Cervical Cancer Screening Guidelines: What's in store for 2020?

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I have no financial interests in anything I will discuss today.

Objectives

- To know the current cervical cancer screening guidelines
- To know what is in store for 2020

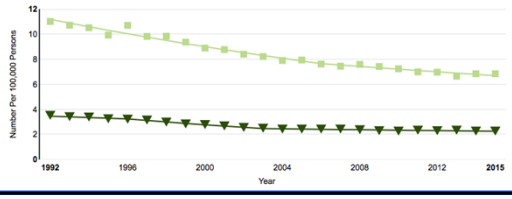
Background: Cervical Cancer

- ~13,000 cervical cancer cases and 4,100 deaths per year in the US (ACS, 2018)
- Most caused by hrHPV types
- ~50-60% of cases occur in never- and poorly-screened individuals
- Most effective approach: screen unscreened and poorly-screened individuals
- High hysterectomy rates in US account for some benefit
- Our challenge: balancing benefits, harms and costs, especially among those engaged in the screening process

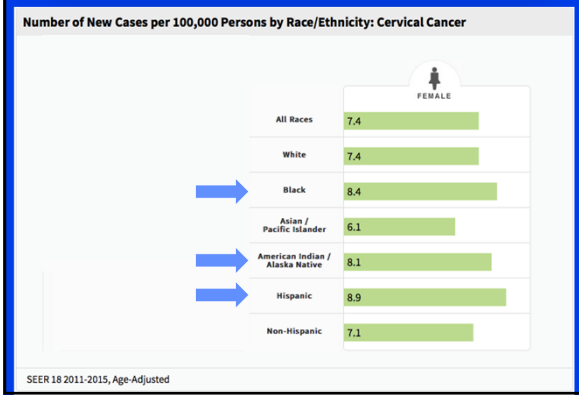
Cervical cancer incidence and mortality stable over last 10 years

% of All New Cancer Cases	0.8%
Estimated Deaths in 2018	4,170
% of All Cancer Deaths	0.7%

5 Years
66.2%
2008-2014



Disparities in cervical cancer *incidence* by race/ethnicity



Screening Guidelines

2012: All major guideline groups* agreed.
For average-risk individuals:

- Begin at age 21
- Cytology ages 21-65 q3 OR
- Cytology ages 21-29 q3, then cytology plus hrHPV testing ages 30+ q5 ("co-testing")
- End at age 65 if 3 consecutive prior normal cytology tests within last 10 years or 2 negative cytology plus hrHPV tests (most recent within 5 years)
- End after removal of cervix (hysterectomy) if no prior CIN2+

*USPSTF, ACS, ACOG

Screening Guidelines

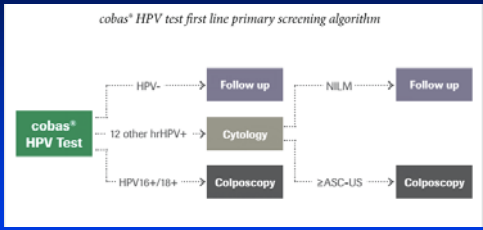
2014:

- FDA approves hrHPV testing alone for those ages 25+
- ACOG: "an alternative strategy" when used as per SGO recommendations

*USPSTF, ACS, ACOG

Society of Gynecologic Oncology: Primary HPV testing

Begin at age 25; re-screening "no sooner than every 3 years"
cobas HPV test (14 HR types)



cobas® HPV test first line primary screening algorithm

https://usdiagnostics.roche.com/en/hpv_ctng.html

VOTE #1: Which strategy do you use?

1. Cytology q3 ages 21-65y

2. Cytology q3 21-29y, then cytology + hrHPV testing q5 (co-testing), ages 30-65y

3. Cytology q3 21-29y, then hrHPV testing alone q5, ages 30-65y

Test accuracy

Strategies	Sensitivity	Specificity
Primary		
Cytology	**0.755**	**0.919**
hrHPV testing	**0.926**	**0.893**
Cytology plus hrHPV testing	**0.937**	**0.858**

Koliopoulos et al *Cochrane Database of Systematic Reviews*. 2017(8).
Li T et al *J Cancer Res Ther.* 2016;12(1):283-289.

USPSTF, Evidence report, 2018

- 8 RCTs (n = 410,556), 5 cohort studies (n = 402,615), and 1 individual participant data meta-analysis
- Trials heterogeneous for screening interval, number of rounds and protocols
- Primary hrHPV screening *vs* cytology:
  - colposcopy rates higher (1.2-7.9% *vs.* 1.1-3.1%)
  - increased detection of CIN3+ in round 1
  - false-positive rates higher (6.6-7.4% *vs.* 2.6-6.5%).

USPSTF, Evidence report, 2018

- Meta-analysis (data from 4 co-testing trials and 1 primary hrHPV trial): lower risk of invasive cervical cancer with any hrHPV screening compared with cytology alone (pooled RR, 0.60 [95% CI, 0.40-0.89]).

USPSTF, Evidence report, 2018

Conclusions:

•"Primary hrHPV screening detected higher rates of CIN 3+ at first-round screening compared with cytology.

•…hrHPV screening strategies had higher false-positive and colposcopy rates than cytology, which could lead to more treatments with potential harms."

Modeling: per 1000 over a lifetime

Strategy	Colpos	False positives	Cancers	Cancer death	Life-years
No screening	0	0	18.86	8.34	63921.34
Cytology q3, HPV triage for ASC-US, 21-65y	645	484	2.34	0.76	64181.89
Cytology + HPV q5, 30-65y	1630	1429	1.08	0.30	64192.97
HPV q5, 16/18 triage, 30-65y	1635	1435	1.05	0.29	64193.38

Kim et al *JAMA*, August 2018

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Kim et al *JAMA*, August 2018

VOTE #2: If choosing only one, which strategy would you recommend?

1. Cytology q3 ages 21-65y

2. Cytology q3 21-29y, then cytology + hrHPV testing q5 (co-testing), ages 30-65y

3. Cytology q3 21-29y, then hrHPV testing alone q5, ages 30-65y

USPSTF Recommendation, 2018

Endorsed 3 strategies:
- cytology alone every 3 years (ages 21-65)*
- cytology alone every 3 years (ages 21-29) then cytology plus HPV testing (ages 30-65)**
- cytology alone every 3 years (ages 21-29) then HPV testing alone every 5 years*

*preferred strategies
**alternative strategy

No recommendation for how to follow-up those with positive hrHPV tests (cytology triage? HPV 16/18 triage?)

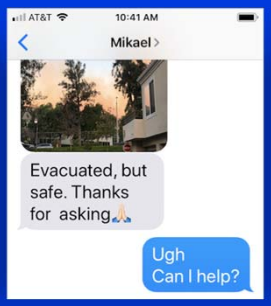
hrHPV testing: a few facts

- Several different tests available: Hybrid Capture 2, Cervista, Aptima, cobas, BD Onclarity
- Each tests for 13 or 14 high-risk HPV types
- Some test for specific high-risk types (16, 18, 45)
- *Only cobas and BD Onclarity are approved for primary screening; others are approved for co-testing and triage of ASC-US cytology*
- HPV-based testing may provide a unique pathway to identify non-squamous lesions of the cervix (about 30% of all cervical cancers; ~4,000 cases/year in the US)

12 current strategies

- Cytology q3 ages 21-65y with 2 ways to manage ASC-US:
  repeat cytology 1 year or hrHPV triage
- Cytology q3, ages 21-29y, then cytology + hrHPV (co-testing) q5, 30-65y with 2 ways to manage those with normal cytology and hrHPV+:
  repeat co-testing in one year or HPV16/18 triage
- Cytology q3, ages 21-29y, then:
  hrHPV q3, ages 30-65y with cytology triage for hrHPV+
  hrHPV q3, ages 30-65y with HPV16/18 triage for hrHPV+
  hrHPV q5, ages 30-65y with cytology triage for hrHPV+
  hrHPV q5, ages 30-65y with HPV16/18 triage for hrHPV+
- Cytology q3, ages 21-24y, then:
  hrHPV q3, ages 25-65y with cytology triage for hrHPV+
  hrHPV q3, ages 25-65y with HPV16/18 triage for hrHPV+
  hrHPV q5, ages 25-65y with cytology triage for hrHPV+
  hrHPV q5, ages 25-65y with HPV16/18 triage for hrHPV+

Woolsey Fire, November 11, 2018



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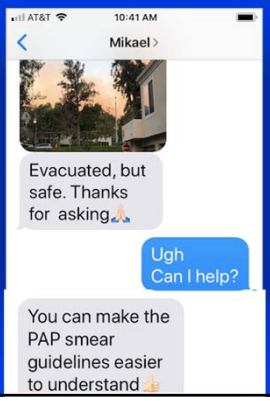

Research

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Estimated Quality of Life and Economic Outcomes Associated With 12 Cervical Cancer Screening Strategies
A Cost-effectiveness Analysis

George F. Sawaya, MD; Erinn Sanstead, MPH; Fernando Alarid-Escudero, PhD; Karen Smith-McCune, MD, PhD; Steven E. Gregorich, PhD; Michael J. Silverberg, PhD, MPH; Wendy Leyden, MPH; Megan J. Huchko, MD, MPH; Miriam Kuppermann, PhD, MPH; Shalini Kulasingam, PhD

Sawaya et al *JAMA Int Med* May 2019

Outcomes

- Colposcopies, false-positive tests, cancers and cancer deaths per strategy (per 1000)
- Quality-adjusted life-expectancy (QALY) per strategy (per 1000)
- Cost-effectiveness, calculated using discounted costs and discounted QALYs (3%)
- Incremental cost-effectiveness ratios (ICERs) calculated in 2016 US dollars per QALY saved

Results: Total costs

- Cost of no screening: $2891/person
- ***Screening is cost-saving***
- Costs of strategies: $1267-1600/person
- Comparison with breast cancer screening: $3060-5260/person; $2030/person for no screening -> not cost-saving (Stout et al JNCI 2014)

CERVICCS: CEA Results
Primary accuracy estimates, Table 3

Screening strategy	Cost, $	QALYs	$/QALY
Cytology q3, hrHPV triage ASC	1267	28.84109	0
hrHPV q5, 16/18 triage, 30	1303	28.76624	Dom
hrHPV q5, cytology triage +, 30	1311	28.75601	Dom
hrHPV q5, 16/18 triage, 25	1355	28.73210	Dom
hrHPV q5, cytology triage, 25	1359	28.72099	Dom
Cytology q3, repeat cytology ASC	1420	28.91174	2166
Cytology + hrHPV q5, repeat co-test	1480	28.81260	Dom
Cytology + hrHPV q5, 16/18 triage	1491	28.81007	Dom
hrHPV q3, 16/18 triage, 30	1492	28.73761	Dom
hrHPV q3, cytology triage, 30	1507	28.71668	Dom
hrHPV q3, 16/18 triage, 25	1589	28.71363	Dom
hrHPV q3, cytology triage, 25	1600	28.68792	Dom

Summary: CEA

Primary cytology dominates co-testing and all primary HPV testing strategies

Cytology q3 with repeat cytology for ASC-US was the most cost-effective option.

VOTE #3: Which strategy would you recommend?

1. Cytology q3 ages 21-65y

2. Cytology q3 21-29y, then cytology + hrHPV testing q5 (co-testing), ages 30-65y

3. Cytology q3 21-29y, then hrHPV testing q5, ages 30-65y

What about higher-than-average risk individuals?

- Defined: immunocompromised (HIV, medical immuno-suppression); *in utero* DES exposure; CIN2+ within the prior 20 years
- Immunocompromised: Begin screening within 1 year of onset of sexual activity or, if already sexually active, within the first year after HIV diagnosis but no later than 21
- Annual screening– can lengthen to every 3 years after 3 normal cytology tests or one negative cytology plus hrHPV test (co-test)
- Manage abnormal results as per immuno-competent individuals

What are the criteria for ending screening in low-risk individuals at age 65 years?

After 3 consecutive negative cytology results

or

2 consecutive negative co-tests

within the 10 years before ceasing screening, with the most recent test occurring within the past 5 years

What about self-sampling for HPV testing?

- Meta-analysis: high level of acceptability; preference for self-sampling over clinician sampling (ease and privacy)[1]
- Meta-analysis: offering self-sampling increased screening rates compared with invitation to clinic (12% absolute increase)[2]
- RCT: Home sampling similar to clinic-based screening for detection of CIN2+[3]Not currently endorsed by any guideline group.
- USPSTF (2019): "Rigorous comparative studies are needed… to identify effective strategies for implementation."
- Helpful for reassuring individuals of low-risk status (90-95%), but higher positivity rates compared with cytology means more follow-up, including colposcopy

[1]Sex Transm Infect 2017 93(1):56-61
[2]Eur J Cancer, 2015 51:2375-2385
3Lancet Oncol 2019; 20:229–38

Ending screening after hysterectomy

- **ACOG, ACS and USPSTF:** all agree that screening following total hysterectomy with removal of the cervix *for benign disease* is not indicated.
  USPSTF: "D" recommendation
- ACOG (2016): Continued routine screening (cytology ever 3 years) recommended for 20 years after treatment.

FAQ 1: How should I screen those who are DES-exposed in utero?

ACOG (2016): “Annual cervical cytology screening is reasonable”

FAQ 2: How should I screen those who are immunocompromised due to medications, not HIV?

ACOG 2016: Reasonable to extrapolate the recommendations for women with HIV infection. No clear guidance on which medications warrant increased screening. Certainly includes women on medications after solid organ transplantation.

VOTE #4: FAQ: Should I screen HPV vaccinated individuals differently than unvaccinated individuals?

1. **Yes**
2. **No**

FAQ 4: Should I re-start screening in those over age 65 who acquire new partners?

No (per ACS 2012)

What's in store for 2020?

- Cervical cancer screening: American Cancer Society guidelines
- American College of Obstetricians and Gynecologists guidelines (maybe)
- Management of abnormal screening tests: app-based and web-based management; no more paper algorithms from ASCCP

VOTE #5: Do you think that using an app or website for managing abnormal test results is an improvement?

1. Yes
2. No

Summary

- 3 ways to screen average-risk individuals: cytology alone (q3 21-65), HPV testing alone (q5 30-65), cytology plus HPV testing (q5 30-65)
- Immuno-compromised individuals: annual (but may lengthen after normal testing), lifelong screening
- App-and web-based guidelines for management