Screening for Non Cervical HPV Cancers: What’s New?

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Oral HPV
Do you have it?
NHANES 2011 to 2014
National Health & Nutritional Examination Survey

Adults 18 - 69 yrs
US prevalence oral HPV
11.5% men & 3.2% women
(11 million men & 3.2 million women)

SEER.cancer.gov
Oropharyngeal Cancer
“Typical” Presentation

Middle-aged White Male
Nonsmoker or Former Smoker
Middle to High Socioeconomic
No Throat Symptoms
Neck Mass (ie Stage IV)

Primary Prevention HPV VACCINE!
Secondary Prevention: Tonsil Paps?

• HPV-driven OPC occurs in tonsillar crypts -technically difficult to reach.

• No Pre cancer?
  • Cohort of 401 HIV-positive individuals tested with liquid based cytology
    • Despite 12% + HPV16 oral infection -no dysplasia was observed.

• Superficial tonsillar brushing -inadequate to reach tonsillar crypts
  • Majority of slides unsatisfactory -too few squamous cells or large lymphocytes.

Fakhry C et al Cancer Prev Res (Phila) 2011;4
Ellerbrock TV et al JAMA 2000;283
Franceschi S et al Int J Cancer 2015
Secondary Prevention: Oral rinses/gargles vs Tissue for HPV detection

• **HPV testing more sensitive** than pap cytology for CIN2-3
  • Negative predictive value >99%
  • Week Specificity; + result can be transient infection (no consequences esp young women)

• Oral HPV (rinse/gargle) in US is 6.9% (5-15%); HR-HPVs in 3.7%
  • **Over estimate** oral rinses/gargles come from oral cavity or non-tonsillar OPA subsites
  • Lack of knowledge on natural history of oral HPV infection (likelihood to persist or progress)

• Tonsil Specimens and HPV
  • 3000+ paraffin benign tonsillectomy specimens (aged 0–69); NONE HPV+
  • 500+ fresh-frozen tonsil tissue/PCR-(men age 25-34 and >44); NONE HPV+

• **This data argues against screening strategies based on oral rinse/gargles.**

Gillison ML et al. JAMA 2012;307
Palmer E et al. Int J Cancer 2014;135
Serological assays of immune response to HPV antigens?

• **Antibodies against HPV-L1 vs E6/E7**
  - HPV L1 antibodies represent lifetime exposure at any site (genital, anal or oral) –doesn’t imply HPV-tumor
  - HR-HPV E6/E7 antibodies occur in response to HPV-driven neoplastic process

• **Antibodies against HPV16 E6 detectable before HPV OPC diagnosis**
  - Seropositivity against HPV16 E6 associated with risk of OPC but for other anatomical sites.
  - Increased risk of OPSCC among HPV16 E6 seropositive people seen >10 years before diagnosis.

• **Serology might be a non-invasive screening tool**

  • Mirghani H et al European Journal Cancer Volume 78, June 2017 , 105-115
  • Kreimer, AR J Clin Oncol, 31 (2013), pp. 2708-2715
Secondary Prevention in High Risk Individuals?

• Screen patients with HPV+cancer and those with oral HPV infection
• And Other High Risk Individuals?
  • Males vs People with certain sexual behaviours (high number of partners...)
  • Men aged 55 to 65 (prevalence at peak) with behavioral features (?)
  • Partners of patients with HPV-driven malignancy
    • the vast majority of partners clear their infection,
    • 12 reports of HPV-driven cancers (some same strain) in spouses
    • 5 larger population registry studies reported increased risk in spouses

Mirghani H et al  Oral Oncol. 2017 Apr;67:138-145
Can we identify lesions when find + screen

Limitations

• Oropharynx filled with lymphoid tissue and mucosal invaginations
• HPV-driven OPCs arise from tonsillar crypts - hard to reach or see
• Appearance of HPV- premalignant lesions not adequately described

Innovative diagnostic approaches—Effective?

• Transoral examination with narrow band imaging (NBI)
  • Filtering white light into specific light wavelengths absorbed by hemoglobin to enhance visibility of neoangiogenetic patterns in mucosal superficial vasculature
  • Flexible video-laryngoscope with NBI enhances defects covered by normal mucosa

• Transcervical and intraoral ultrasonography.
  • Visualize the base of the tongue to identify the primary site—pilot study only
  • Ultrasound helps identify certain oropharyngeal lesions as small as 5 mm.

Ebisumoto K et al Head Neck 2016 Apr;38(S1)
Piazza C et al Acta Otorhinolaryngol Ital 2008;28
Coquia SF et al AJR Am J Roentgenol 2015;205
Blanco RG et al PLoS One 2014 Jan 30;9
Fakhry C et al Oral Oncol 2014;50:640e5.
Serum Antibodies & the Houston Study

AIMS

• Is serological HPV antibody screening effective for OPC?
• Are other screening tools effective?

• 5,000 men; 50-64
  • demographic and sexual behavior questionnaires
  • serologic HPV testing and oral gargle sample for HPV testing.
  • High risk (testing positive for antibodies) matched with sample of Low Risk (testing negative for antibodies) will be recruited

• Uncertain risk cohort
  • Approx. 50 men with HPV16 on oral rinse will be followed for viral prevalence and persistence
  • Any men with circulating HPV16 DNA will be included (rare).

Oral Oncology. 2015;51:662-667
Cancer. 2017;123:4886-4894
Clinical Cancer Research. 2015;21:2861-2869)
Houston Study Stage II: Screening

- During first visit and q6 months (5 years)- screened for OPA cancer
  - Complete head and neck exam
  - Narrow band imaging and brushing of oropharyngeal mucosa to test for integration of HPV DNA and persistence of oral HPV
  - Ultrasound of the neck lymph nodes and oropharynx

- Screened for anal and penile cancer.
  - Anal screening: anoscopy, anal Pap/HPV testing, and high resolution microendoscopy in Colorectal Clinic
  - Penile screening includes urinalysis, penile swab for HPV, and counseling on self-exam in Urology Clinic.

- Collect blood samples to test for circulating HPV16 DNA.
Anal Cancer

8,080 new cases annually (2,920 men and 5,160 women)
1,080 deaths annually    (440 men and 640 women)
Increased risk of anal cancer

- Anal carcinoma caused by persistent HPV infection
- The anal dysplasia & cancer screening:
  - Women with a history of high-grade cervical, vulvar, vaginal dysplasia or cancer
  - HIV-positive men and women
  - Men who have sex with men
  - Individuals with a history of anal warts
  - Iatrogenic immunosuppression (eg. transplant recipients, long term oral corticosteroids)
No formal anal dysplasia screening recommendations

Anal Cancer: U.S. Screening Guidelines

- No national screening guidelines
- CDC: Acknowledges that some experts recommend anal cytologic screening for HIV+ men and women
- ACS: Anal cytology, sometimes called the anal Pap test, may be useful in early diagnosis of anal cancer and precancer (called *anal intraepithelial neoplasia* (AIN))...Some doctors already recommend this test for people at high risk for anal cancers, such as those who are HIV positive.
- New York State Department of Public Health AIDS Institute:
  - Clinicians should obtain anal cytology at baseline and annually in the following HIV-infected populations:
    - Men who have sex with men
    - Any patient with a history of anogenital condylomas
    - Women with abnormal cervical and/or vulvar histology
The Prevalence of Anal Dysplasia & Cancer among Women with Cervical/Vulvar/Vaginal Dysplasia & Cancer (PANDA Study)

Primary Objective: To estimate the prevalence of anal dysplasia and invasive cancer in women with high-grade dysplasia or carcinoma of the cervix, vagina or vulva

Secondary/Exploratory Objectives: To estimate and compare the sensitivity, specificity, PPV, NPV of: 1) anal Pap, 2) anal HPV testing and 3) anoscopy to diagnose anal dysplasia in these women
Secondary Prevention Solutions are still very important!

- Several generations were too old to be effectively vaccinated
  - Typical age for Cervical cancer 45
  - Typical age for OPA cancer 55
  - Typical age for Vulvar/Anal cancer 60

- The benefits vaccination on HPV-related cancer incidence will not be realized for several decades
Thank you & Questions?

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