HPV Vaccines & GYN Cancers

“An ounce of prevention is worth a pound of cure.” Benjamin Franklin

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I have no conflicts of interest to disclose
Objectives

1. Case studies: *real people, not just statistics*
2. Cervical Dysplasia & Cervical Cancer
3. Vulvar Dysplasia & Vulvar Cancer
4. HPV Vaccines: *Safety, efficacy, impact*

Case study #1

• 29-year-old G4P3 woman currently 25 weeks pregnant presented to my office for second opinion for suspected cervical cancer
• Diagnosed with abnormal pap test 1.5 years previously during last pregnancy, but never followed up postpartum
• Had abnormal vaginal bleeding on and off since that time
Case study #1

• Risk factors include HPV exposure, history of abnormal pap tests, and nicotine abuse (1 ppd x 9 years)
• Never had HPV vaccine
Case study #1

• Patient not a candidate for curative surgery or radiation because of pregnancy
• Offered neoadjuvant chemotherapy but declined
• Radical Cesarean hysterectomy after fetal lung maturity aborted secondary to extra-cervical disease

Case study #1

• Treated with definitive chemoradiation
• Multiple treatment delays and missed appointments
• Lung mets 6 months after completing therapy
Case study #1

• Palliative chemotherapy 13-16 months after initial diagnosis
• Palliative radiation for bone mets
• Expired from progressive disease, age 30

Case study #2

• 36-year-old P0 female, with remote history of sexual abuse
• Presents with 4 cm fungating cervical mass
• Biopsy confirms invasive carcinoma
• Patient desires future fertility
Case study #2

- Referred to reproductive endocrinologist for consideration of embryo creation
- Fertility attempts unsuccessful
- Robotic oophoropexy to spare ovarian function in anticipation of radiation
- Whole pelvic radiation with weekly chemotherapy x 6 weeks
- Fatigue, diarrhea, missed work, vaginal narrowing with sexual dysfunction

Case study #3

- 45-year-old woman with longstanding history of vulvar pruritis
- Treated unsuccessfully for presumed fungal infection
- Fungating vulvar mass eventually biopsied, squamous cell carcinoma of vulva confirmed
Case study #3

- Radical vulvectomy with inguinal lymph node biopsies
  - Multiple positive lymph nodes
- Chemoradiation
- Recurrence in radiation field diagnosed 11 months after completing therapy
- 5 months of palliative chemotherapy
- Placed on hospice, age 47
Case studies

• Case 1: Pregnant woman with advanced cervical cancer, dies leaving behind 4 young children
• Case 2: Nulliparous woman with cervical cancer—treatment results in infertility and sexual dysfunction
• Case 3: Advanced vulvar cancer diagnosed mid-40’s, fatal

Case studies

• These cases illustrate devastating aspects of gynecologic cancers
• Common thread: all of these cancers are related to Human Papilloma Virus
• Majority of HPV-related cancers may be preventable
Cervical Dysplasia

Not just cancer

- Cervical Intraepithelial Neoplasia (CIN)
  - Premalignant condition of uterine cervix
  - Screening includes cervical cytology (pap test) & testing for oncogenic subtypes of HPV
    - Low grade (CIN 1): low risk for progression to malignancy (4% of pap tests)
    - High grade (CIN 2/3): High(er) risk of progression to malignancy (5% of pap tests)

Georgios Papanikolao

- Developed Pap test in 1923
- First paper published 1928
- Introduced in USA 1949
Abnormal Pap

10,000 Cancers

300,000 HSIL

1.25 million LSIL

2-3 million ASC

50-60 million women screened

Cervical Dysplasia

• Abnormal pap test worked up by colposcopy
• Goals of colposcopy:
  – Prevent cervical and vulvo-vaginal cancer
  – Diagnose precancerous lesions
  – Rule out invasive cancer
The Transformation Zone

"Area of metaplastic squamous epithelium located between original squamocolumnar junction and new squamocolumnar junction"
Visualization of Cervix

Acetic acid

Lugol's
Epidemiology: risk factors

- **HPV infection** (16, 18, 31, 33, 45, etc.)
- Smoking
- Immunosuppression (HIV, etc.)
- Socioeconomic status, ethnicity
- Diet?
- OCP’ s?
- Age

Human Papilloma Virus

- Non-enveloped ds-DNA encased in capsid

Integration disrupts
E2 leading to increased E6/E7 transcription

E7 binds pRb
E6 binds p53

E2 transcriptional regulation of HPV genes

Late genes encode capsid proteins
HPV: necessary but not sufficient

- 99.7% of invasive cervical cancers associated with oncogenic HPV¹
- >80% of women infected with HPV at some point in lifetime²
- Only small fraction of women infected with HPV will develop CIN2+

1. Walboomers et al., 1999
2. Dunne et al., 2007

HPV Testing- ALTS distribution

*Missing or false neg values

HPV Triage reduces Colpo of ASCUS by 50%
HPV infection → cancer

1. HPV transmission
2. Acute HPV infection
3. Persistent HPV infection → precancerous changes
4. Invasive cervical cancer

1. Schiffman M et al., 2007

HPV

• Over 100 HPV types, approximately 40 are oncogenic
• Low-risk HPV (6, 11)
  – 10% of low-grade lesions
  – 90% of condylomatous genital warts
• High-risk HPV (16, 18, 31, 33, 45, 52, 58)
  – Strongly associated with high-grade lesions
  – HPV 16 & 18: 25% of low grade lesions, 50-60% of high grade lesions, 70% of cervical cancers
Figure 1. Prevalence of high-risk HPV and incident cases of cervical cancer in the United States, 2003-2005.

Surveillance Epidemiology and End Results (SEER) data for incident cases among females aged 15 to 19 years and 50 to 64 years. Data are from references 27 and 45. HPV = human papillomavirus.

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3)*

Adequate Colposcopy

Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3

Either Excision* or Ablation of T-Zone*

Diagnostic Excisional Procedure*

Cotesting at 12 and 24 months

2x Negative Results

Any test abnormal

Repeat cotesting in 3 years

Routine screening

Colposcopy With endocervical sampling

*Management options will vary in special circumstances or if the woman is pregnant or age 21-28.
*CIN2,3 is identified at the margin of an excisional procedure or excisional procedure ECC, cryotherapy and ECC at 4 cm is preferred, but repeat dilatation is acceptable if dilatation is not feasible.

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LEEP Diagram

Cold cone biopsy: a large area of tissue around the cervix is excised for examination

Cervix viewed through speculum with patient in lithotomy position
**Treatment of Cervical Dysplasia**

- Excisional (LEEP, cone), ablative (cryotherapy)
- Excisional treatment preferred if CIN 3
- Efficacy: 90-95% reduction of cervical cancer first 8 years after treatment
- Success depends on margin status
  - 4417 women with CIN 3 status post cone, followed for mean of 18 years; Negative margins: recurrent dysplasia in 0.35%, 8.9 years after treatment
  - 390 women with positive margins: persistent, recurrent, or progressive disease in 17-52% of patients 6-30 years after follow-up

1. Reich O et al., 2001
2. Reich O et al., 2002

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**Cancer Epidemiology: USA**

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
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<tr>
<td>Cervix</td>
<td>13,170</td>
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<td>24,590</td>
<td>6,960</td>
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Seigel RL et al., 2019
Histological subtypes

- Squamous-cell carcinoma (~75%)
- Adenocarcinoma (~20%)
- Adenosquamous
- Glassy cell
- Adenoid cystic
- Adenoid basal
- Neuroendocrine/anaplastic small cell
- Carcinoid
- Mixed epithelial and mesenchymal
Cervical cancer: worldwide

- 529,800 cases; 275,100 deaths
- Most common cancer in developing countries
  - 88% of cases & deaths
- 3rd most common cancer in women worldwide (7th overall)

Jemal, 2010
Cervical cancer treatment

- Three distinct entities:
  - Microinvasive lesions (IA1)-fertility sparing?
  - Early stage (IA2-IIA1)-radical surgery or RT
  - Advanced stage (IIA2-IV)-Chemoradiation

Radical hysterectomy
Sequelae of treatment

- Pelvic radiation
  - GI: diarrhea, constipation, bleeding, pain, nausea, fistula, perforation
  - GU: Radiation cystitis
- Premature menopause
- Fertility issues
- Sexual dysfunction

Recurrent disease

- Prior history of radiation?
- Appropriate surgical candidate?
  - Pelvic exenteration (total, anterior, posterior)
    - Central recurrence
    - Adequate performance status
- Palliative chemotherapy, clinical trial
- Hospice
Vulvar Dysplasia

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Cervix Uteri Cancer

SEER 18 2005-2011, All Races, Females by SEER Summary Stage 2000
Epidemiology

• Vulvar squamous cancer precursors (Vulvar Intraepithelial Neoplasia, VIN)
  – Incidence rising worldwide
    • 400% increase in USA 1973-2000
  – Typically occurs in women in their 40s (average age 46)
  – 2.86 per 100,000 women
  – HPV in 85% of VIN
  – 3% of women being treated for VIN will have invasive disease

VIN Classification

• Two distinct types of VIN, differ in etiology, pathogenesis, and clinical significance
• Usual type VIN is HPV-related
  – Warty, basaloid, mixed subcategories
  – Associated with classic CIN risk factors, (eg. smoking, immunosuppression)
• Differentiated type VIN non HPV-related (<5% of VIN)
  – Older women
  – Associated with lichen sclerosis, keratinizing squamous cell carcinomas
uVIN vs. dVIN

Comparison of clinicopathological features between uVIN and dVIN

<table>
<thead>
<tr>
<th>Feature</th>
<th>uVIN</th>
<th>dVIN</th>
</tr>
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<tbody>
<tr>
<td>Prevalence</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Age</td>
<td>Young women (40–49 years)</td>
<td>Postmenopausal women (65–69 years)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Multifocal</td>
<td>Usually unifocal</td>
</tr>
<tr>
<td>Risk factors</td>
<td>HPV infection, immunosuppression</td>
<td>Chronic skin inflammatory conditions (LS, lichen simplex chronic, squamous cell hyperplasia)</td>
</tr>
<tr>
<td>Morphology</td>
<td>Nuclear atypia (high nuclear/cytoplasmic ratios, nuclear enlargement, hyperchromasia)</td>
<td>Basal cell nuclear atypia</td>
</tr>
<tr>
<td></td>
<td>Decreased cellular maturation</td>
<td>Atypical mitosis in basal layer</td>
</tr>
<tr>
<td></td>
<td>Increased mitotic activity above</td>
<td>High maturation of superficial</td>
</tr>
<tr>
<td></td>
<td>basal layer</td>
<td>squamous cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis, prominent nucleoli,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>elongation and anastomosis of rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ridges</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prominent intercellular bridges</td>
</tr>
<tr>
<td>Type of SCC</td>
<td>Basaloid/dysplastic SCC</td>
<td>Keratinizing SCC</td>
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Reyes MC et al., 2014

Cancer Epidemiology: USA

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Seigel RL et al., 2019
Vulvar cancer

- Vulvar squamous cancer relatively uncommon
  - 1.4-2.7 cases per 100,000 women
  - 6-8% of all GYN cancers
  - Typically occurs in women >60 years old
- HPV: 10-50% vulvar cancers
- Mainly a disease of older women
- Treatment: surgical & chemoradiation

Vulvar cancer: treatment

- Surgery is cornerstone of treatment
- Radical vulvectomy with “en bloc” bilateral inguinofemoral and pelvic LND described in 1940’s
- Improved 5-year survival over WLE
  - 20% → 60%
Morbidity of radical surgery

- Wound breakdown (50%)
- Wound infections
- Lymphocysts, lymphedema (24-70%)
- Chronic cellulitis
- Difficulty with urination, defecation, coitus
- Psychosexual
More conservative surgical approach

- Omission of pelvic lymphadenectomy (GOG 37)\(^1\)
- Unilateral inguinofemoral lymphadenectomy (GOG 74)\(^2\)
- Separate incisions
  - Cochrane review: 1% recurrence in skin bridge

1. Homesley et al., 1986
2. Stehman et al., 1992

Inguinofemoral LN mets: most important prognostic factor

<table>
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<th># positive lymph nodes</th>
<th>5-year survival</th>
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<tr>
<td>0</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
</tr>
<tr>
<td>3 or more</td>
<td>12%</td>
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Incidence of LN mets

- Dependent on stage
- Range 5-30% in FIGO stage IB (>2 cm)
- Majority of patients with early stage cancer undergo potentially morbid procedure unnecessarily

Sentinel lymph nodes

- Rationale: less morbidity than full dissection
- No accurate non-invasive means to evaluate inguinofemoral LN mets
  - Palpation (25% accurate)
  - Sono, sono-guided fine needle biopsy
  - PET/CT, MRI
Vaginal cancer

- Similar risk factors as cervical cancer
- HPV DNA: >80% of pre-cancerous lesions; 60% of patients with invasive cancers
- Treatment: radiation & surgery

HPV Vaccines
HPV vaccines

• What vaccines are available?
• When, how often, and to whom, should they be given?
• How effective are they?
• How safe are they?

Available HPV Vaccines

• 3 Prophylactic vaccines developed:
  – Quadrivalent HPV Vaccine (Gardasil): 16, 18, 6, 11
  – 9-valent (Gardasil 9): 16, 18, 31, 33, 45, 52, 58, 6, 11*
  – Bivalent (Cervarix): 16, 18

• Therapeutic vaccines not yet clinically available

*Only Gardasil 9 currently available in USA
Impact of HPV Vaccines

• Modeling study: if entire US population of 12-year-old girls vaccinated:
  – 200,000 HPV infections prevented per year
  – 100,000 abnormal cervical pap tests
  – 3,300 cases of cervical cancer

• Even greater impact predicted with Gardasil 9

  Drolet M et al., 2015

HPV Vaccine Administration

• Advisory Committee on Immunization Practices (ACIP):
  – Both males and females, age 11-12 years
  – Vaccine may be administered age 9
  – Females: catch-up vaccine age 13-26
  – Males: catch up vaccine age 13-21 (males age 22-26 may be vaccinated)
  – Although the vaccine is approved by the FDA for males and females through age 45, ACIP does not recommend routine vaccination of persons older than 26 at this time

  Petrosky et al., 2015
HPV Vaccine Administration

- Individuals initiating vaccine before age 15: Two doses of vaccine at 0 and at 6-12 months
- Individuals initiating vaccine at 15 or older: Three doses of HPV vaccine at 0, 2, and 6 months
- Immunocompromised: Three doses

Petrosky et al., 2015

HPV Vaccine Efficacy

- Antibody responses:
  - Seroconversion rates of 93-100% females, 99-100% in males
  - Gardasil: 2 randomized double-blind trials: HPV vaccine vs. placebo
    - 17,000 females age 15-26
    - After 3 years, efficacy of vaccine in preventing CIN 2+ due to vaccine types was: 97-100% among HPV naïve population
    - 44% among overall population

3. FUTURE II Study Group, 2007
HPV Vaccine Efficacy

• Gardasil-9: International randomized trial in 14,000 females age 16-26 vs. quadravalent vaccine

• Efficacy in preventing CIN 2+, VIN2+, VaIN2+ associated with HPV types 31, 33, 45, 52, 58
  – 97% among HPV-naïve population
  – Overall population, rates of cervical, vulvar, vaginal disease were 14/1000 cases in both groups

  Joura EA et al, 2015

HPV Vaccine Efficacy

• Duration of protection:
  – Continued protection against high-grade cervical, vaginal, vulvar neoplasia has been observed through at least 10 years following vaccination
  – Persistent antibody levels and protection against HPV infection have been reported up to 10 years following vaccination

  Lehtinen M et al., 2012
HPV Vaccine Safety

• All HPV vaccines have documented safety in large clinical trials, supported by post-licensure data
• Vaccines all use virus-like particles (VLPs) which mimic viral capsid, do not contain genetic material
• World Health Organization (WHO) Global Advisory Committee on Vaccine Safety: benefit risk profile is favorable

Frazer IH, et al., 2006

HPV Vaccine Safety

• June 2006-March 2013: 57 million doses of quadrivalent HPV vaccines distributed in USA
  – 21,194 reports of adverse events recorded in Vaccine Adverse Event Reporting System (VAERS)
  – 92% considered mild (0.003% severe reaction)
  – Headache, nausea, vomiting, fatigue, dizziness, syncope, generalized weakness most common severe events reported
  – No increased risk of Guillain-Barre Syndrome vs. other vaccines
  – 1,896 syncopal episodes, 15% resulted in fall or injury

1. Slade BA et al, 2009
HPV Vaccine Safety

- Other adverse events reported, although causality difficult to establish based on isolated reports
  - 31 patients with venous thromboembolism; 28 had other risk factors
  - Anaphylaxis 0.1 case per 100,000 doses
  - Multiple sclerosis: no association found in study of 4 million Swedish & Danish women age 10-44
- Gardasil 9: Similar overall safety profile, may have slightly higher frequency of mild local reactions

Take Home Points

- CIN, Cervical Cancer, affects younger woman
  - Impact on families, careers, society
- Success of cervical & vulvar cancer treatment related to stage at diagnosis, but poor prognosis if advanced stage, distant mets
- Even when cure achieved, there may be long-term sequelae from treatment
- High-grade CIN, Cervical Cancer, VIN, Vulvar Cancer:
  - Highly associated with oncogenic HPV
Take Home Points

• Gardasil 9 vaccinates against 7 oncogenic HPV types that cause ~90% of cervical cancers, and 2 HPV types that cause ~90% of condylomata

• Favorable impact on cervical, vulvar, & vaginal dysplasia, vulvar & vaginal cancer, as well as non-gynecologic cancers

• HPV vaccines are safe and effective, and public health efforts to increase vaccination rates are warranted

HPV Vaccines & GYN Cancers

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