

HPV: From Disease “Burden” to Prevention:  
Can we eradicate cervical cancer in our  
lifetime?

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## Conflicts of Interest

None

Preventing Cancer:  
Combining science and policy to prevent cancer



## Objectives

- To share my enthusiasm for the rapid advances and changes in the field of HPV related cancer and prevention
- To show you that the answer is yes—we will eradicate cervical cancer, and may prevent many other HPV related cancers if we vaccinate all, and screen those who aren’t vaccinated for cervical cancer.
- To demonstrate that we need to think creatively about delivering care, given the variation in resources around the world

## Percentage of Cancers Attributable to HPV, US

- Cervix 91%
- Vagina 75%
- Vulva 69%
- Anus 91%
- Oropharynx 70%
- Penis 63%

Source: <https://www.cdc.gov/cacer/hpv/statistics/cases.htm>

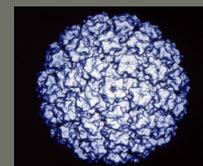
## What is HPV?

A virus that infects human skin  
and mucosal surfaces

Transmitted easily by touching

Classified as a carcinogen

Most females and males will be  
infected with at least one type of  
mucosal HPV at some point in  
their  
Lives



HPV

There are 13/14 high risk HPV  
types associated with cervical ca

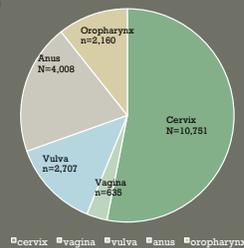
80% of US women will test

### How many people are affected by HPV?

- 79 million Americans are estimated to be infected with HPV
- 3 million Americans seek medical care for HPV each year
- 34,000 develop HPV-related cancers
- HPV currently causes as many deaths annually as measles did in the pre-vaccine era

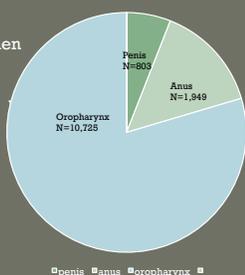
### Number of HPV related cancers US 2011-2015

per site in women  
N=20,260



### Number of HPV related cancers US 2011-2015

Per site in men  
N=13,477



### Cervical Cancer Incidence and Mortality

- >500,000 women worldwide are diagnosed annually with cervical cancer
- ~266,000 women die from cervical cancer worldwide annually
- >12,000 women are still diagnosed each year in the US, and >4000 die annually
- Mortality rates vary dramatically from <2/100,000 in Australia to >20/100,000 in some developing countries.

### Mortality Rate of Cervical Cancer



### Boston



## A Story

- 35 yo G0 presented to the BWH EW with vaginal bleeding. Due to changes in her insurance she has not had a Pap in many years. Exam shows her to have stage 3 cervical cancer.
- She was treated with chemo/radiation at BWH.
- I recently celebrated her 10 year anniversary with her.

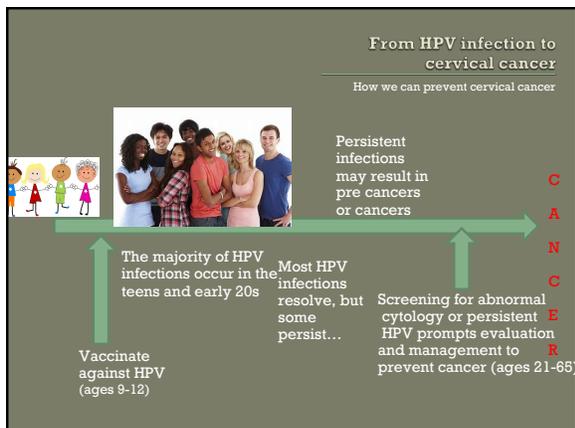
## Rwanda



- 35 yo mother of 8 presents in Rwanda with vaginal bleeding
- Exam shows her to have cancer involving her cervix measuring about 1cm. Biopsy confirms cervical cancer.
- There is no one trained to do radical hysterectomy in Rwanda. There are no radiation machines in country. The closest one is in Uganda and there is a 6 month wait.
- Hmm... All of the guidelines for treatment assume optimal resources available.....

## We should be able to prevent cervical cancer

- We know what causes it- persistent HPV infection leading to oncogenic changes (dysplasia) in cervical cells
- We know how to screen for and treat cervical dysplasia
- We know how to prevent initial infection with HPV through vaccination



We can prevent progression from infection to cancer....

Traditional Cervical Cancer Prevention includes:  
(also known as “secondary prevention”)

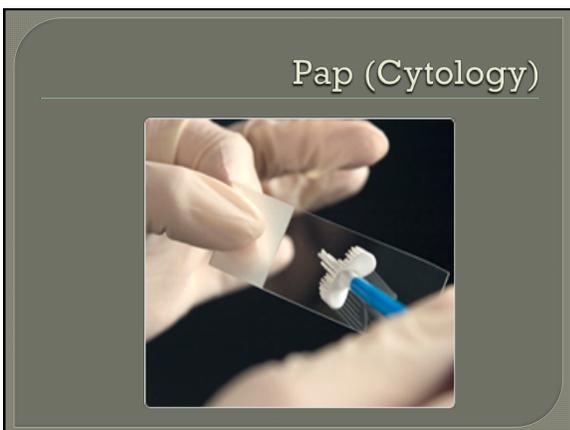
Screening to detect abnormalities among asymptomatic patients (eg Pap, HPV testing or Visual Inspection with Acetic Acid VIA)

Biopsy +/- colposcopy to provide a pathologic diagnosis of pre-cancer or cancer

Treatment to prevent progression to cancer either by ablation (cryosurgery or laser) or excision (LOOP or cold knife cone)

The first screening test used to prevent cancer is the Pap test. Screening is detecting disease in asymptomatic patients.

- 1923-Dr Papanicolaou discovers Pap
- 1960s-ACS endorses screening
- 1980s first ACS guidelines for Pap screening
- “The most successful cancer screening test”



### HPV Screening

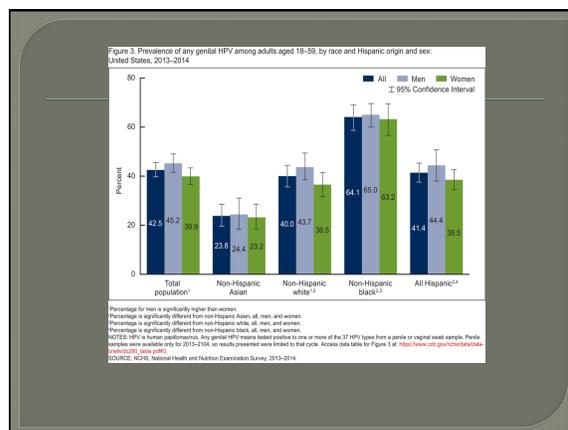
### Long Term Risk of CIN3+ after HPV infection: role of persistence

Kjaer, et al. J Natl Cancer Inst 2010 Oct 6; 102(19):1451-3

8656 women in Denmark  
Co-testing-underwent pap and HC2 testing  
2 exams, two years apart  
Then followed in registry for 12 years

**Estimated risk of CIN3+ for women who were HPV16+ at two years apart=47.4%**

Risk of CIN3+ after HPV negative= 3%



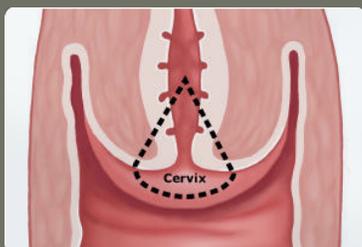
### Primary HPV screening (screening with HPV test alone)

- May be self administered or detected in urine, but has lower sensitivity than when performed by the clinician
- Cost has come down through global health initiatives
- Can also be performed at Point of Care (POC) so results may be immediate
- Recently added to USPSTF guidelines for primary screening in the US

We know how to diagnose cervical dysplasia (precancerous changes) with colposcopy and biopsy



And how to treat before dysplasia progresses to cancer.... With either ablation or excision of abnormal lesions



### Screening and Management of Precursors

- Resource intensive
- Require personnel trained in screening, diagnosis and treatment as well as adequate pathology services
- Complicated

Even in the US with a lot of resources.....

- **Guidelines are complicated**
  - (see Davis, M et al. Making Sense of Cervical Cancer Guidelines)
- **New Guidelines may miss cancer, especially in women under 30**
  - (see Nitschmann, C et al. Screening History Among Women with Invasive Cervical Cancer in an Academic Medical Center)
- **We don't always have good systems for tracking and follow-up of abnormal results**
  - (See Schapira, M et al. Inadequate Systems to Support Breast and Cervical Cancer Screening in Primary Care Practice)
- **Patients may still have barriers to care**
  - (see Luckett, R, et al Effect of patient navigator program on no-show rates at an academic referral colposcopy clinic.)

### Primary Prevention: HPV vaccination

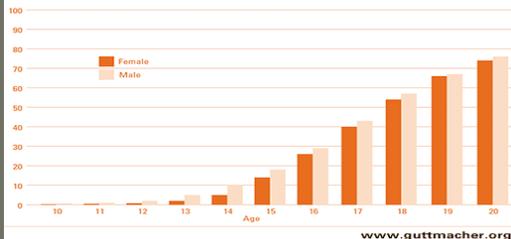
Prevent HPV infection before exposure

## Rationale for vaccinating early: Protection prior to exposure to HPV

### Teen Sexual Activity

Adolescence is a time of rapid change.

% of adolescents who have had sex by each age



## HPV is even found in virgins

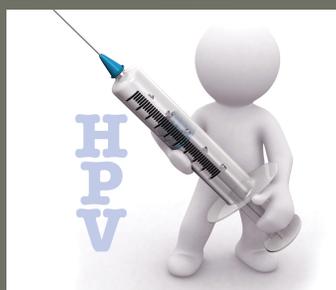
A study was done to look at a group of young women who had *never* had vaginal sex to see how many of these women had vaginal HPV

The study found that:

- HPV was found in 46% of the women; **almost half of the women had HPV before ever having sex**
- But most did have some type of intimate contact that could explain how they got HPV

Shew, J Infect Dis, 2012

## Vaccination before exposure prevents infection



## New HPV Vaccine Recommendation

Feb 2015

Advisory Committee on Immunization Practice (ACIP)

- 9-valent HPV vaccine (9vHPV) (Gardasil 9, Merck)
- FDA approved December 2014
  - Females 9-26, Males 9-15
- Recommended 9v HPV
- ACIP reviewed data and expanded male age groups
  - Males generally up to 21
  - thru 26 for immuno-compromised men, or who have sex with men

MMWR March 27, 2015 / 64(11):300-304

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## 9-Valent HPV vaccine against Infection and Intraepithelial Neoplasia in Women

Joua et al NEJM 2015;372:711-23

- 14,215 RTC women, 16-26, 40 months mean f/u
- 4v HPV vs 9v HPV vaccine
- 48% HPV+ on Day 1 (serology or PCR)

Rate of high grade cervical, vulvar, vaginal disease 14/1000 person-yrs overall in both vaccination groups

- In initially HPV neg women, 96.7% of high grade cervical, vulvar, and vaginal dysplasia due to the 5 added HPV types was prevented by Gardasil 9

### Updated HPV Vaccination Recommendations

- **Females 9vHPV**
  - Routine Age 11-12 –protect before exposed!
  - 9-26 years old , not previously vaccinated or not completed the 3 dose series
- **Males 9v HPV**
  - Routine Age 11-12
  - 9-21 years old, not previously vaccinated or not completed the 3 dose series
  - Thru 26 for men who have sex with men or immuno-compromised (HIV+ etc.)

### Dosing for HPV vaccine: ACIP

| Population   | Recommended number of HPV vaccine doses | Recommended interval between doses |
|--|---|------------------------------------|
| Persons initiating HPV vaccination at ages 9 through 14 years,* except immunocompromised persons†  | 2                                       | 0, 6–12 months‡                    |
| Persons initiating HPV vaccination at ages 15 through 26 years‡ and immunocompromised persons† initiating HPV vaccination at ages 9 through 26 years | 3                                       | 0, 1–2, 6 months**                 |

*No need to start over if already started vaccination*

### HPV vaccine side effects

|          | 9V HPV vaccine       | 4v HPV vaccine       |
|----------|----------------------|----------------------|
| Pain     | 89.9%                | 83.5%                |
| severe   | 4.3%                 | 2.6%                 |
| Swelling | 40%                  | 28.8%                |
| severe   | 3.8%                 | 1.5%                 |
| Erythema | 34%                  | 25%                  |
| Systemic | 55.8%                | 54.9%                |
| Headache | 14.6%                | 13.7%                |
| Pyrexia  | 5%                   | 4.3%                 |
| Nausea   | 4.4%                 | 3.7%                 |
| Deaths   | None vaccine related | None vaccine related |

NO SERIOUS SIDE EFFECT ATTRIBUTABLE TO THE VACCINE

Report events 800-822-7967 <http://vaers.hhs.gov>

### HPV vaccine long-term safety data

Among 190,000 girls in the U.S.  
No increase in emergency room visits, hospitalizations, or any of 200 categories of illnesses

No concerns noted in safety systems in over 80 countries

Arnheim-Dahlström, BMJ, Oct 2013 Klein NP, Archives of Pediatrics and Adolescent Medicine Oct 2012 Scheller. *JAMA*. 2015

### New FDA approval October 5, 2018

- FDA approves expanded use of Gardasil 9 for men and women ages 27-45
- One study showed 88% efficacy against HPV types, cancers and precancers covered by the vaccine

*CDC/ ACIP has not yet endorsed  
Not clear if insurance will cover*

### How many cancers could be averted with vaccination?

- Potential to prevent more than 90% of HPV related cancers
- Could prevent more than 33,000 cases of cancer in the US annually
- **This year in the US # cases of oropharyngeal cancer surpasses cervical cancer**

## US Vaccination Rates

- Only 48.6% of teens fully vaccinated (2017) \*
- 80% coverage rate of kids < 12 yo would prevent 53,000 cervical cancer cases

\*65.5% in MA (2017)  
 Data source: 2017 National Immunization Survey-Teen

## Vaccinating early has a major impact!

An Australian study looked at 39,000 girls who were vaccinated between age 14 and 17:

- It showed a 75% reduction in cervical pre-cancer for girls vaccinated by age 14
- It showed a 35% reduction in cervical pre-cancer for girls vaccinated after 14
- The vaccine was twice as effective in children who received the vaccine before age 14 because they had a better immune response *and* were less likely to have been exposed to HPV



## HPV Vaccine – Main Messages

HPV cancers are rising

- Oropharyngeal cancer now surpasses cervical cancer as most common HPV related cancer and is more common in men
- 6 different types of HPV-associated cancers

HPV vaccine is safe, effective, and long-lasting

- Over 100 million doses distributed in US
- Infections with HPV types that cause most HPV cancers and genital warts have dropped 71% in teenage girls

We need to increase HPV vaccination rates to decrease HPV associated cancer

- The 9vHPV vaccine has the potential to prevent 92% of HPV-attributable cancers, which equals 31,000 cancer cases!
- Your strong recommendation is vital!

<http://www.cdc.gov/od/oc/media/press/2014/s014.htm>  
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Given how far we've come, anything may be possible...

