HPV Testing

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Faculty Disclosures: Teresa M. Darragh, MD

- In the past 12 months...
- Hologic: Research supplies for anal cytology
Objectives

- Review role of HPV in cervical cancer, in brief
- Review HPV tests currently available
- Discuss clinical uses of HPV testing
HPV Fact Sheet

• HPV is the most common sexually transmitted infection.
• 79 million Americans are currently infected with HPV.
• About 14 million people become newly infected each year.
• HPV is so common that most sexually-active men and women will get at least one type of HPV at some point in their lives.

http://www.cdc.gov/std/hpv/stdfact-hpv.htm
Cervical HPV Prevalence: Types 6, 11, 16 and 18

Prevalence, %

Age Group
14-19
20-24
25-29
30-39
40-49
50-59

Natural History of HPV

- Most HPV infections “clear” in 4 - 24 months
- ↑prevalence: young sexually active women & men
  - More tests = greater detection
- More partners → higher risk of HPV infection
  - “serial monogamy”
- HPV Persistent HPV = risk for cancer (RR ~300)
  - Necessary, but not sufficient…
  - Clearance of HPV means lower cancer risk
HPV16 and HPV18 infections and HSIL+ (CIN3+)

Cumulative incidence rate of ≥CIN3 (%)

Follow-up time (months) 4.5 15 27 39 51 63 75 87 99 111 119.5

- HPV16+: 17.2% (11.5, 22.9)
- HPV18+: 13.6% (3.6, 23.7)
- Other high-risk HPV+: 3.0% (1.9, 4.2)
- High-risk HPV−: 0.8% (0.6, 1.1)

HPV Testing

• All high-risk HPV tests used should be:
  – FDA approved
  – Or supported by peer-reviewed published data on sensitivity/ specificity with performance similar to assays used in clinical trials
    \[ \geq 92 \pm 3\% \text{ sensitivity for CIN 3+} \]
    \[ \geq 85\% \text{ specificity in screening setting} \]

• No role for low-risk HPV testing

• Choice of HPV test usually made by laboratory

# FDA-approved high-risk HPV tests

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HPV Testing: Clinical Uses

• **Screening:**
  – Primary screening with genotyping
  – Cotesting in women ≥ 30 years
  • With reflex genotyping if hrHPV+ and Pap Negative

• **Triage:**
  – Reflex testing for ASC-US (women ≥ 25 years)
  – *(Reflex testing for LSIL in post-menopause)*

• **Post-colposcopy Management**
  – Cotesting in women ≥ 25 years *(rare exceptions)*

• **Post-treatment Management**
  – Cotesting in women ≥ 21 years
Management options

- Repeat screen at regular intervals
- Increased surveillance
  - Shorter screening interval
- Colposcopy
- Treatment
Harmonizing Management According To Risk

Screening

HPV Testing

Cytology

Colposcopy

Biopsy

Post-Colpo

Increased Surveillance

Treatment

100%

10%

40%

Increasing Risk of Precancer (CIN3+)

~0%

HPV-

HPV+/Cyto-

< CIN2

Biopsy

CIN2

Biopsy*

HSIL & HPV+ & H-G Colpo

HPV+/ASC-US

HPV-/Cyto-

HPV-/ASC-US

HPV+/Cyto+

Cyto-

LSIL

ASC-US

HSIL

All

Screening

30 year old G2 patient presents for her routine Gyn exam. Her Pap test at age 27 was negative. She’s never had an abnormal Pap.

How will you screen for cervical cancer this visit?

A. No screening for cervical cancer
B. Pap test: liquid-based or conventional
C. Co-testing with cytology & HPV DNA
D. HPV 16/18 genotyping
Screening

30 year old G2 patient presents for her routine Gyn exam. Her Pap test at age 27 was negative. She’s never had an abnormal Pap.

A. No screening for cervical cancer
B. Pap test liquid-based or conventional
C. Co-testing with cytology & HPV DNA
D. HPV 16/18 genotyping
ACS/ ASCCP/ ASCP & ACOG:
From age 30 – 65, co-testing every 5 years is recommended. If HPV testing not available, continue with cytology alone every 3 years.

USPSTF:
Screen women age 21 – 65 with cytology every 3 years. For women age 30 – 65 co-testing with cytology and HPV DNA every 5 years is a reasonable alternative for those women wishing to extend the screening interval.
Why add HPV to the Pap test?
Studies from U.S. and Europe

• Co-testing leads to earlier diagnosis of CIN 3+ and Cancer
• Incorporating HPV finds more AIS than cytology alone
• Negative cytology plus negative HPV allows spacing screening beyond every three years.
Our 30 y.o. is screened with co-testing. Both her Pap and HPV test are negative.

When should you screen her again for cervical cancer?

A. Routine screening at 2 years
B. Increased surveillance
C. Age appropriate screening at 3 years
D. Cotest at 5 years
Our 30 y.o. is screened with co-testing. Both her Pap and HPV test are negative.

When should you screen her again for cervical cancer?

A. Routine screening at 2 years
B. Increased surveillance
C. Age appropriate screening at 3 years
D. Cotest at 5 years
A negative HPV DNA test offers better protection after 5-6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295

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<td>Pap –</td>
<td>0.51%</td>
<td>0.69%</td>
<td>0.83%</td>
<td>0.97%</td>
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<tr>
<td>HPV-</td>
<td>0.12%</td>
<td>0.19%</td>
<td><strong>0.25%</strong></td>
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*Dillner, J. et al. BMJ 2008;337:a1754*
Screening

40 y.o. has cotesting with *genotyping*: Negative Pap / hrHPV+ and HPV 18+
She should have:

A. Cotest at 1 year
B. Routine screening at 2 years
C. Age appropriate screening at 3 years
D. Colposcopy
Screening
40 y.o. has cotesting with genotyping: Negative Pap / hrHPV+ and HPV 18+
She should have:

A. Cotest at 1 year
B. Routine screening at 2 years
C. Age appropriate screening at 3 years
D. Colposcopy
Management of Women ≥ Age 30, who are Cytology Negative but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative
    - Repeat cotesting @ 5 years
  - ≥ASC or HPV positive

- **HPV DNA Typing**
  - *Acceptable
  - HPV 16 or 18 Positive*
    - Repeat Cotesting @ 1 year
  - HPV 16 and 18 Negative
    - Manage per ASCCP Guideline

- **Colposcopy**
  - Manage per ASCCP Guideline

2012, Copyright American Society for Colposcopy and Cervical Pathology
Screening

40 y.o. has cotesting with genotyping: Negative Pap / HPV+ and HPV 18+

- Answer D
  - Colposcopy

- Increased risk of HSIL (CIN2/3+) with HPV 16/18

- Risk above ‘risk threshold’ for colposcopy
  - But below treatment threshold

- HPV 18 associated with endocervical AIS
  - More difficult to detect by Pap
Identification of Endocervical Adenocarcinoma & AIS

• Pap more specific than HPV testing
• HPV testing more sensitive for endocervical AIS and adenocarcinoma¹
• Compared with SCCs, cytology has been relatively ineffective in decreasing the incidence of invasive cervical adenocarcinoma²
• Increasing in incidence³

HPV Genotyping

- Management based on genotyping results?

- Currently, genotyping changes management when:
  - Negative Pap, positive for high-risk HPV
    - HPV 16 and/or 18 positive → Colposcopy
    - If HPV 16/18 negative or unknown → Repeat cotest 1 year
  - *With HPV primary screening…*

- Not recommended to influence treatment
- Not recommended prior to offering HPV vaccination
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  - Cotesting in women ≥ 21 years
Post-treatment:
A 24 year old treated by loop excision for HSIL (CIN3) Margins are negative
She should be followed with:

A. Pap tests at 6 and 12 months
B. Pap & Colposcopy at 6 months
C. Pap test at 12 months
D. Cotesting at 12 and 24 months
Post-treatment:
A 24 year old treated by loop excision for HSIL (CIN3) Margins are negative
She should be followed with:

A. Pap tests at 6 and 12 months
B. Pap & Colposcopy at 6 months
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Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2 and 3 (CIN2,3)*

*Adequate Colposcopy

Either Excision† or Ablation of T-zone*

Cotesting at 12 and 24 months

Repeat Cotesting in 3 years

Routine Screening

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

Diagnostic Excisional Procedure†

Post-treatment Management

Any Test Abnormal

Colposcopy With endocervical sampling

* Management options will vary in special circumstances or if the woman is pregnant or ages 21–24
† If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4–6 mo is preferred, but repeat excision is acceptable and hysterecomy is acceptable if reexcision is not feasible.
Post-treatment:
A 24 year old treated by loop excision for HSIL (CIN3) with negative margins

• Answer D
  – Cotesting at 12 and 24 months

• 2012 ASCCP Management guidelines
  – Cotesting at 12 and 24 months

• 2006 ASCCP Management guidelines
  – Pap tests at 6 and 12 months
  – Pap & Colposcopy at 6 months
Testing After Treatment of HSIL (CIN2/3)

- If Cotest at 12 & 24 months are negative:
  - Repeat cotest in 3 years: if negative → routine screening (i.e. cotesting in 5 years)
  - Routine screening is recommended for at least 20 years
  - Even if this extends screening beyond age 65 years

- Repeat treatment or hysterectomy based on a positive HPV test is unacceptable
Post-treatment:
A 24 year old undergoes loop excision for HSIL (CIN3) with positive margins

• If margins positive (or +ECC at time of excision) for HSIL (CIN2/3)
  – Pap and ECC at 4-6 months preferred
  – Repeat excision acceptable
Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia —
Grade 2 and 3 (CIN2,3)*

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Remember to read the fine print!

Cotesting at 12 and 24 months

2x Negative Results

Any Test Abnormal

Repeat Cotesting in 3 years

Routine Screening

Colposcopy

With endocervical sampling
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Equal Management for Equal Risk

Image: Alan Waxman, M.D.