MALIGNANT AND PRE-MALIGNANT CONSEQUENCES OF HPV INFECTION

cervical, vulvar, vaginal, anal, penile and oropharyngeal cancers and their respective pre-cancerous lesions

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HPV INFECTIONS

- HPV is the most common sexually transmitted infection in the USA
- Small DNA virus 7900 bp
- Many subtypes exist (> 100)
  - Their prevalence can differ with:
    - Worldwide location
    - Disease with which it is associated
- HR and LR subtypes with varying degrees of oncogenic potential
  - Even among oncogenic subtypes
Human papillomavirus

- **Low risk**
  - 6,11,42,43,44

- **Intermediate risk**
  - 33,35,39

- **High risk**
  - 16,18,31,45,51,52,56,58,59,68,92
  - 16, 18, 31, 33, 45
  - Have been found in 63-97% of cervical cancers worldwide (Smith et al 2003)
HPV DNA is commonly present in cancers of the lower genital tract, anus and oropharyngeal sites.

Viral oncogenes, E6 and E7, are demonstrated in these lesions:
- E6 and E7 proteins are required to maintain cancer phenotype.

The best epidemiologic etiologic data comes from cervical cancer which shows HPV to be the major risk factor.
HPV INFECTIONS
Etiologic role in cancers

- HPV 16 is most commonly linked with the pre-malignant lesions and is associated with the highest risk of progression to cancer

Percentage cancers probably caused by HPV (CDC)
- Cervix ca: 91-100%
- Vulva scca: 69%
- Vaginal scca: 75%
- Anal scca: 91%
- Penis scca: 63%
- Oropharyngeal scca: 72%
Genital warts
- 6/11

Cervical cancer
- 16,18, 31, 33, 35, 45, 52, 58, 59, 68, 73, 82
- 71% 16
- 20% 18

Vulvar cancer
- 16,33 (55.5%)

Vaginal cancer
- 16, 18 (70%), 31, 33

Anal cancer
- 16,18

Penile cancer
- 16 (60%) 18 (30%)

Oropharyngeal
- 16 and 18,31,33
The highest predictor of genital HPV infection
- Sexual Activity
- Close skin to skin contact with an infected area
- Unprotected intercourse
  - Need not be penetrative
- Digital/anal contact
- Digital/vagina contact
- Oral/LGT contact
- Fomites
- Primary and secondary immunodeficiencies
Transmission is often asymptomatic
Type specific concordance between partners
  - 25%
More transmissible from females to males
  - Female to male higher rate than male to female
The ano-genital cancers are typically preceded by pre-invasive disease that is also caused by HPV infection.

Co-factors for development of pre-invasive and invasive disease are similar.
Relatively common

ACS estimates for 2014
- About 12,360 new cases of invasive cervical cancer will be diagnosed.
- About 4,020 women will die from cervical cancer.

Approximately 11,967 HPV-related cases per yr

Demographic breakdown/10^5 women (CDC) 2004-8 in USA
- 7 white
- 10 black
- 7 american indian/alaska native
- 7 asian/pacific islander
- 11 hispanic vs 7 non hispanic
Vulvar Cancer Rates

- Uncommon to rare
- ACS estimates for 2014
  - About 4850 new cases of invasive cancer will be diagnosed.
  - About 1030 women will die
- Approximately 3100 HPV-related cases per yr
- Demographic breakdown/$10^5$ women (CDC) 2004-8 in USA
  - 1.9 white
  - 1.4 black
  - 1.1 american indian/alaska native
  - 0.4 asian/pacific islander
  - 1.2 hispanic vs 1.9 non hispanic

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Rare

ACS estimates for 2014
- About 3170 new cases of invasive cancer will be diagnosed.
- About 880 women will die

Approximately 730 HPV-related cases per yr

Demographic breakdown/10^5 women (CDC) 2004-8 in USA
- 0.4 white
- 0.7 black
- 0.3 american indian/alaska native
- 0.3 asian/pacific islander
- 0.4 hispanic vs 0.4 non hispanic
Penile Cancer Rates

- Rare
- < 1% cancers in men (1640 new/320 deaths ACS 2014 estimates)
- Approximately 1000 HPV-related cases per yr
- Demographic breakdown/10^5 men (CDC) 2004-8 in USA
  - 0.8 white
  - 0.9 black
  - 1.0 american indian/alaska native
  - 0.4 asian/pacific islander
  - 1.3 hispanic vs 0.7 non hispanic
Anal Cancer Rates

- Uncommon
  - ACS 2014 estimates
    - 7,210 new cases (4,550 in women and 2,660 in men)
    - 950 deaths (580 in women and 370 in men)
- Approximately 3000 HPV-related cases/yr women
- Approximately 1700 HPV-related cases/yr men
- Demographic breakdown/10^5 women or men (CDC) 2004-8 in USA
  - 2.0 women and 1.1 men   white
  - 1.4 women and 1.6 men   black
  - 1.0 women and 0.7 men   american indian/alaska native
  - 0.4 women and 0.2 men   asian/pacific islander
  - 1.4 women and 0.8 men   hispanic
  - 1.9 women and 1.2 men   non hispanic

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Oropharyngeal Cancer Rates

- Increasingly more common than non-HPV related
- Base of tongue and tonsils
- 85,000 per year in both sexes worldwide
- Men are 4 times more likely than women to be affected.
  - Approximately 2370 HPV-related cases /yr women
  - Approximately 9356 HPV-related cases /yr men
- Demographic breakdown/10⁵ women or men (CDC) 2004-8 in USA
  - 1.4 women and 6.4 men white
  - 1.4 women and 6.3 men black
  - 0.8 women and 3.2 men American Indian/Alaska Native
  - 0.5 women and 1.7 men Asian/Pacific Islander
  - 0.7 women and 3.5 men Hispanic
  - 1.5 women and 6.5 men non Hispanic
CERVICAL CANCER

Epidemiology

- Median age at diagnosis is 48
  - 50% of women are between the ages of 35-55
  - Rarely occurs in women younger than 20
    - With exception of in utero DES related cancers
- 78% occur in developing countries
  - Second most common cancer among women worldwide
- Some researchers estimate that non-invasive cervical cancer (carcinoma in situ) occurs about 4 times more often than invasive cervical cancer
- Risk factors
  - Multiple
  - No recent pap tests
Risk of progression of CIN to cancer

- All CIN: 1%
- CIN 1-2: 1-10%
- CIN 3: 16-40%

- 4x more common than invasive cancer
- Average time for CIS is 10-15 years
- A subset progresses more quickly
  - < 3 years
  - High socioeconomic status
  - Younger
  - 1/3 are adenocarcinomas
CERVICAL CANCER PREVENTION

PAP TESTS

- 50% of women with cervical cancer have not had a recent pap test
  - Despite recent encounters with health care professionals within the last 6 months
- 1/3 will have had a recent normal pap test
  - More likely to occur with adenocarcinomas
  - False negative
    - Also found to be more likely with adenocarcinomas
  - Rapid progression of disease
- A VACCINE COULD PERHAPS FILL SOME OF THE GAP
CERVICAL CANCER
RISK FACTORS

- Early age at first sexual intercourse
- Multiple partners or partners with multiple partners (the so called high risk male)
- Tobacco use
- History of HR-HPV infection
- History of an abnormal pap smear
- History of LGT/anal cancer or pre-cancer of LGT/anus
- Immunosuppression
- Long interval between pap smears (> 5 years)
- Diet low in fruits and vegetables
- Obesity (adenocarcinoma)
- Low socioeconomic status
- Family history of cervical cancer
CERVICAL CANCER
RISK FACTORS

- Chlamydia infection

- In utero DES exposure
  - 1/1000 DES exposed women
  - Average age 19

- High parity
  - 3 or more FT pregnancies

- OCP use
  - Risk of cervical cancer goes up the longer a woman takes OCPs
  - Risk goes back down again after the OCPs are stopped
    - 3x increased in women who took birth control pills longer than 5 years
    - Risk returned to normal 10 years after they were stopped

Moreno lancet 2002
Cervical cancer in the USA

- The number of cervical cancer deaths decreased by 74% between 1955 and 1992
  - Attributed, in great part, to the use of the pap smear

- However, the 5 year survival has not improved significantly in 30 years (approx 70%)
  - Suggests that prevention is a better option
Epidemiology

- Median age at diagnosis is 65
- Age at diagnosis is falling
- Two types
  - HPV and non HPV related
- Risk factors
  - HPV
  - Cigarette smoking
  - Vulvar dystrophy
  - CIN or VIN 2/3
  - Immuno-compromise
VAGINAL CANCER

Epidemiology

- Median age at diagnosis is 6th to 7th decade
- Approximately 10% occur in women < 40 yrs
- Most are metastatic (80-90%)
- Pre-invasive disease is more common in younger women
- 72% are invasive
  - 79% scca  14% adeno (<20 yrs)
- Risk factors
  - Similar to cervical cancer
  - 6.8 increased risk if history of CIN 3 or higher
  - 4 fold risk found for the 25 years after CIN 3 diagnosis
Epidemiology

- Mean age at diagnosis is 60
- Like cervical cancer, it is more common in the developing world
- Risk factors
  - Single, never married
  - Circumcised at an older age
  - Never circumcised
    - 12x higher
  - Prior penile injury or tear
  - Phimosis especially when not circumcised
  - History of genital warts
  - HPV infection
  - Immuno-compromise
  - Tobacco use
  - Zoophilia
Epidemiology

- Average age at diagnosis is early 60's
  - Uncommon before age 30 or 40 depending on immune status
- Like the cervical canal, tissues are fusions of endodermal and ectodermal tissue with a squamo-columnar junction that has active metaplasia
- Consequences of anal SIL are similar to that of cervical SIL
  - therefore treated similarly
- Similar progression pattern as CIN
  - AIN 1 not a precursor lesion
  - AIN 3 regresses and progresses
    - Few studies
      - < 1 year untreated
      - 5-6 years treated
Epidemiology

- No current screening guidelines but some screen HR populations
  - After the age of 30 if immuno-compromised
  - After 40 if immunocompetent
- Cytology
- Anoscopy
- Pre-invasive more common in younger women and men
ANAL CANCER and AIN

Epidemiology

- Risk factors
  - Tobacco use both
  - IV drug use
  - History of cervical and vulvar cancer or HGSIL
  - HPV infection in both
    - Similar LR and HR types to cervix
  - HR sexual behavior in men
  - MSM
  - Immuno-compromise both
  - Similar to cervical cancer
  - In HIV infected women, high concurrence with cervical SIL
  - In women, anal receptive intercourse and HPV infection
Epidemiology

- Median age at diagnosis is 10 yrs younger for HPV related types (late 30’s-40’s)
- Now account for > 50% of H/N cancers in the developed world
- Base of tongue and tonsils
- Present at earlier stage
- Better prognosis than non-HPV related cancers
- No good correlation between infection and disease

Risk factors
- Not the usual of smoking, smokeless tobacco and EtOH
- HPV infection (may be 10 yrs pre)
- 4 fold risk found for the 25 years after SIL 3 diagnosis
A cross-sectional study of men and women, aged 14 to 69 years, studied the prevalence of oral HPV.

Overall prevalence of HPV DNA in oral exfoliated cells was 6.9%.
- Prevalence of HPV16 was 1%.

HPV prevalence was approximately three-fold more common in men compared with women.
- 10.1% versus 3.6%.

A study analyzed oral rinse samples for the presence of HPV in 164 patients with HPV associated oropharyngeal cancer and their long-term sexual partners.

- Oral HPV was detected in 65%.
- Oncogenic HPV strain was identified in 61%.

88 of 100 positive for oncogenic HPV had HPV16.

93 partners available for testing.

- Overall incidence of HPV infection was 4%.
- One had oncogenic HPV16.

These findings suggest that most partners effectively clear any active infection to which they are exposed.

HPV in Head and Neck Cancers

Based on meta-analyses

Cases Positive for HPV DNA, %

- Oral Carcinoma
- Tonsillar Squamous Cell Carcinoma
- Laryngeal Squamous Cell Carcinoma
- Sino-nasal Carcinomas


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In general pre-invasive disease of all of these sites can be treated with less destruction
- Topical
- Ablative
- Wide local excisions

We know most about screening for cervical cancer and anal cancer

Early stage disease is easier to treat than advanced stage

Advanced disease often requires multi-modal therapy
- Radiation +/- chemotherapy
- More radical surgery
- More treatment sequelae
Is Cervical Cancer Preventable?

YES
Methods to Prevent Cervical Cancer

- By detecting and treating pre-cancers before they become cancer
  - Regular pap test screening
- By preventing the pre-cancers
  - HPV vaccine
  - Use condoms to reduce HPV infection
  - Do not smoke
  - Avoid behaviors such as:
    - Having sex at an early age
    - Having many sex partners
    - Having a partner who has had many sex partners

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HPV RELATED DISEASES

PREVENTION HAS TO START EARLY
HR HPV prevalence by age

- 3-10% < 11y/o
- 30-50% 2\textsuperscript{nd} and 3\textsuperscript{rd} decades
- 15% 26-30 y/o
- 10% 31-35 y/o
- 5-15% 4\textsuperscript{th}, 5\textsuperscript{th}, 6\textsuperscript{th} decades
- Peaks up to 30% for women > 50 y/o
- Cumulative lifetime prevalence of 80%
- The incidence parallels the prevalence
Risk of Acquiring HPV After First Intercourse in Female Adolescents

Cumulative risk of cervical HPV infection in female adolescents with only 1 sexual partner

Prior infection with HPV does not automatically give you immunity against subsequent infection.

The level of protection from natural infection is variable.
- Hence the rationale for giving the vaccine to those with a prior history of an infection.

No absolute cross protection from infections with various types of HPV.
- So coverage of many types is needed.
- And a reason to vaccinate even if one HPV related infection has occurred.
HPV VACCINES

- Quadrivalent (FDA approved 6/2006)
  - Protects against 6, 11, 16, 18
- Bivalent (FDA approved 2009)
  - Protects against 16, 18
  - Possible role for oropharyngeal cancer prevention?
  - In Costa Rican trial of 7466 women (2013) eval cx HPV efficacy
    - It was estimated that the efficacy for prevention of oral HPV was 93%
      - Fewer vaccine recipients vs controls had oral hpv
      - Small numbers 1 and 15
- Adequacy of cross-protection against other closely related HR HPV types is uncertain
  - Bivalent shows some for 31 and 45
  - HPV 31 related to 16
  - HPV 45 related to 18
Current vaccines are made from VLP’s

VLP’s
- Virus-like particles
- L1 virus capsid proteins can assemble into VLP’s following expression in microorganisms (yeast or bacteria)

They resemble HPV particles and elicit antibody responses, but cannot cause infection

Contain no DNA, RNA, mercury or egg products

*Generates initial antibody levels several fold (80-100) higher than those seen with a natural infection

These are persistently higher at 18 mo (10-26x) for bivalent and still several fold higher for quadrivalent at 36 months (at least for type 16)

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Duration of protection in initial phase 2 studies

- Quadrivalent vaccine up to 48 months
- Bivalent vaccine up to 53 months

Long-term Study of a Quadrivalent Human Papillomavirus Vaccine.

Ferris D1, Samakoses R2, Block SL3, Lazcano-Ponce E4, Restrepo JA5, Reisinger KS6, Mehlsen J7, Chatterjee A8, Iversen OE9, Sings HL10, Shou Q10, Sausser TA10, Saah A10.

Sexually naive boys and girls aged 9 to 15 years (N = 1781) were assigned (2:1) to receive HPV4 vaccine or saline placebo at day 1 and months 2 and 6. At month 30, the placebo group (n = 482) received HPV4 vaccine following the same regimen and both cohorts were followed through month 96.

Among 429 subjects who received HPV4 vaccine at a mean age of 12, none developed HPV6/11/16/18-related disease or persistent infection of ≥12 months' duration.

CONCLUSIONS: When administered to adolescents, the HPV4 vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years.
If HPV Related Cancer Prevention Is the Goal, Uptake and Acceptance of HPV Vaccine Can Likely Be Enhanced by:

- Taking the shame out of these diagnoses
- Providing information about HPV, its consequences, and the benefits of vaccination; especially for:
  - Physicians who need to inform patients and parents
  - Parents who may not know about HPV
- Better communication between physicians and parents to gain acceptance of the vaccine by the parents
- Evaluation of data from ongoing long-term trials which will let us know duration of protection
SOME FINAL TRUTHS

- Cervical cancer screening will necessarily continue
  - The same group not screened is likely to be the group who may not get the vaccine
- We will learn more about whether to use HPV testing as primary screening for the more common HPV related cancers and pre-cancers
  - Cervix, vulva, anal, oropharyngeal especially
- HPV directed vaccines are effective, safe, well tolerated and likely universally applicable
  - They also appear to provide protection beyond the initial intent of reduction of condylomatous and cervical disease