HPV

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HPV

- Who are they
- What do they do and how
- Prevention
  - Vaccines
  - Barriers
HPV: who are they

- Species-specific viruses that
- Infect skin or mucous membranes
- > 130 types
- Skin infection can lead to warts
- ~ 40 infect anogenital cells or oropharynx
- Associated with ~90% of anogenital dysplasias and carcinomas, in both women and men
- Genital warts - condyloma acuminata: most common types = 6 and 11
- Cervical and penile carcinoma - most common types = 16 and 18

Human Papilloma Viruses

- Late 19th century human wart extracts were shown to produce warts with injection into humans.
- Ciuffo, 1907, transmitted warts with cell-free filtrates – deduced viral nature

- But not readily propagated in culture, so rapid growth in knowledge about HPVs dates from the 1970s, when molecular techniques became available
- The genital tract is the main reservoir for mucosal HPVs, but two mucosal HPVs infect the oral cavity exclusively.
HPV

- most common STI (sexually transmitted infection)
- > 6 million new infections per year in USA
- > 30 HPV types infect the genital tract.
- prevalence, by PCR, is > 40% in young, sexually active adolescent and college-aged women.
- prevalence highest ages 15 to 25; declines in females (60%, males)
- Infection risk increases with number of partners, recent change in partners, and the sexual history of the partner.
- Most women with HPV infections: normal cytology, no symptoms
  - ? Does infection with one HPV type prevent reinfection with the same type?
  - With HIV or other immunodeficiencies, the prevalence of HPV infections and cervical changes are more common – the importance of the immune system

Nobel prize 2008

- Harald zur Hausen
- "for his discovery of human papilloma viruses causing cervical cancer"
- Most genital warts contained DNA sequences from HPV 6 and 11
- HPV 16 and 18 cloned from cervical cancer cells
Papillomaviruses

- Types: classified by genotype
- Nonenveloped, double stranded DNA
- Icosahedral capsid composed of 72 capsomeres
- Virion contains ≥2 capsid proteins
- L1 - major capsid protein = 80% of the virion by weight --- vaccine antigens
- L2 - minor capsid protein
- Significant conservation in L1 among HPV types

Genital HPV

- Genome has early (E) and late (L) genes
- L genes are structural external proteins
- E genes include oncogenes (E6, E7)
- “High risk” types: high oncogenic potential
- Low risk types: low
- Almost 100% of cervical cancer contain HPV DNA from high risk types
- Type 16 – 50-70%
- Type 18 – 7-20%
HPV: what do they do

- Stealth viruses
- Infect basal keratinocyte
  - mucosal or cutaneous epithelium
  - low genome copy #
- Infected cell enters proliferating epithelium
  - Viral gene expression remains low
  - Oncogenes E6 and E7 very limited
- Cell enters differentiating level
  - massive upregulation of all genes
  - from 50-100 to 1000 copies of DNA per cell
- Then L1, L2 proteins – and viral assembly

HPV: stealth viruses (2)

- Basal and parabasal cells: express early genes
  - viral DNA is replicated in low copy numbers, no L1, L2.
  - Low level viral antigens helps evades immune system
- Upper layers of epithelium: viral genes upregulate - production of infectious virus, oncogenes
  - Infectious virus shed constantly: contagious
- E6, E7 genes if inappropriately expressed in dividing cells deregulate cell division and differentiation
- High risk CIN’s are genetically unstable……
Terminology: cell changes

- VIN: vulvar intraepithelial neoplasia
- VaIN: vaginal intraepithelial neoplasia
- ICC: invasive cervical carcinoma
  - Squamous cell, Adenosquamous, Adenocarcinoma
- AIS: adenocarcinoma in situ
- CIN: cervical intraepithelial neoplasia (precursor lesions):
  - grade 1: low grade atypia
  - grade 2: high grade atypia (CIN 2/3 or CIN 2+)
  - grade 3: high grade atypia (carcinoma in situ)
  - grade 3 has 30-40% risk of progression to ICC

Cervical intraepithelial neoplasia

- CIN

- aka cervical dysplasia
- abnormal squamous cells on cervix surface
- not cancer, usually curable
- Most cases remain stable or are eliminated by the immune system without intervention
HPV: stealth viruses

- Great majority of infections are silent
- 80-90% self-resolve
  - High risk in ~12-18 mos
  - Low risk in ~ 4 - 9 mos
- 10-20% remain DNA+
- High grade lesions may progress to cervical CA without intervention
- grade 3: 30-40% risk of progression to ICC

Cervical Cancer

- Squamous cell carcinoma of the cervix
- #2 female malignancy worldwide
- #1 female malignancy in developing world
- ~ 500 K new cases, ~ 250 K deaths worldwide per year
- ~10,000 cases, ~3700 deaths USA/yr
Cervical Cancer (2)

- From initial infection with lesions invasive cancer: years to decades.
- HPVs are found in almost 100% of cancers and precursor lesions
- HPV types and cervical cancers contain
  - > 50% due to type 16
  - ~ 70% due to types 16 & 18
  - ~ 80% due to types, 16, 18, 45, 31
- HPV-18 associated preferentially with adeno-CA of the cervix.
- Viral genome
  - free copies with normal cervical histology or low-grade lesions
  - integrated into cellular DNA in most invasive cancers

Cervical Cancer (3)

- Rates in USA have decreased due to cervical screening
- Cervical lesions detected by Pap smear can be treated
- But 3-4,000 cases per year of ICC still occur:
  - limitations of screening methodology
  - failure to undergo testing
- In young women, infection is low risk, often resolves
- High risk HPV infections for cervical cancer
  - HPV infections in older women
  - persistent HPV infections with progressive cytologic abnormalities in women of any age
- Women with HIV infection at high risk of
  - persistent HPV infection with
  - progression to cervical cancer
HPV: other cancers

- Vaginal: ~ 1100 cases, 400 deaths USA/yr
- Vulvar: ~ 3500 cases, 880 deaths
- Anal: ~ 5000 cases, 720 deaths (est)
  - ~ 1.6/100,000 vs.
  - ~ 8.1/100,000 for cervical cancer
  - much higher HIV+ males, women ICC
  - Type 16 – 70%; 16 & 18 – 84%
- Penile: ~ 1290 cases, 300 deaths (est)

HPV: genital warts

- > 500 K cases USA/yr
- ~ 15 fold more subclinical infection
- 4-13% of STD clinic cases have warts
- Mean duration 95 days
  - Males 116 days
  - Females 60 days
- More common in WSW
- Treatment – recurrence, resistance
HPV & children

- Recurrent respiratory papillomatosis
  - Incidence: 0.24 per 100,000 children
  - Prevalance: 1.11 per 100,000
- Anogenital HPV in prepubertal children may occur from non-sexual (horizontal) and vertical transmission
- Types 6, 11 most common in both

HPV vaccines

- Antigen is L1 capsid protein
- Produced with recombinant technology
- Self assembled into virus-like particles (VLP)
- Contain NO VIRAL DNA – no cancer risk
- Induce neutralizing antibody (Ab)
- Aluminum adjuvants
- No thimerosal
HPV vaccines
FDA Approval

• Gardasil (Merck):
  – June 2006: girls and women
  – October 2009: boys and men
  – VLP antigens: 6, 11, 16, 18

• Cervarix (Glaxo) October 2009:
  – October 2009: girls and women
  – VLP antigens: 16, 18

HPV vaccines: ACIP rec’s

Gardasil
• Cervical cancers and precancers
• Vaginal and vulvar cancers and precancers
• Genital warts
• Males - permissive rec: to reduce likelihood of genital warts

Cervarix
• Cervical cancers and precancers
HPV vaccines: Efficacy **Cervarix**

- In 18,644 females, 15-25, efficacy was…
- 92.9%: CIN 2,3 or AIS (16, 18 related)

But for females w/o evidence of oncogenic HPV at baseline:
- 98.4%: CIN 2,3 or AIS (16, 18 related)
- 100%: CIN 3 or AIS (16, 18 related)

HPV vaccines: Efficacy **Gardasil**

- For females HPV-naïve (neg PCR and serology), age 16-26
- 98.2%: CIN 2,3 or AIS (16, 18 related)
- 100%: VIN 2,3 or VaIN 2,3 (16, 18)
- 99% genital warts females (6,11,16,18)
- 89.4% genital warts males (6,11,16,18)
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<th><strong>HPV vaccines: Efficacy Gardasil</strong></th>
<th><strong>HPV vaccines: cross protection</strong></th>
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<tr>
<td><strong>MSM</strong></td>
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<td>• 94.9%: Persistent infection (6,11,16,18)</td>
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<td>• 77.5%: A (anal) IN &amp; anal cancer (6,11,16,18)</td>
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<tr>
<td><strong>Gardasil</strong></td>
<td><strong>Cervarix</strong></td>
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<tr>
<td>• HPV-31</td>
<td>• HPV-31, 45, 52</td>
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<td>• Adjuvant: aluminum hydroxyphosphate sulfate</td>
<td>• Adjuvant: aluminum hydroxide with ASO4 (novel, proprietary)</td>
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<td>• Higher titers – but “protective” level undefined</td>
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**HPV vaccines: safety**

- No serious AE’s for either vaccine
- Transient muscle weakness: 1 case
  - Full recovery same day
- Minor injection site reactions
- Media reports of dramatic events - carefully investigated - no causal link
- VAERS data base can be confusing
- Syncope: 0.2% *
- Can be given with Adacel, Menactra with comparable immune response *

**HPV vaccine: barriers**

- Teens:
  - Infrequent healthcare visits
  - Busy schedules
  - Discomfort of vaccine
- Ref: Wong et al, PIDJ 1994; 13: 936
- **Parental attitudes**
  - “That vaccine…”
  - “that sex vaccine…”
HPV barriers

- Some families are not receptive to discussion.
- For those who are:
  - Strong clear recommendation
  - Provider rec’s are the most influential factor affecting parents’ vaccine decisions.
- Health Connect facilitates handouts