Otis W. Brawley, MD, MACP, FASCO, FACE

Chief Medical and Scientific Officer
American Cancer Society
Professor of Hematology, Medical Oncology,
Medicine and Epidemiology
Emory University
Atlanta, Georgia

Cervical Cancer

- One of the most common cancers seen worldwide.

- Two types of cervix cancer
  - Squamous cell carcinoma (most common)
  - Adenocarcinoma

HPV and Cancer

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Human Papilloma Virus

- Is linked to cancer of:
  - Cervix
  - Vulvar
  - Vagina
  - Penis
  - Anus
  - Head and Neck Cancer
    - Oropharynx*
    - Tonsil*

* Not all from HPV

HPV Vaccine

- Effective at preventing cervical dysplasia.
- Safe and Expensive!!!
- Initially promoted for girls and women
- Increasing emphasis on vaccination of boys
- Significant uptake in Africa and some Asian countries

Cervix Cancer Screening

What is the objective of screening?

To reduce morbidity/mortality from cervical cancer

- Not to find abnormal Paps or CIN
- Not to find HPV infection

These are surrogate risk markers, not inevitable cancer precursors—useful but not determinative

Cervical Cancer Screening

- Pap smear
  - Requires cytologists/cytotechnologists
  - Subjective (even with Bethesda System)
- HPV DNA testing
  - High tech and subjective
  - Not a good test for women 20 to 30.
- Visual inspection of cervix
  - Appropriate in some settings

Smith RA et al, CA Cancer J Clin 2012

Cervical Cancer Screening

- Is highly effective!
- Diagnosis and treatment of precursor lesions can prevent development of invasive disease and prevent deaths.
- In the US more than half of women developing invasive disease have never been screened.

Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ, Flannery JT, Polednak AP Am J Public Health. 1995;85(6):791.

Guideline Recommendations

Women <21	No screening
Women ages 21-29	Cytology alone every 3 years (liquid or conventional) Recommend AGAINST annual cytology
Women ages 30-65	HPV + cytology "cotesting" every 5 years (preferred) or Every 3 years with cytology alone (acceptable) Recommend AGAINST more frequent screening
Women ages >65	Discontinue after age 65 if 3 negative cytology tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years
Post-Hysterectomy	Discontinue if for benign reason
Screening after HPV vaccination	Follow age-appropriate recommendations (same as unvaccinated women)

Management of Discordant Results

HPV-negative ASC-US	**Rescreen with cotesting in 3 years* (preferred) or Rescreen with cytology in 3 years (acceptable)**
HPV positive, cytology negative	**<u>Option 1</u> -- 12-month follow-up with cotesting <u>Option 2</u> -- Test for HPV16 or HPV16/18 Genotyping If HPV16 or HPV16/18 positive: refer to colposcopy If HPV16 or HPV16/18 negative: 12-month follow-up with cotesting**

* Updated in 2015

Comments

Women at any age should NOT be screened annually by any screening method
HPV testing should NOT be used for screening women <30 years of age*
Screening by HPV testing alone is not recommended for most clinical settings*
Women with a history of CIN2 or a more severe diagnosis should continue screening for at least 20 years
These guidelines do NOT address women **1) with a history of cervical cancer,** **2) who were exposed in utero to diethylstilbestrol (DES),** **3) who are immune-compromised, e.g. HIV+**

* See Interim Guidance, 2015

Women <21 years

Cervical cancer screening should begin at age 21 years. Women under the age of 21 should not be screened regardless of the age of sexual initiation or other risk factors.

- Cancer is rare: 1-2 cases per year per million females ages 15-19 years
- Cancer may not be preventable: Screening adolescents has not reduced this rate
- Overtreatment leads to net harm

Screening Periodicity

Women at any age should NOT be screened annually by any screening method.

- Not supported by evidence
- Leads to increased rate of harms: very large excess of unnecessary procedures and treatments
- Does not increase benefit: very small increment in cancers prevented

Why not screen annually?

Most abnormal screens represent transient HPV infection, not pre-cancer

Cancer risk 18 months after 3 neg Paps = 1.5/100,000

Cancer risk 36 months after 3 neg Paps = 4.7/100,000

→99,997 women screened uselessly to help 3

Risk of HSIL/cancer <3y after negative Pap not significantly higher than risk after 1y

Why not screen annually?

Screening harms: lifetime risk of colposcopy

- Screening q3y: 760 colpos/1000 women
- Screening q2y: 1080 colpos/1000 women
- Screening annually: 2000 colpos/1000 women

Women ages 21-29

Screen with cytology alone every 3 years.

- Annual screening results in slightly greater cancer risk reduction (lifetime risk 3 per 1000 women) but twice the number of colposcopies compared to screening every 3 years

- No significant difference in cancer reduction between a 2- and 3-year screening interval (lifetime risk 4-6 vs 5-8 per 1000 women) with a 40% increase in number of colposcopies

Women ages 30-65

Screen with cotesting every 5 years (preferred) or cytology alone every 3 years (acceptable).

- Cotesting leads to increased detection of prevalent CIN3 with a concomitant decrease in CIN3+ or cancer detected in subsequent rounds of screening
- This permits a longer interval between screens with incident cancer rates similar to or lower than screening with cytology alone at shorter intervals
- Cotesting also increases detection of adenocarcinoma

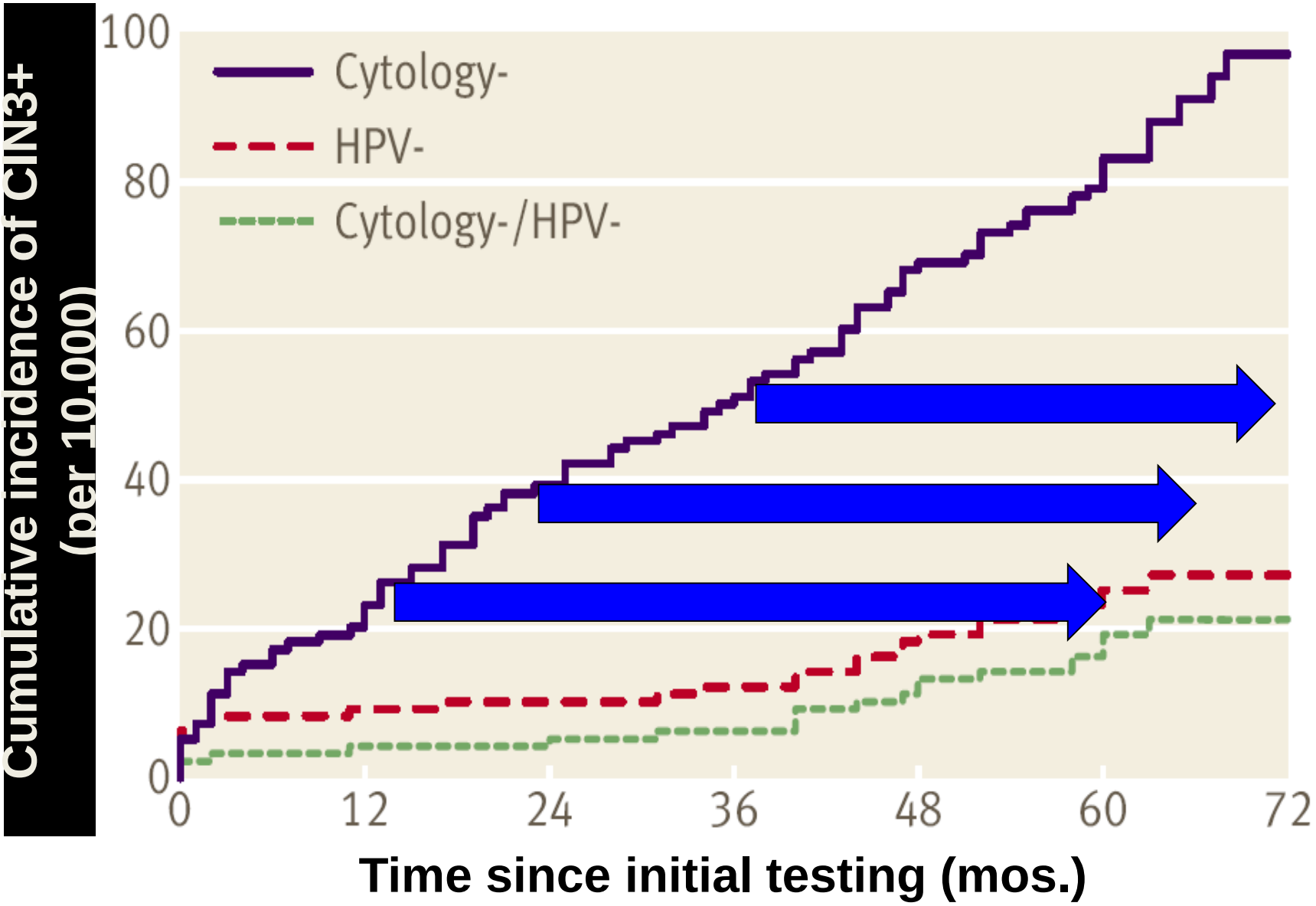
Why prefer cotesting?

Pooled analysis of 7 European studies:

Risk of CIN3+

6 years after negative co-test	3 years after negative cytology
0.28%	0.51%

CIN3+ Risk Following a Negative Test



Women >65 years

Women over the age of 65 with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened.

- In well-screened women >65, CIN2+ prevalence is low and cancer is rare
- Potential for harms outweigh small potential benefit
- Most new HPV infections in women >65 should clear spontaneously

Women >65 years

- Cervical cancer occurs 15-25 years after HPV infection
- Low risk of HPV progression
- Screening 1000 women from age 65 to 90 years would prevent 1.6 cancer cases and 0.5 cancer deaths
- High risk of false-positive results and low PPV, leading to anxiety, unnecessary procedures, and cost
- Colpo/biopsy/treatment more difficult--harms are magnified

Women with a Hysterectomy

Women at any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer using any modality.

- Vaginal cancer is rare with an age-specific incidence similar to or less than that of other cancers for which screening is not performed, such as breast cancer in men
- Abnormal vaginal cytology is rarely of clinical importance

Screening after HPV Vaccination

Recommended screening practices should not change on the basis of HPV vaccination status.

- Vaccine coverage must be higher in order to delay onset of screening or extend screening interval, e.g. >70-80%
- Evidence on the duration of protection and absolute reduction of risk of CIN3+ is needed
- Documentation of vaccination status at an age likely prior to HPV exposure is needed

Screening after HPV Vaccination

- Many women will be vaccinated after exposure to HPV
- Vaccines do not protect against HPV types that cause ~30% of cancers*
- In the absence of vaccine registries, difficult to know who has been vaccinated, at what age, and with how many doses

Key Evidence Supporting New Recommendations

- Several large studies showing greater benefits and reduced harms of co-testing (HPV plus Pap) at longer screening intervals
- Modeling studies showing harms of over-screening
- Studies showing lack of benefit of screening teens
- Emerging evidence on HPV testing alone** and screening after vaccination

Important Messages

- Focus efforts on unscreened women
- Frequent (annual, biennial) cervical screening leads to more harms than benefits
- Screening with HPV plus Pap has many advantages: “preferred” for ages 30+
- “Co-testing” every 5 years is extremely safe: better detection, less procedures
- New guidelines are based on a rigorous review and achieved broad consensus

Conclusion

The biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among women who have not been screened or who have not been screened regularly. . . Clinicians, hospitals, health plans, and public health officials should seek to identify and screen these women.

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