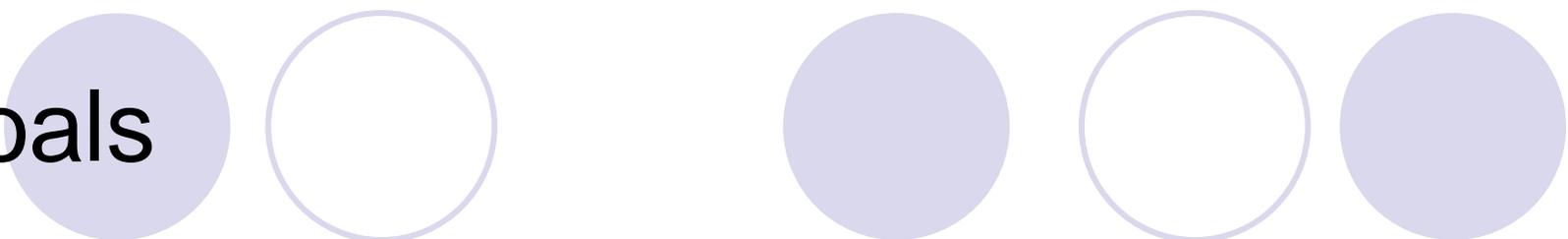




# Human Papillomavirus

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March 25, 2009

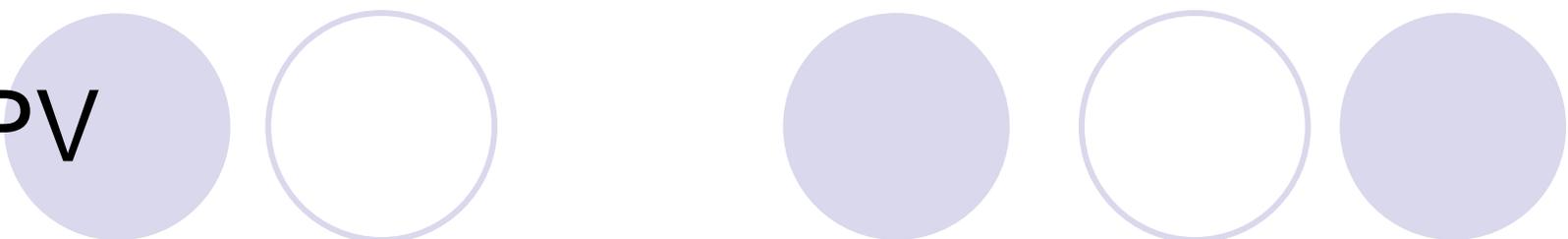


# Goals

- Review Pathology of HPV
- Epidemiology in US
- HPV in Human Cancers
- HPV Vaccine
- Screening & Vaccination Recs

# HPV

- Member of family Papillomaviridae
- Nonenveloped, icosahedral capsid
- DS DNA genome
- Oncogenic HPV types immortalize human keratinocytes
  - E6 protein facilitates degradation of p53
  - E7 protein binds Rb gene product and related proteins



# HPV

- Pathogenesis:

- Incubation is usually 3-4 months
- Infects all types of squamous epithelium

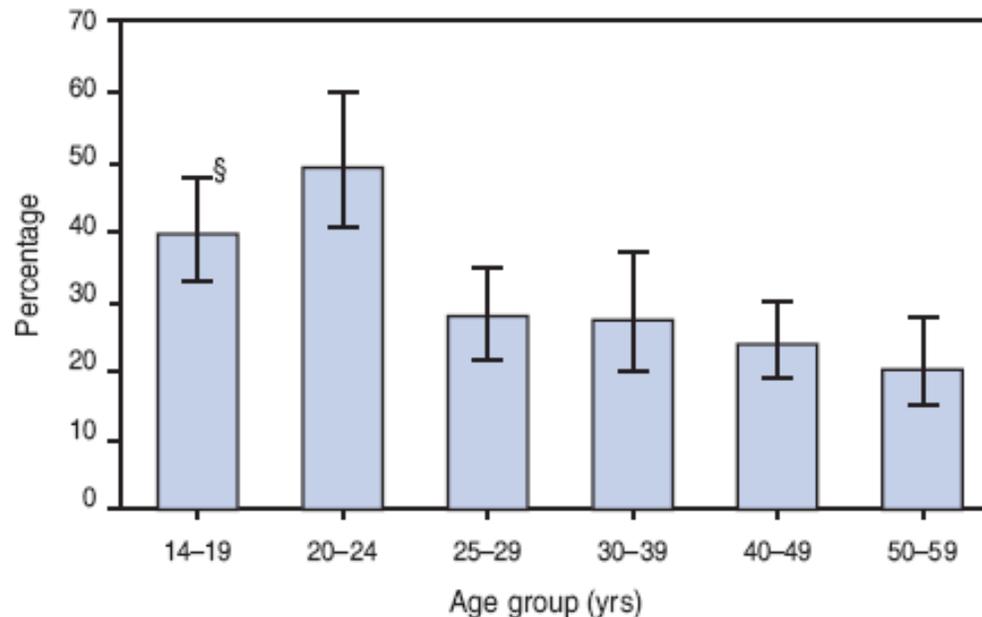
- >100 recognized HPV types

- HPV-1-4 causes plantar warts
- HPV-6 and 11 cause anogenital warts
- HPV-16 and 18 linked to cervical dysplasia

Reichman Richard C, "Chapter 178. Human Papillomavirus Infections" (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17th Edition: <http://www.accessmedicine.com.liboff.ohsu.edu/content.aspx?aID=2895508>.

# Prevalence of HPV in US Women

Prevalence of HPV Infection Among Sexually Active Females Aged 14--59 Years, by Age Group --- National Health and Nutrition Examination Survey, United States, 2003--2004



§ 95% confidence interval

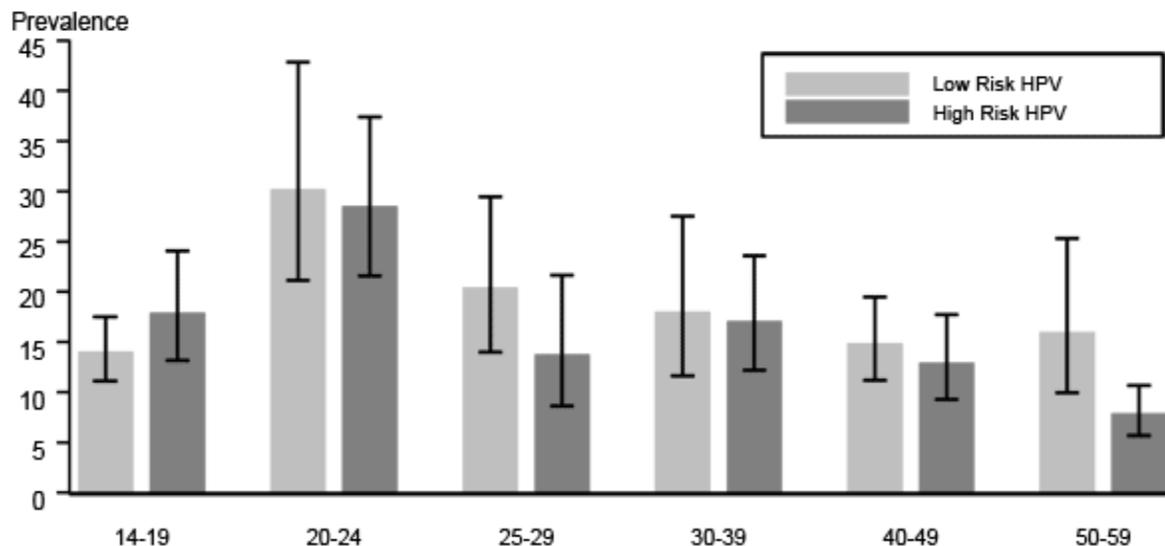
- Overall, 26.8% positive for any HPV.

- Risk factors included age, marital status, and increasing #s of lifetime and recent sexual partners.

Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA 2007;297:813--9.

# Prevalence of HPV in US Women

**Human papillomavirus (HPV) — Prevalence of high-risk and low-risk types among females 14 to 59 years of age reported from a national survey, 2003–2004**



Overall:

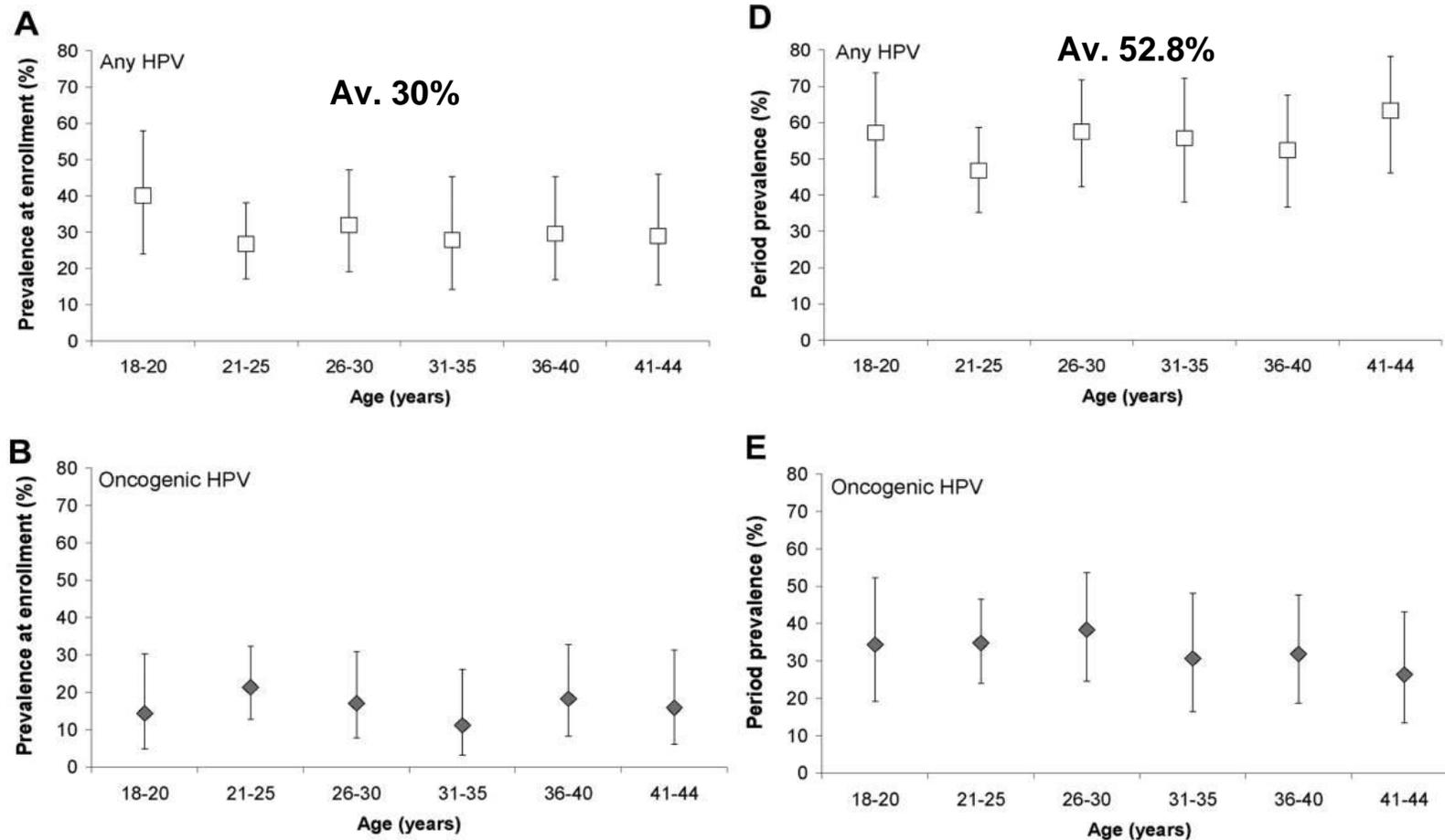
- High-risk 15.2%
- Low-risk 17.8%

Note: Error bars indicate 95% confidence intervals. Both high-risk and low-risk HPV types were detected in some females.

Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA 2007;297:813--9.

# Prevalence of HPV in US Men

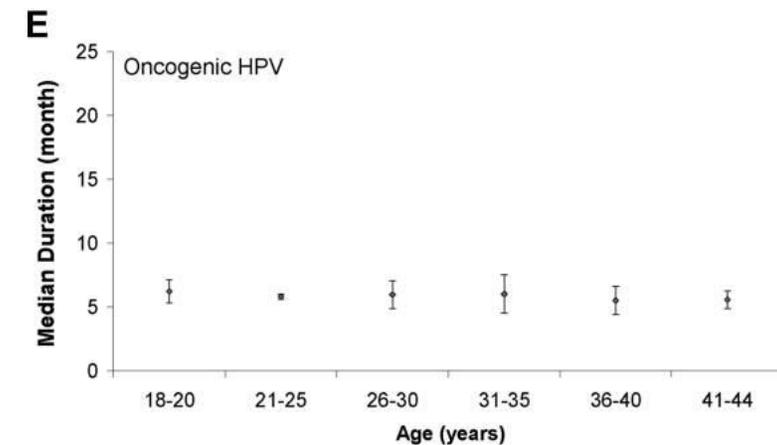
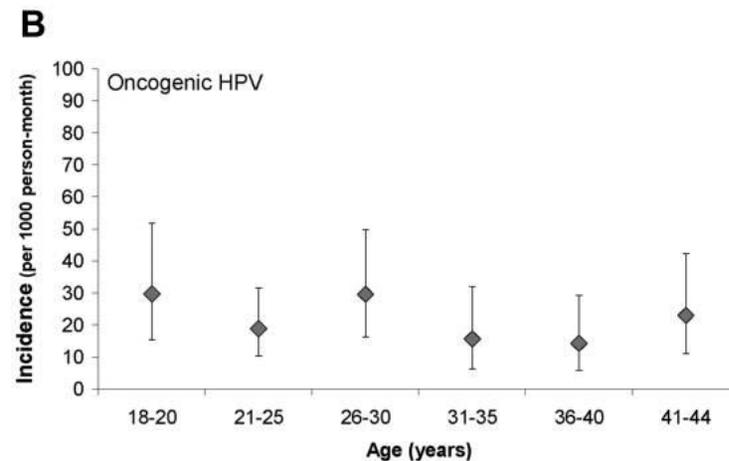
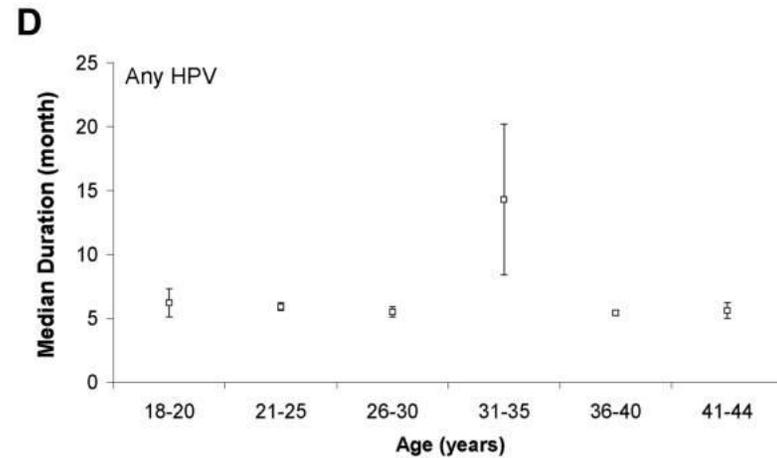
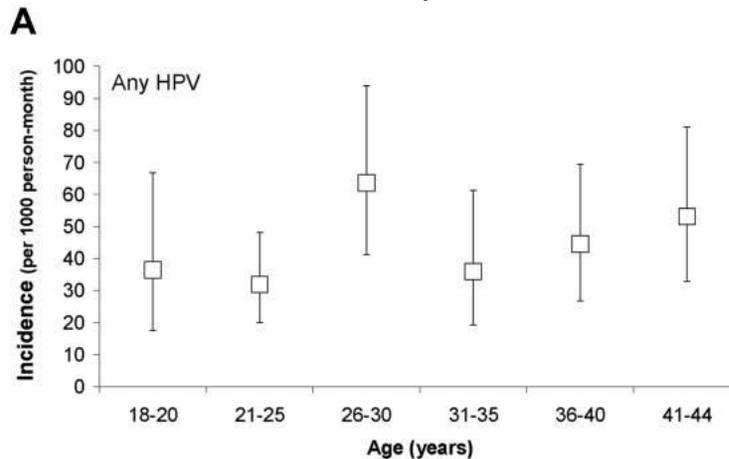
● 290 US men age 18-44y, mean follow-up 15.5 months



Giuliano AR, Lu B, Harris RB, et al. Age-specific prevalence, incidence and duration of human Papillomavirus infections in a cohort of 290 US men. JID 2008;198:827-835.

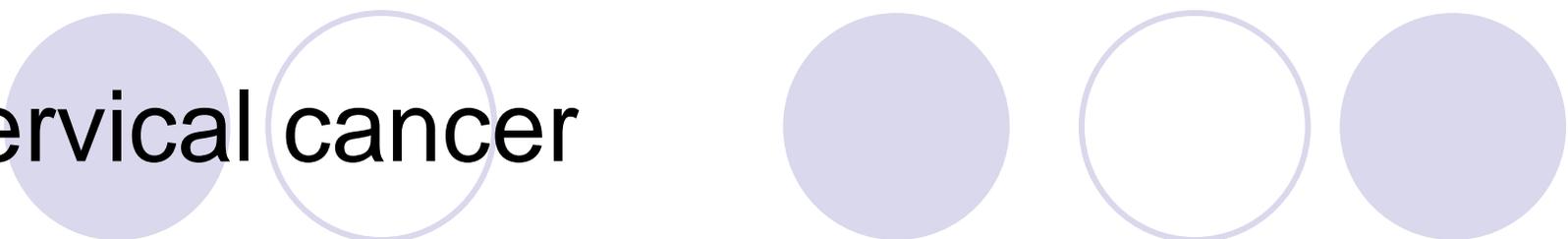
# Incidence & Duration of HPV Infection in US Men

- Incidence of any HPV 42.3/1000 person-months
- 12-months incidence of a new HPV infection was 29.2%
- Median time to clearance of any HPV was 5.9 months



Giuliano AR, Lu B, Harris RB, et al. Age-specific prevalence, incidence and duration of human Papillomavirus infections in a cohort of 290 US men. JID 2008;198:827-835.

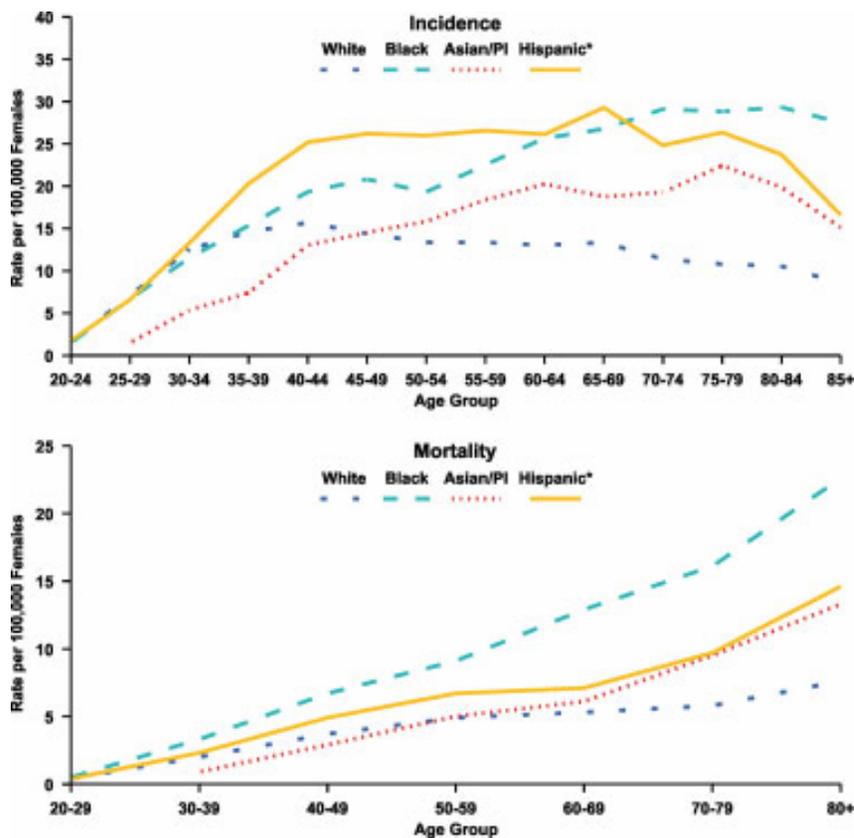
# Cervical cancer



- 1998-2003 SEER data, 65,074 cases of invasive cervical carcinoma
  - 10-11,500 cases/yr
  - 72% SCC, 19% AC
- Increased rates in black women, compared to white, and average younger age at diagnosis
- Hispanic women had increased rates and younger age at diagnosis compared to non-Hispanic women
- Highest incidence in the South

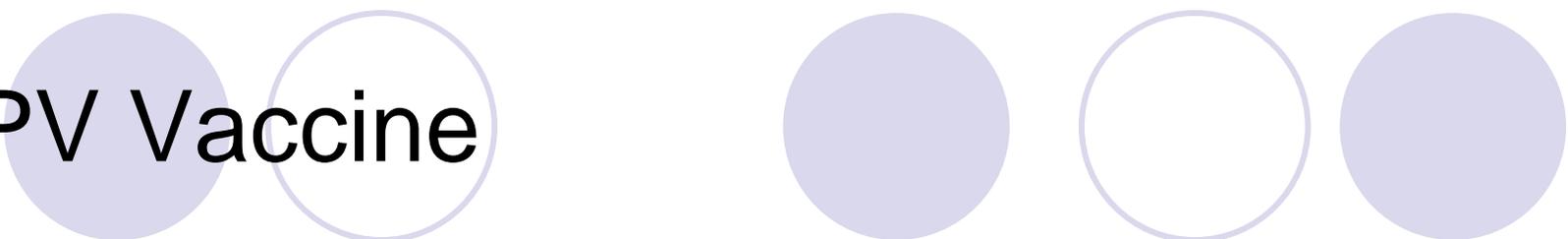
# Cervical Cancer

Incidence rates of invasive cervical carcinoma by age and race and ethnicity



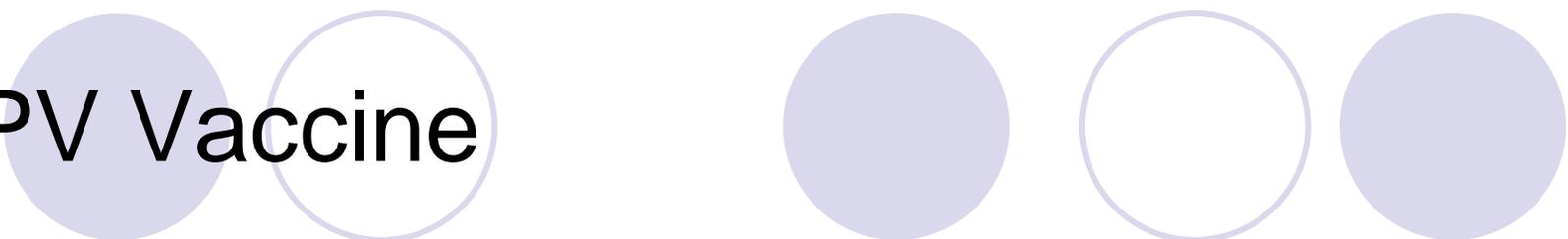
- Incidence rate 8.9 per 100,000 women
- Rate of death 2.7/100,000 women, or >4000 women per year
- Can the HPV vaccine reduce disparities in the incidence and mortality of cervical cancer?

# HPV Vaccine



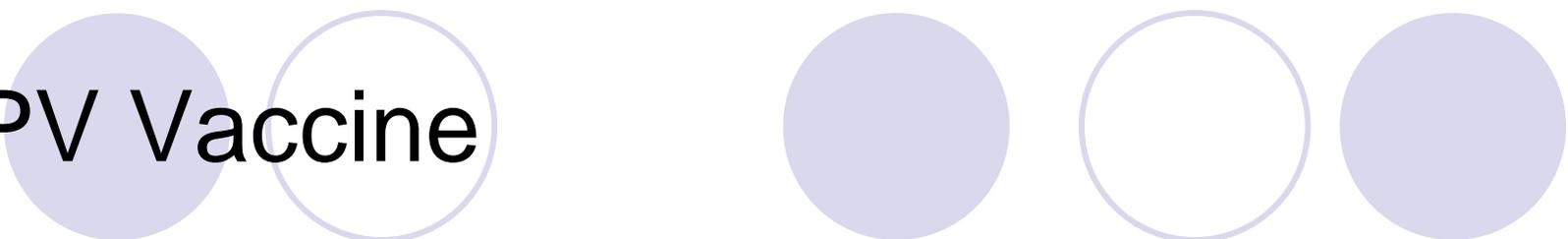
- Gardasil: quadravalent vaccine for HPV types 6, 11, 16 & 18
- Given in 3 doses at 0 time, 2 months & 6 months
- Cost \$375 or VFC eligible if <18y
- Currently, 25% of 13-17yo females have received 1 dose
- Villa et al. showed disease prevention efficacy at 5 years of 100%, in 241 women

# HPV Vaccine



- FUTURE1, with 5455 women, showed 100% efficacy at preventing HPV 6, 11, 16, & 18 infection at 3 years
- FUTURE2, with 12,167 women from 13 countries, showed 98% reduction in vaccine-type related cervical lesions, though only a 17% reduction in any cervical lesions
  - 93% of subjects sexually active prior to enrollment
- In FUTURE2, 68% maintained high levels of antibody to HPV 18 at 3 years

# HPV Vaccine



- ACIP recommendations:
  - Routinely recommended for 11 and 12 year-old girls
  - Can be started at 9 years
  - Catch-up vaccination for 13 through 26 year-old females
- A bivalent (16, 18) is being considered for licensure by the FDA

Longo Dan L, "Hot Topic: Clinical Efficacy of Gardasil in the Prevention of Human Papillomavirus Infection" (Update). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17th Edition: <http://www.accessmedicine.com.liboff.ohsu.edu/updatesContent.aspx?aid=1001118>.

# HPV Vaccination & Cervical Cancer Prevention Programs

- Preventing infections of HPV-16 and 18 would eliminate 70% of cervical cancers worldwide
- 15 types of HPV cause cervical cancer
- Vaccine does not treat pre-existing infections
- Minor evidence of cross-protection for a few closely related HPV types
- At this time vaccination not recommended for women >26y

# Cost-Effectiveness of HPV Vaccination

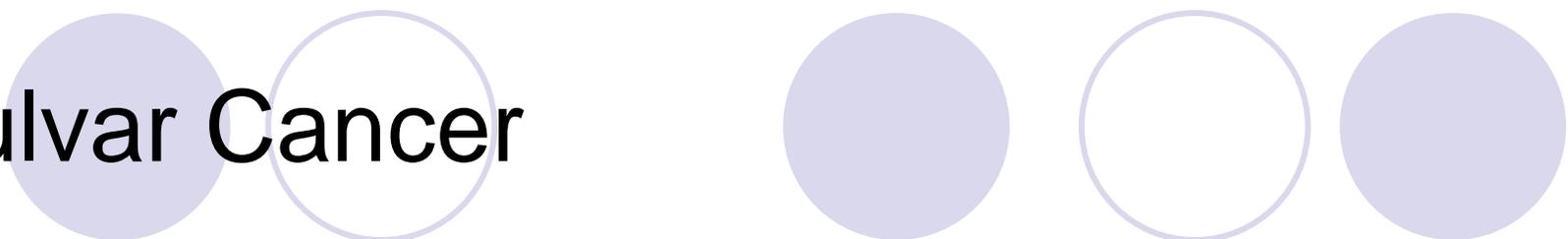
- Assuming life-long immunity, the cost-effective ratio of vaccination of 12-year-old girls was \$43,600 per QALY gained
- Catch-up immunization for girls to 18y was \$97,300 per QALY
- Catch-up to 26y was \$152,700 per QALY



# Cervical Cancer Prevention

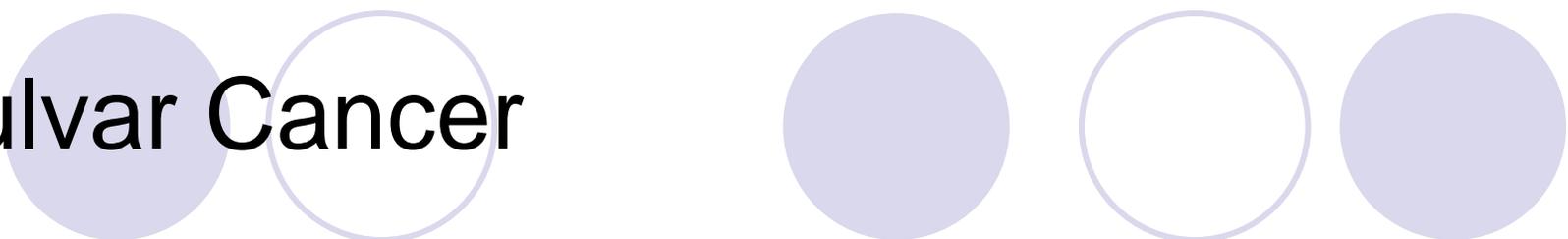
- Adding the cost of vaccination results in redundancy at increased costs, without necessarily further reducing cervical cancer mortality
- Possible changes:
  - Delay screening from 3 years after beginning sexual activity to 5y, to avoid transient HPV infections
  - Extend interval between screenings
  - Switch from dual HPV/cytology to HPV testing with cytology of HPV-positive results
  - If HPV genotyping becomes available, only the presence of 16 and 18 would trigger colposcopy

# Vulvar Cancer



- In US, vulvar cancers account for 4% of cancers in female reproductive organs
  - 0.6% of all cancers in women
- HPV vulvar cancer is typically
  - Squamous cell
  - Undifferentiated
  - Multifocal
  - Younger women
  - Similar risk factors for cervical cancer

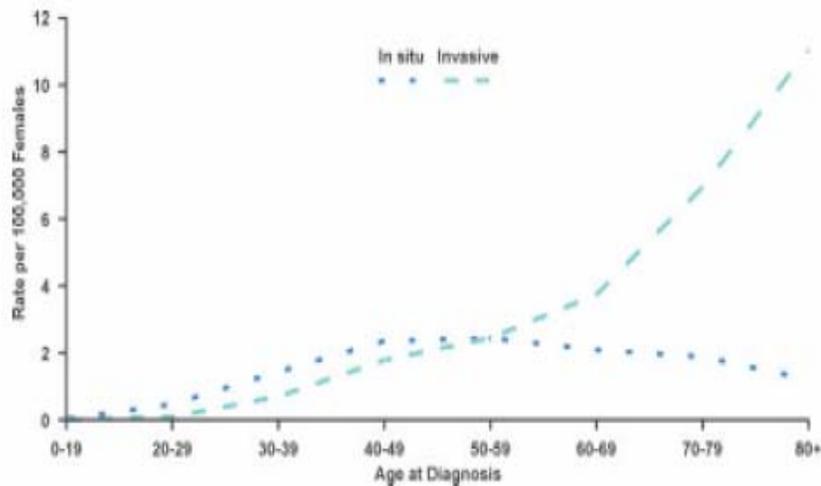
# Vulvar Cancer



- One study of 2168 vulvar cancers showed HPV DNA prevalence of 36% in invasive vulvar cancers
- HPV DNA present in 55% of basaloid and warty vulvar cancers
  - <10% of keratinizing vulvar cancers,
- HPV-16 is main type, HPV-18, 31, 33, and 45 are also present

# Vulvar Cancer

- Age-specific incidence rates of in situ and invasive vulvar cancer, 1998-2003



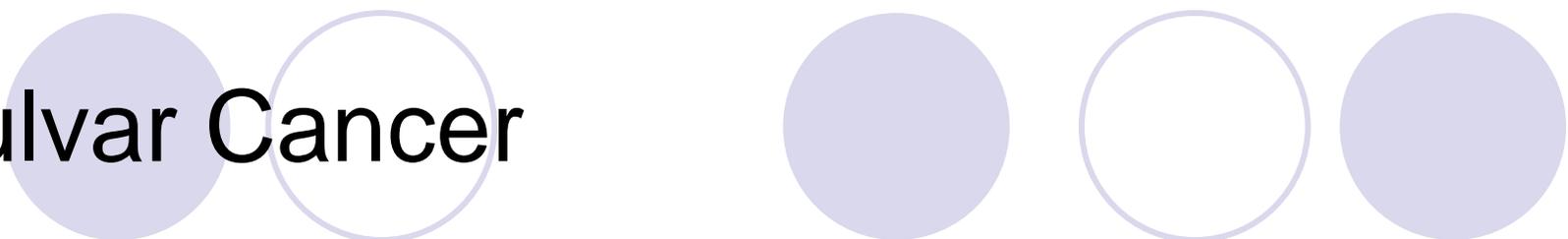
- Incidence rates highest in white women

- rates 28% lower in black women
- 54% lower for Hispanic women

- Incidence rates are significantly lower in the West and South regions

Saraiya M, Watson M, Giuliano AR, et al. Incidence of in situ and invasive vulvar cancer in the US, 1998-2003. *Cancer* 2008;113:2865-2872.

# Vulvar Cancer

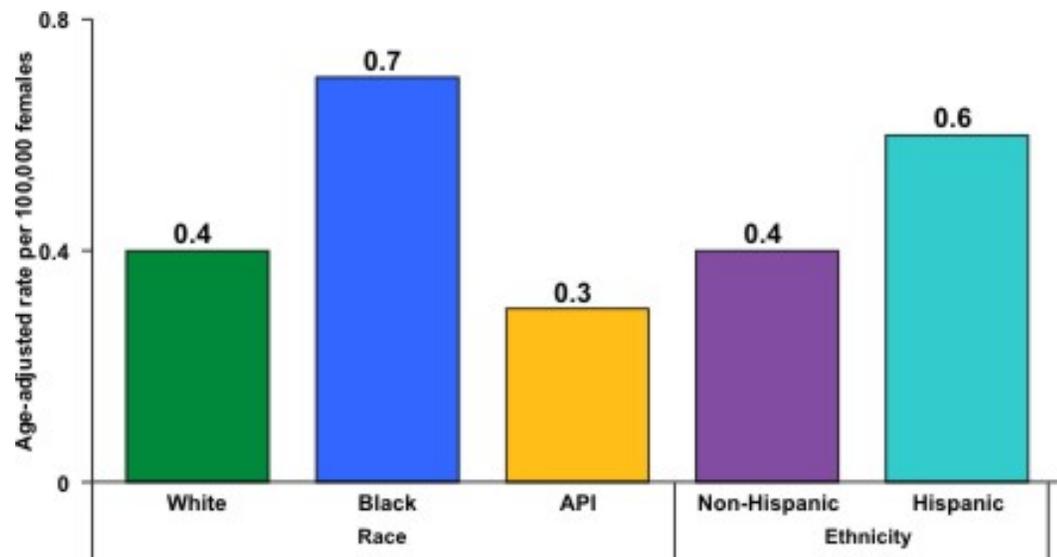


- Among women naïve to HPV-16 or 18, who received all 3 doses, the vaccine was 100% effective against VIN 2 of 3 (precancerous lesions)
- Among the intention-to-treat population, vaccine efficacy against VIN 2 of 3 was 62%
- Broad use of HPV vaccine has the potential to reduce by 40% the 3800 cases of HPV-associated squamous cell in situ and invasive vulvar cancer reported per year

# Vaginal Cancer

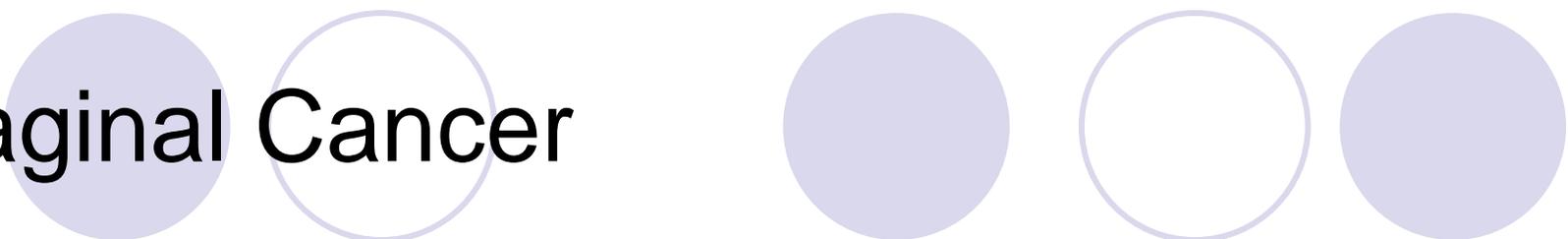
- ~600 new cases of vaginal cancer in the US per year
- SEER data estimates HPV to cause 40% of vaginal cancers

Age-adjusted incidence rates for vaginal cancer in the United States during 1998–2003

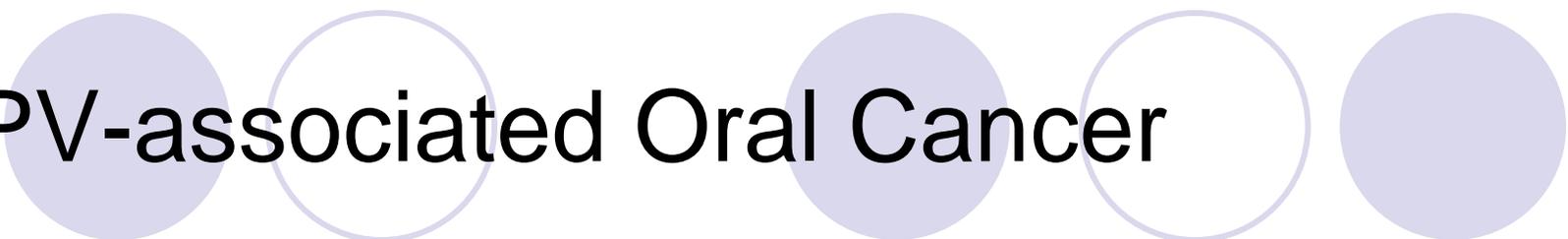


Wu X, Matanoski G, Chen VW, Saraiya M, Coughlin SS, King JB, Tao XG. Descriptive epidemiology of vaginal cancer incidence and survival by race, ethnicity, and age in the United States. *Cancer* 2008;113:2873–2882.

# Vaginal Cancer



- Another review found HPV prevalence of 65.5% in vaginal cancer
  - Among HPV+ cases, 85.5% was attributable to HPV16 and 14.8% to HPV18
- Estimate the HPV 16/18 vaccination could reduce one half of vaginal cancers

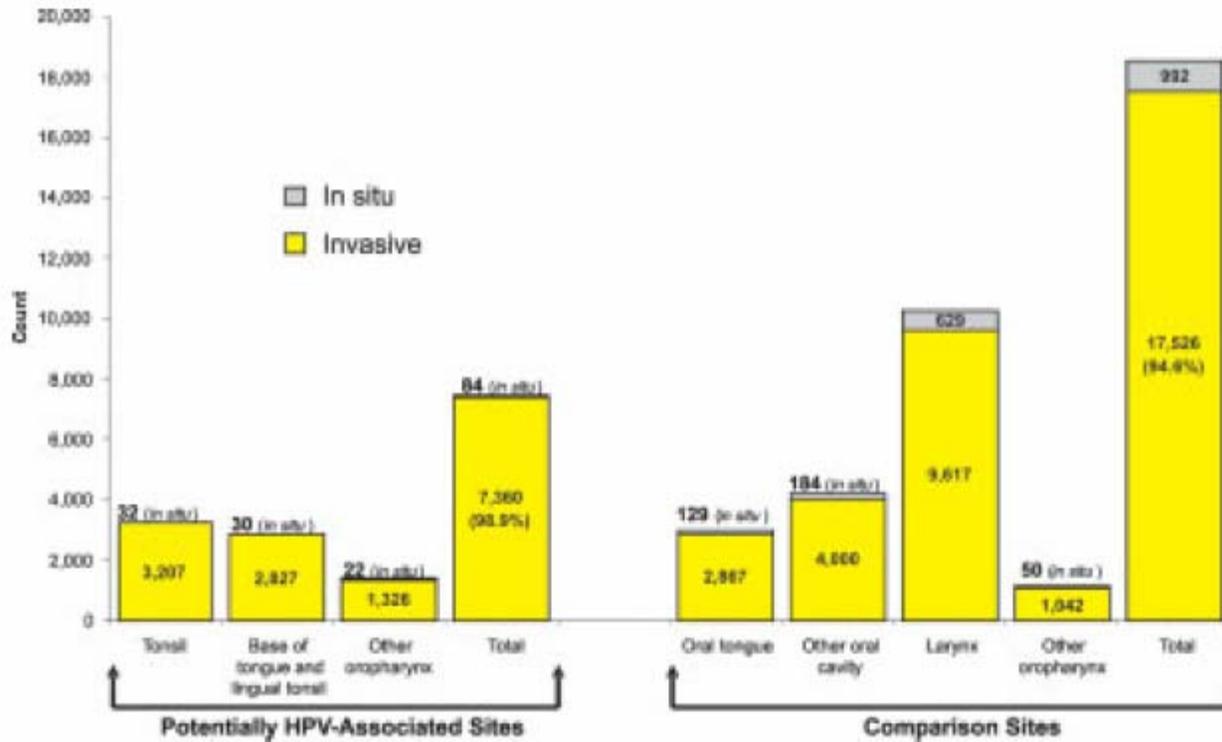


# HPV-associated Oral Cancer

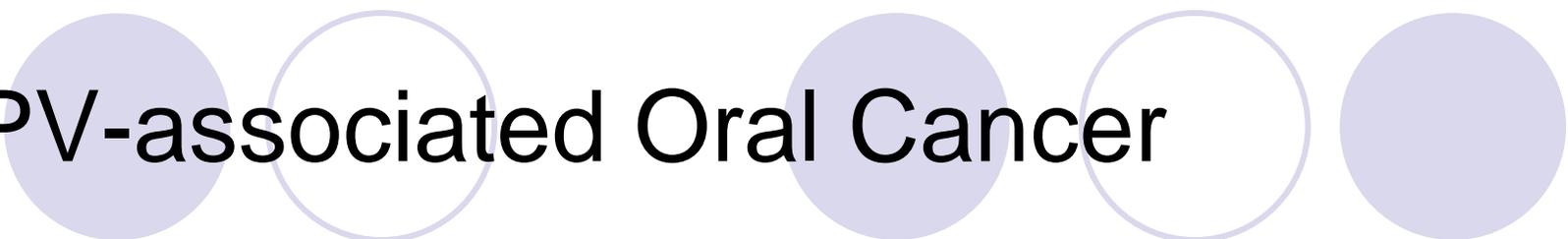
- Considerable variation in proportion of HPV-positive oropharyngeal cancers
- Applied data from previous studies on incidence of HPV in various oropharyngeal sites to NPCR and SEER data
- Compared sites considered potentially associated with HPV (tonsils including Waldeyer ring, base of tongue and lingual tonsil, and “other” sites including overlapping lesions and lesions NOS)

# HPV-associated Oral Cancer

- 44,160 cases of potentially HPV-associated cancers over study period
- Average of 7360 per year, or about 30% of all oropharyngeal cancers



Ryerson AB, Peters ES, Kawaoka K, et al. Burden of potentially Human Papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998-2003. *Cancer* 2008;113:2901-2909

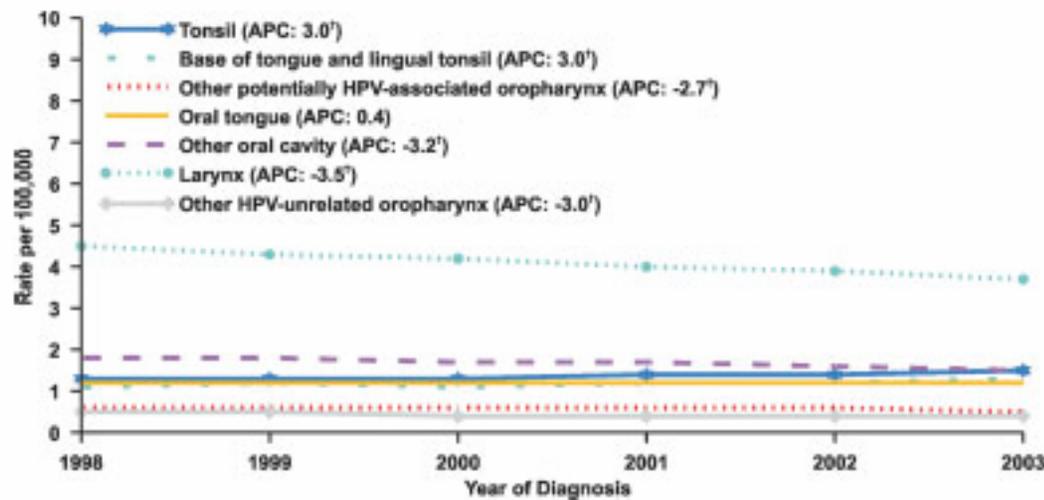


# HPV-associated Oral Cancer

- Age-adjusted incidence rates were 3 times higher for men than women for all sites
- Incidence rates also higher among blacks, higher among non-Hispanics than Hispanics, and higher among those who lived in the South
- More likely to be diagnosed at a late stage than non-HPV associated oral cancer

# HPV-associated Oral Cancer

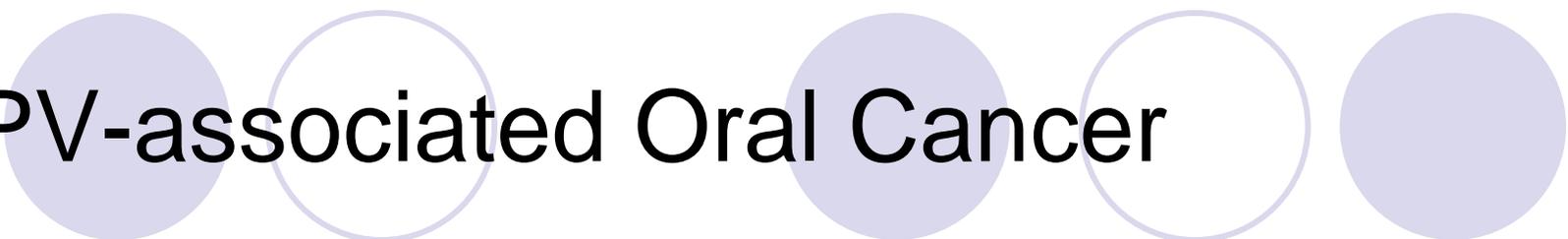
Trends in age-adjusted incidence rates of potentially HPV-associated and comparison sites of the oropharynx and oral cavity, 1998 to 2003



- IR of tonsillar and base of tongue cancers increased significantly (APC 3.0), whereas rates declined significantly at almost all comparison sites

# HPV-associated Oral Cancer

- In review of 60 studies, Kreimer et al. calculated average HPV-DNA positivity rate to be 35.6% for oropharyngeal carcinomas and 23.5% for oral cavity carcinomas
  - Overall 25% of these cancers have been associated with high-risk HPV types
  - HPV-16 accounts for 87% oropharyngeal, 68% oral cavity
- A study by Fakhry et al. found 63% of oropharyngeal carcinomas were HPV+
  - 95% HPV-16+



# HPV-associated Oral Cancer

- None of the vaccine trials have assessed the efficacy to reduce HPV infection in the oropharynx or oral cavity
- Average of 7360 potentially HPV-associated oral cancers per year, with high morbidity and mortality, reducing HPV infection could potentially prevent thousands of cases per year

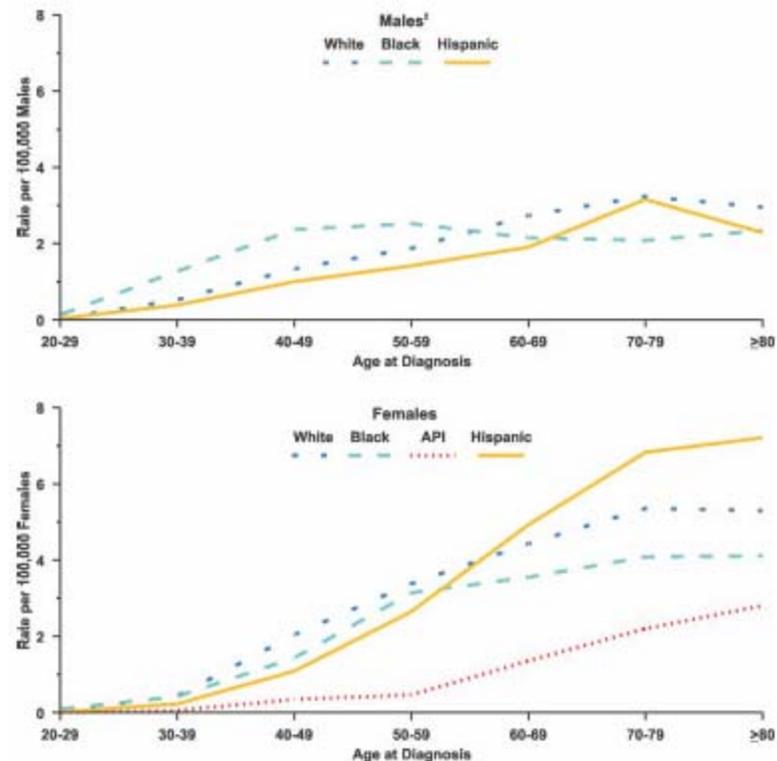
# HPV-associated Anal Cancer

- Uncommon malignancy
  - 1.5% of all GI cancers
  - 4% of cancers involving the lower GI tract
- Annual incidence rate has increased over the past 3 decades
- 80%-93% of anal cancers are associated with HPV, mainly 16 and 18
- Average annual count of 3566 cases of invasive anal cancer
  - 85% SCC
  - 14% AC, 1% small cell/NE

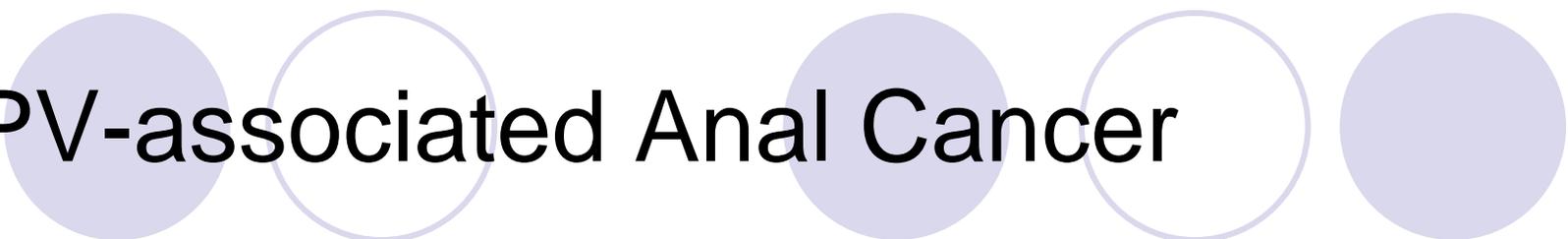
# HPV-associated Anal Cancer

- Rate of invasive anal cancer was higher among women
- No difference between blacks and whites
- Non-Hispanics had higher rate than Hispanics
- Rates higher in South
- Invasive anal SCC rates increased significantly from 1992 to 2004, by 2.7% per year among males and by 2.8% per year among females

Age-specific incidence of invasive SCC anal cancer according to NPCR and SEER data, 1998-2003



Joseph DA, Miller JW, Cress RD, et al. Understanding the burden of Human Papillomavirus-associated anal cancers in the US. Cancer 2008;113:2892-2900.

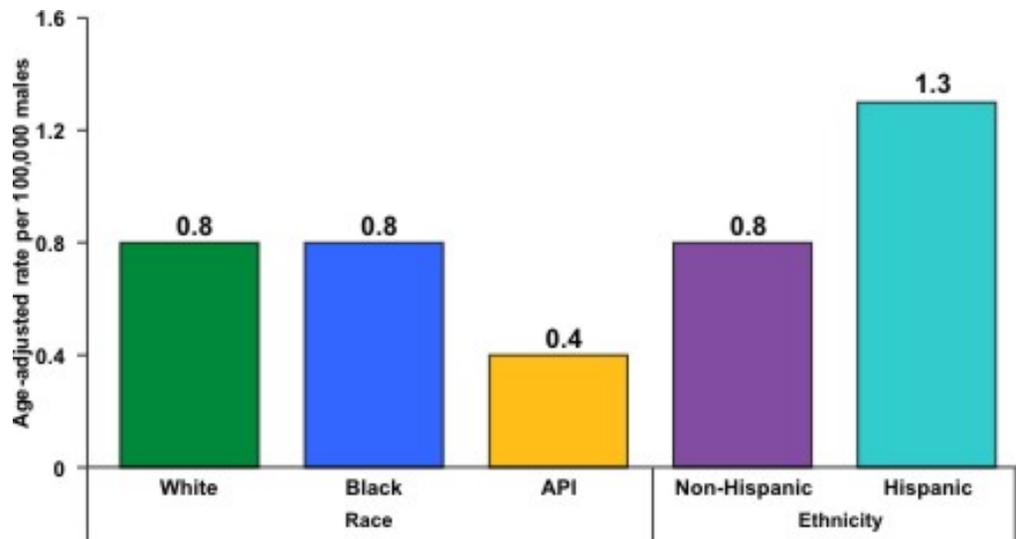


# HPV-associated Anal Cancer

- HPV vaccines against 16 and 18 have the potential to prevent SCC anal cancers in
  - 86-89% of women
  - 40-53% heterosexual men
  - 95% of HIV+
- Research underway to detect efficacy in men
- Some suggest screening those at high risk with anal pap smears; however, no data on whether screening reduces mortality or improves outcomes

# HPV-associated Penile Cancer

Age-adjusted incidence rates for penile cancer in the United States during 1998–2003.



- Average incidence rate of 0.81 per 100,000

- In general, HPV is thought to be associated with 40% of penile cancers, all SCCs.

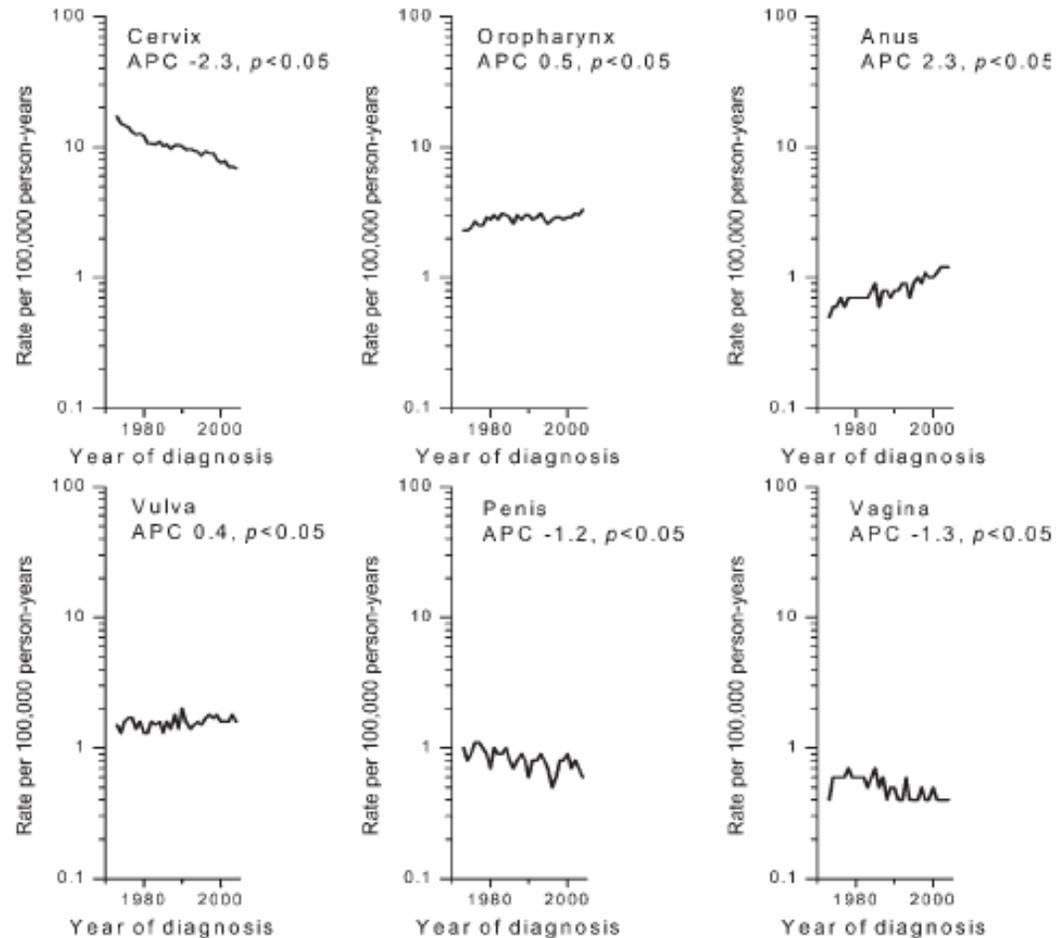
- 25% attributed to HPV 16 & 18

Hernandez BY, Barnholtz-Sloan J, German RR, Giuliano AR, Goodman MT, King JB, Negoita S, Villalon-Gomez JM. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998–2003. *Cancer* 2008;113:2883–2891.

# HPV Vaccine in Preventing Non-Cervical Cancers

- Vast majority of cervical and anal cancers are caused by HPV 16 and 18
  - Impact of the vaccine can be measured by IR over time.
- Other HPV-associated cancers are only partially caused by HPV and are differentiated using surrogate markers, such as anatomic location, age, and histology.
  - Risk factors such as sexual behavior and smoking can strongly influence incidence patterns

Incidence of HPV-associated oral cancers, anal and vulvar cancer is increasing, while incidence of cancers of the cervix, penis and vagina is decreasing.



Gillison ML, Chaturvedi AK, Lowry DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 2008;113:3036-3046

# HPV Vaccine in Preventing Non-Cervical Cancers

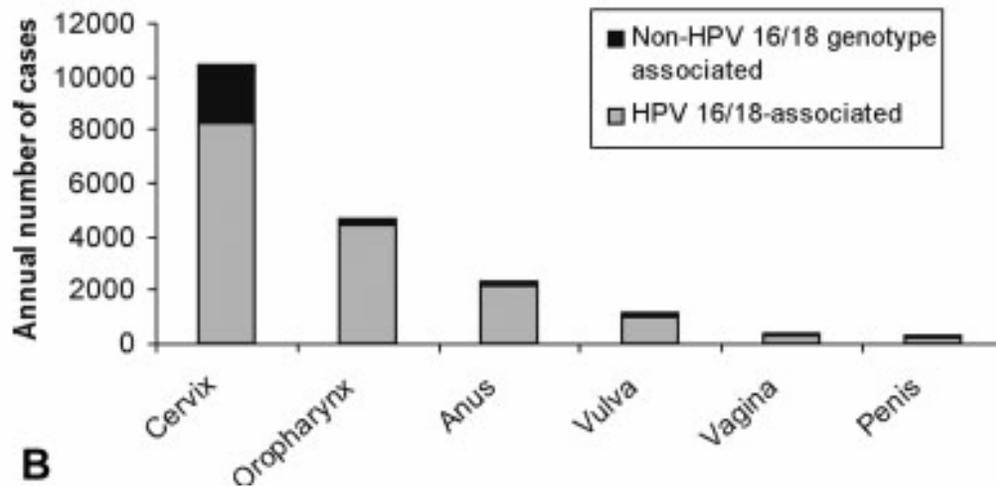
**TABLE 4**  
**Estimated Annual Number of Cases for HPV-associated and HPV16/18-associated Invasive Cancers in the US,**

	Proportion of All Cancers That Is HPV-Associated, %, (95% CI) <sup>a</sup>	Proportion of All Cancers That Is HPV16/18-Associated, %, (95% CI) <sup>a</sup>	Proportion of HPV-Associated Cancers That Is Attributable To HPV16/18 (95% CI) <sup>a</sup>
<b>US-specific Estimates</b>			
Cervix <sup>c</sup>	96 <sup>d</sup> (95-97)	76 (NA) <sup>e</sup>	76 (NA)
Oropharynx <sup>f</sup>	63 (50-75)	60 (47-72)	95 (82-99)
Anus <sup>g</sup>	93 (86-97)	87 (82-91)	93 (89-96)
Vulva <sup>h</sup>	51 (37-65)	44 (30-58)	86 (76-96)
Vagina <sup>i</sup>	64 (43-82)	56 (35-76)	88 (62-98)
Penis <sup>j</sup>	36 (26-47)	31 (22-42)	87 (69-96)
Total			
<b>Worldwide Estimates<sup>m</sup></b>			
Cervix	100	70	70
Oropharynx	35	31	89
Anus	90	83	92
Vulva	40	32	80
Vagina	40	32	80
Penis	40	25	63
Total			

Gillison ML, Chaturvedi AK, Lowry DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 2008;113:3036-3046.

# HPV Vaccine in Preventing Non-Cervical Cancers

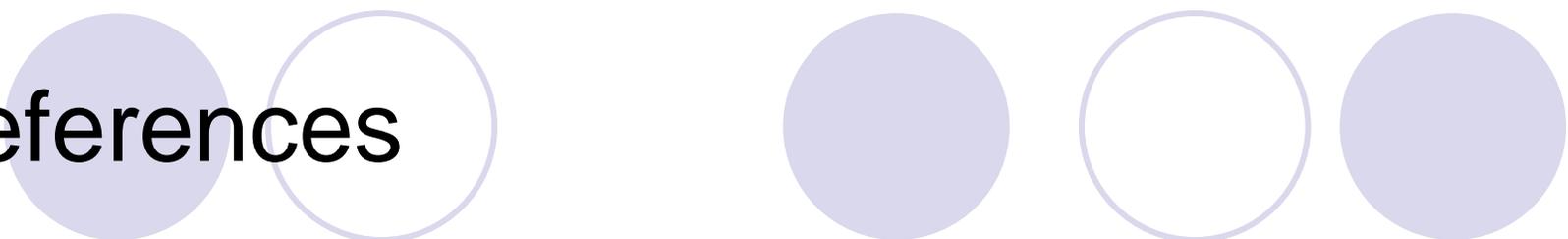
Estimated annual number of HPV-associated cancers in the US, 1998-2003, based on US-specific estimates



1. # of noncervical cancers caused by HPV each year approximates the # of cervical cancers
2. Cancers of the oropharynx , which occur largely in men, are the second most common HPV-associated cancer
3. # of noncervical cancers that occur in men approximate the # of noncervical cancers in women
4. Majority of HPV-associated cancers are attributable to HPV16 and 18 infections

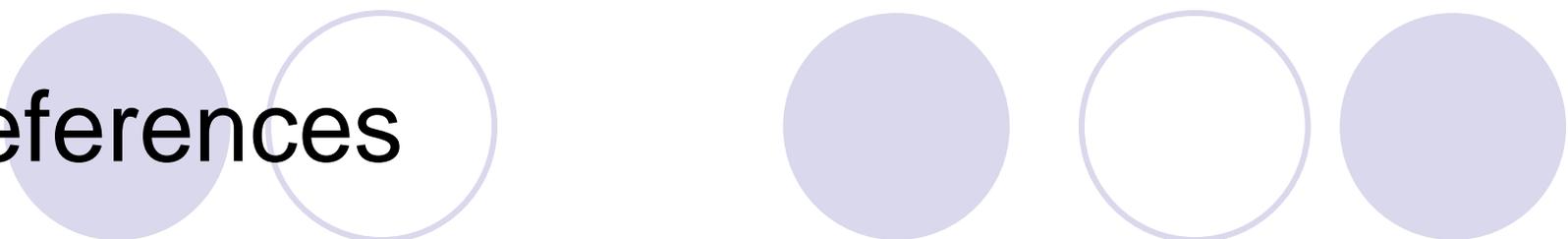
# HPV Vaccine in Preventing Non-Cervical Cancers

- Effect of vaccines will depend on efficacy against anal and oropharyngeal infections
- Vaccination must precede infection – peripartum or oral transmission?
- No screening for HPV-associated non-cervical cancers, thus vaccination may have greatest potential in prevention
- It is unlikely that nonmandatory vaccination of adolescent females will lead to significant herd immunity
- Future vaccines with more high-risk types will add limited benefit, except for cervical cancer



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