Prevention of HPV Disease

History
- 1952 HPV was discovered
- 1978 - HPV was first identified in skin cancer
- 1982 - connection between HPV 16 and 18 and cervical cancer was established
- 2006 - First HPV vaccine approved by FDA
- 2007 - FUTURE II Study of Vaccine Effectiveness published
- 2008 Nobel Prize given to Harald zur Hausen for discovery of HPV as cause of cervical cancer

Disease Burden Statistics

How common is HPV?
- Lifetime likelihood of getting genital HPV = 75-90%
- Risk of HPV exposure = 15-25% per partner
- 1.2% of population has genital warts, 10% lifetime risk
- 2-5% have abnormal pap at any one screening

Incidence of HPV related Cancer
- 12,000 Cervical cancer diagnoses
- 4000 Cervical cancer deaths
- 1,500 Vulvar cancer diagnoses
- 500 Vaginal cancer diagnoses
- 400 Penile cancer diagnoses
- 2,700 women and 1,500 men Anal cancer diagnoses
- 1,500 women and 5,600 men Oropharyngeal cancer diagnoses
[Note: Many of these cancers may also be related to tobacco and alcohol use.]

Global Cervical Cancer Incidence
- 530,000 new cases in 2008
- 275,000 deaths in 2008
- 85% of cases are in less developed parts of the world
- Age Standardized Rates are over 30/100,000 in Africa
- ASR in Australia/New Zealand are <6/100,000
HPV related cancer

- Cervical Cancer – 70% caused by HPV 16 or 18, 30% caused by other subtypes of HPV
- Anal Cancer – 85% caused by HPV 16
- Vaginal, Vulvar and Penile Cancer – 50% caused by HPV 16 and 18
- Oropharyngeal Cancer - ~50% caused by HPV 16
- 25.9% age 35 – 44
- 10.7% age 65 – 74;
- Smoking (2X the risk of Cervical CA)
- How does HPV cause CIN3+ over next 5 years
- Median age at diagnosis: 48 years old.
- 2% under age 20
- 14.0% age 20 – 34
- 25.9% age 35 – 44
- 23.9% age 45 – 54
- 16.7% age 55 - 64;
- 10.7% age 65 – 74;
- 6.1% age75 – 84
- 2.6% 85+ years of age.
- How can we prevent cervical cancer?

Risk factors for Cervical Cancer

- Smoking (2X the risk of Cervical CA)
- HPV
- Chlamydia Antibodies
- Diet/low in fruits and vegetables
- OCP (2X risk if took OCP>5 years but back to normal after stopping for 10 years)
- IUDs decrease risk
- Multiparity - 3 or more term IUPs increases risk
- Age <17 at first term IUP (2X risk of age >25 at first IUP)
- Poverty
- DES exposure (last given in 1971)
- Family History of Cervical Cancer (2-3 X if mother or sister had cervical CA)
**Screening for Cervical Cancer**

- Pap smears have never been studied in large randomized control trials.
- However, there is good evidence from multiple large observational studies showing very large decreases in incidence and mortality after pap smear surveillance was started in many different countries.
- In Iceland, cancer diagnoses decreased by 80% with pap smear screening.
- According to the National Cancer Institute, regular screening decreases cervical cancer incidence and mortality by 90%.
- Screened HPV+ cervical cancer was the most frequent cause of cancer death in women in 155.
- Now it is the 14th most frequent cause of cancer death in women.

**New Pap Smear Guidelines in 2012**

- Age < 21 - NO SCREENING
- Age 21-29 - Pap w/reflex HPV for ASC-US every 3 years
- Age 30-65 - HPV (not reflex) cotesting with Pap every 5 years OR Pap w/reflex HPV for ASC-US every 3 years*
- Age >65 - No screening following adequate negative prior screening

**Harms of Pap Smear Screening**

- 50% of women undergoing regular pap smear screening will undergo an additional diagnostic test.
- 5% will be treated with LEEP for CIN 1.
- Unknown impacts of future fertility.
- Negative effects are most prominent when screening young women because they are least likely to develop cancer.

**Screening with pap smears**

- 50% of cervical cancer is found in women who have NEVER had a pap smear.
- 10% of cancer is found in women who have not had a pap in >5 years.
- SO THE MOST IMPORTANT PERSON TO PAP IS THE 50 Y/0 RECENT IMMIGRANT WITH DIABETES! NOT THE 22 Y/0 ON YOUR SCHEDULE FOR BIRTH CONTROL.

**What is the most common pap smear result prior to Cancer diagnosis?**

- NILM
- ASC-US
- LSIL
- HSIL

**Chance that a woman with abnormal pap has HPV?**

- Cancer pap
- HSIL
- LSIL
- Atypical Squamous Cells of Undetermined Significance (ASC-US)
Significance (ASC-US) – 60%

FUTURE II Results
- In women without prior HPV, vaccine efficacy = 98% for HSIL due to HPV 16 or 18 (per protocol)
- In all women (regardless of HPV status before vaccination), vaccine efficacy = 44% for HSIL due to HPV 16 or 18 (intention to treat)
- In all women (regardless of HPV status before vaccination), vaccine efficacy = 17% for HSIL due to any type of HPV

Vaccination
- Gardasil (Merck) approved in US June 2006 – covers HPV 6,11, 16 and 18
- Cervarix (GlaxoSmithKline) approved in US Oct 2009 - covers HPV 16 and 18

Future II – Study*
- Ages 15-26, no abnl paps, and <5 lifetime partners
- No evidence of HPV infection thru 1 months after the 3rd dose
- 12,167 women got 3 doses of Gardasil starting June 2002
- Followed for 3 years after first dose
- End point CIN 2 or 3, adenoCA in situ or CA related to HPV 16 or 18
*Trial designed, managed and analyzed by Merck

Future II Results
- 219 of 6087 vaccinated women (3.6%) diagnosed with CIN2,3 or AIS
- 266 of 6080 unvaccinated women (4.4%)
- However, in analysis by lesion type efficacy is only significant for CIN 2
- 129 women need to be vaccinated to prevent 1 case of CIN 2,3

Chance that a woman with abnormal pap has HPV?
- Cancer pap – 100%
- HSIL – 99%
- LSIL - 90%
- Atypical Squamous Cells of Undetermined Significance (ASC-US) – 60%
PATRICIA Study of Cervarix

- Ages 15-25, 18644 Women
- Prevention of CIN2,3 or AIS due to HPV 16/18 in women not exposed to HPV - 93%
- No evidence of prevention of CIN2,3 or AIS due to HPV 16/18 in women who were already antibody positive
- There may be some cross reactivity of the vaccine in that there was a 37% reduction in CIN2+ due to non vaccine types of HPV

Why not a better effect?

- Vaccine appears not to help women with previous HPV 16/18 exposure
- ~30% of CIN2,3 is caused by other subtypes of HPV (Did other types HPV fill the niche left by 16/18?)

Combined FUTURE I and II data

- HPV vaccination reduces CIN2,3 by 43% in women who have not yet been exposed to HPV
- HPV vaccination reduces CIN2,3 by about 18% in a population that includes women who have been exposed and are naïve
- HPV vaccination reduces risk of colposcopy by 20% in all comers
- I could not find any analysis of only women who were not HPV naïve
- Studies have not gone out more than 7 years yet

How long does immunity last?

- At 2 years 90% are seropositive for HPV 6, 11, and 6 = 90%
- At 2 years immunity for HPV 18 =68%

Recommendations for HPV Vaccination

- CDC/ACIP Recommend Routine Vaccination of Females Age 9-26 (Recommended age 11-12)
- CDC/ACIP says Males aged May be given Gardasil to decrease the risk of genital warts but it is not recommended for routine vaccination
- ACS recommends Routine Vaccination of Women Age 9-18
- ACS says there is insufficient data to recommend vaccination of males or women older than 19 but if a woman has fewer than 3 lifetime partners, she could benefit from the vaccine.

What about vaccination in older women

- Merck attempted to get FDA approval for Gardasil form women age 27-45. However, in 2010 this was denied. However, FDA did change label information based on this request
- The study submitted showed only a decrease in persistent (6 months) HPV infx or CIN 1
- No efficacy for CIN2+ was demonstrated. In fact, there were more cases of CIN2 in the Gardasil group compared with placebo!
My questions

- How long will vaccine immunity last?
- What will the impact of exposure to HPV after immunity wanes at older ages be?
- First enrollment ages 15-26 was 2002 – we await data when those women are in high risk age (35-65) which should be 2013 -2052

Adverse Effects

- Vaccine Adverse Event Reporting System (VAERS) – run by CDC and FDA
- As of Sept 2011, 40 million doses of Gardasil distributed
- 20,096 adverse events – 8% considered serious
- Non serious events – local pain and swelling, dizziness, nausea, fainting

Serious Adverse Events

- Hypersensitivity/Anaphylaxis
- Transverse myelitis
- Pancreatitis
- Guillain-Barre Syndrome –
- Blood Clots
- Death - 71 reported – 34 confirmed. In those confirmed cases no pattern or cluster is found.
  None of these events seems to occur above the background rate of these diseases in the relevant age group.

Cost of the HPV Vaccine

- Vista bills $172/dose
- Cost to Vista is $137/dose
- All kids up to age 18 are covered
- After age 18 coverage varies by insurance

Take Home Points

- Pap smear screening is very effective for prevention of cervical cancer.
- Screening and treatment recommendations do not vary with vaccination.
- More data/time is needed to understand the impact of HPV vaccination on the risk of cervical cancer