls increased to 57.3 percent in 2013, from 25.1 percent in 2007.