JAMA | US Preventive Services Task Force | MODELING STUDY

Screening for Cervical Cancer in Primary Care
A Decision Analysis for the US Preventive Services Task Force

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IMPORTANCE Evidence on the relative benefits and harms of primary high-risk human papillomavirus (hrHPV) testing is needed to inform guidelines.

OBJECTIVE To inform the US Preventive Services Task Force by modeling the benefits and harms of various cervical cancer screening strategies.

DESIGN, SETTING, AND PARTICIPANTS Microsimulation model of a hypothetical cohort of women initiating screening at age 21 years.

EXPOSURES Screening with cytology, hrHPV testing, and cytology and hrHPV cotesting, varying age to switch from cytology to hrHPV testing or cotesting (25, 27, 30 years), rescreening interval (3, 5 years), and triage options for hrHPV-positive results (16/18 genotype, cytology testing). Current guidelines-based screening strategies comprised cytology alone every 3 years starting at age 21 years, with or without a switch to cytology and hrHPV cotesting every 5 years from ages 30 to 65 years. Complete adherence for all 19 strategies was assumed.

MAIN OUTCOMES AND MEASURES Lifetime number of tests, colposcopies, disease detection, false-positive results, cancer cases and deaths, life-years, and efficiency ratios expressing the trade-off of harms (ie, colposcopies, tests) vs benefits (life-years gained, cancer cases averted). Efficient strategies were those that yielded more benefit and less harm than another strategy or a lower harm to benefit ratio than a strategy with less harms.

RESULTS Compared with no screening, all modeled cervical cancer screening strategies were estimated to result in substantial reductions in cancer cases and deaths and gains in life-years. The effectiveness of screening across the different strategies was estimated to be similar, with primary hrHPV-based and alternative cotesting strategies having slightly higher effectiveness and greater harms than current guidelines-based cytology testing. For example, cervical cancer deaths associated with the guidelines-based strategies ranged from 0.30 to 0.76 deaths per 1000 women, whereas new strategies involving primary hrHPV testing or cotesting were associated with fewer cervical cancer deaths, ranging from 0.23 to 0.29 deaths per 1000 women. In all analyses, primary hrHPV testing strategies occurring at 5-year intervals were efficient. For example, 5-year primary hrHPV testing (cytology triage) based on switching from cytology to hrHPV screening at ages 30 years, 27 years, and 25 years had ratios per life-year gained of 73, 143, and 195 colposcopies, respectively. In contrast, strategies involving 3-year hrHPV testing had much higher ratios, ranging from 2188 to 3822 colposcopies per life-year gained. In most analyses, strategies involving cotesting were not efficient.

CONCLUSIONS AND RELEVANCE In this microsimulation modeling study, it was estimated that primary hrHPV screening may represent a reasonable balance of harms and benefits when performed every 5 years. Switching from cytology to hrHPV testing at age 30 years yielded the most efficient harm to benefit ratio when using colposcopy as a proxy for harms.

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JAMA. 2018;320(7):706-714. doi:10.1001/jama.2017.19872

In 2012, cervical cancer screening guidelines were harmonized across several major guidelines-making organizations, including the US Preventive Services Task Force (USPSTF),[1-3] recommending routine cytology screening every 3 years starting at age 21 years, with an option to switch to cytology and high-risk human papillomavirus (hrHPV) "cotesting" every 5 years starting at age 30 years (A recommendation). Screening is recommended to end at age 65 years, provided a history of regular screening without abnormalities in the past 10 to 20 years.[1-3] Since 2012, new evidence on primary hrHPV testing has emerged, contributing to the US Food and Drug Administration approval of the first stand-alone hrHPV test for primary screening in women 25 years and older. Interim clinical guidance on the use of primary hrHPV testing has been issued from several professional organizations.[4]

Although empirical studies such as randomized clinical trials provide high-quality evidence on the effectiveness of screening, outcomes are usually based on intermediate end points (eg, precancer detection or colposcopy rates) after limited rounds of screening. Mathematical disease simulation models can complement such evidence by extrapolating data beyond the trial period to project long-term outcomes of screening (eg, life expectancy) over multiple rounds of screening. Models can also explore alternative scenarios that have not been examined in empirical studies. This decision analysis using a cervical cancer disease simulation model accompanied an evidence report for the USPSTF to update the evidence and address gaps in the expected benefits and harms of cervical cancer screening strategies in primary care.[5]

Methods

The full decision analysis technical report is available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening2. The full report contains additional model calibration and validation results, as well as results from additional scenario and sensitivity analyses.

Model Description

The disease microsimulation model has a natural history component and a screening component that are used to project the life histories of simulated women under different screening strategies.[6,7] In the natural history model, each simulated woman faces monthly transitions between health states that describe underlying disease status, including HPV infection, precancer (ie, cervical intraepithelial neoplasia [CIN] grades 2 and 3), and invasive cancer (ie, local, regional, distant stages) (**Figure 1**). Health states are further stratified by oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58, each considered separately; pooled other high-risk types; and pooled low-risk types. Each month, women have risks of hysterectomy and death from all causes,[8,9] as well as death from cervical cancer based on survival data from the Surveillance, Epidemiology, and End Results (SEER) program.[10] Transition probabilities can vary by age, HPV type, duration of infection or lesion status, and a woman's history of prior HPV infection and CIN treatment. Uncertain parameters, such as HPV incidence, CIN progression and regression, and HPV natural immunity, were calibrated to data on HPV prevalence and type distribution among women with and without cervical disease.[11-13] The model focuses on squamous cell carcinoma, the most common histologic subtype of cervical cancer.

Screening is used to detect the presence of high-grade precancers, which can be treated before progressing to cancer, or for the earlier detection of invasive cancer. Screening assumptions in the model can vary by screening start and stop ages, frequency, coverage, follow-up (ie, triage) testing, and adherence to recommended follow-up. Tests for primary screening and triage include cytology, hrHPV DNA testing, and cytology and hrHPV cotesting, with varying test characteristics (**Table 1**).[14-18] Diagnostic colposcopy and biopsy were assumed to be 100% accurate in confirmation of histologic status, and the effectiveness of precancer treatment (eg, loop electrosurgical excisional procedure) was assumed to be 100%, but both assumptions were varied in sensitivity analysis. Details on the selection of input data and assumptions are available in the full report.

The model was validated against data from SEER cancer registries (years 2000-2013), under assumptions of current screening practice patterns (eFigure 1 in the Supplement).[19-21] Additional model validation exercises included comparing model projections against reported outcomes from the HPV for Cervical Cancer Screening (HPV FOCAL) trial, a randomized trial evaluating stand-alone hrHPV testing for primary screening.[22]

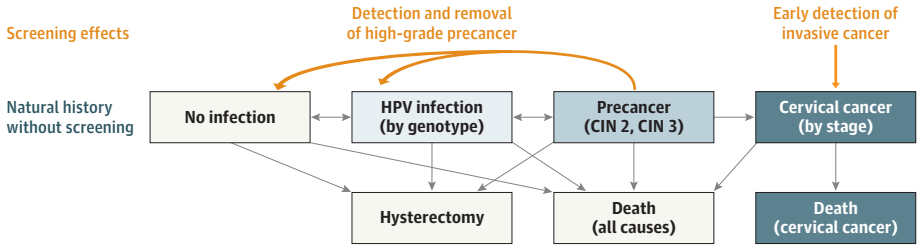
Screening Strategies

The analysis focused on the comparative effectiveness and harms of primary hrHPV testing, compared with currently recommended screening strategies. **Table 2** summarizes the 19 main strategies evaluated. Guideline-based screening strategies comprised cytology alone every 3 years from ages 21 to 65 years (strategy 1) and cytology alone every 3 years from ages 21 to 29 years, with a switch to cytology and hrHPV cotesting every 5 years from ages 30 to 65 years (strategy 2).[1-3] Follow-up of women with equivocal or abnormal test results was assumed to follow established guidelines.[2,23] For cotesting, hrHPV-positive/cytology-negative women underwent repeat cotesting at 12 months, with referral to colposcopy for any positive result.

The primary HPV testing strategies (strategies 3-14) were varied by (1) age to switch from cytology to hrHPV screening, (2) rescreening interval after an hrHPV-negative result, and (3) triage options for hrHPV-positive results. Age to switch to hrHPV screening was evaluated at ages 25, 27, and 30 years, following cytology-only screening starting at age 21 years. The rescreening interval for primary hrHPV testing was evaluated every 3 years and every 5 years, consistent with current guidelines for cytology-only testing and cotesting. Two triage strategies for hrHPV-positive screening results were examined (eFigure 2 in the Supplement): (1) assuming HPV-16/18 genotype information is available, HPV-16/18–positive women are referred to colposcopy, whereas women positive for other high-risk HPV types receive cytology triage (those with a cytology result of atypical squamous cells of undetermined significance (ASCUS) or worse are referred to colposcopy; those with a cytology-negative result receive a follow-up test in 12 months); (2) all women with hrHPV receive cytology triage. Additional cotesting strategies (strategies 15-19) were also included, varying the age to switch and rescreening interval.

In the base-case analysis, the age to stop screening was 65 years, assuming no recent history of abnormal results, consistent with current guidelines; sensitivity analysis was used to evaluate the effect of extending the age threshold at which to terminate screening to 70 and 75 years. The analysis assumed full adherence to screening initiation, rescreening interval, and follow-up for both diagnostic and

Figure 1. Natural History Model of Cervical Cancer and the Effects of Screening



The main health states of the natural history model comprise no infection, human papillomavirus (HPV) infection (by genotype), precancer (cervical intraepithelial neoplasia [CIN] grades 2 and 3), invasive cancer (by stage), hysterectomy, and death (from all causes or from cervical cancer). Movement between these health states occur as monthly transitions. The model focuses on squamous cell carcinoma, the most common histologic subtype of cervical cancer. Screening is used to detect the presence of CIN 2 or CIN 3, which can be treated and removed before it progresses to cancer, as well as for early detection of invasive cancer.

Table 1. Screening Test Characteristics

	Screening Test		Sensitivity Analysis		
Test Characteristic[a]	Base-Case Value	Source	Worst-Case Value	Best-Case Value	Source
Cytology[b]					
Sensitivity	0.727	Koliopoulos et al, 2007[14]	0.514	0.815	Koliopoulos et al, 2007[14] Cox et al, 2013[15]
Specificity	0.919		0.880	0.936	
hrHPV[c]					
Relative sensitivity	1.24	Cox et al, 2013[15]	1.15	1.37	Cox et al, 2013[15] Arbyn et al, 2012[16] Ronco et al, 2006[17] Ronco et al, 2006[18]
Relative specificity	0.97		0.96	0.98	
Cotest[c]					
Relative sensitivity	1.31	Cox et al, 2013[15]	1.20	1.42	Cox et al, 2013[15] Arbyn et al, 2012[16] Ronco et al, 2006[17] Ronco et al, 2006[18]
Relative specificity	0.93		0.93	0.94	

Abbreviation: hrHPV, high-risk human papillomavirus.

[a] Sensitivity (specificity) for all tests defined as probability to detect presence (absence) of cervical intraepithelial neoplasia, grade 2 or worse.

[b] For cytology testing, positivity threshold is atypical squamous cells of undetermined significance.

[c] For hrHPV testing and cotesting, given the wide variation in absolute test characteristics across studies attributable to differences in protocols and populations, we elected to use relative sensitivity and specificity values, compared with cytology testing (positivity threshold of atypical squamous cells of undetermined significance). For example, the base-case test sensitivity value for primary hrHPV testing was 0.901 (0.727 × 1.24) and for cotesting was 0.952 (0.727 × 1.31).

precancer treatment referrals. Furthermore, the base-case analysis focused on women who did not receive HPV vaccination.

Screening Outcomes

The model was used to generate a number of outcomes associated with each screening strategy, reflecting both health benefits and harms over the lifetime of screening starting at age 21 years. Harms included total number of cytology and hrHPV tests (including screening, triage, and surveillance), colposcopies, and false-positive screening results (defined as total number of colposcopies without underlying CIN 2, CIN 3, or cancer); benefits included CIN 2 and CIN 3 detected, CIN 3 or worse (CIN 3+) detected (including CIN 3 and cervical cancers detected through screening), cervical cancer cases and deaths averted, and life-years gained. These measures were calculated as the cumulative number of events or time spent in the different health states, which were then modified by the interventions, over the selected time horizon (ie, lifetime).

Analysis

The relative efficiency of each screening strategy was evaluated to examine the trade-off of harms vs benefits for the general population of women being screened and was expressed as the incremental number of colposcopies per life-year gained. This efficiency ratio was defined as the additional number of colposcopies divided by the additional life-years of a specific strategy compared with the strategy with the next fewer colposcopies. Strategies with more harms (colposcopies) and less benefits (life-years) than an alternative strategy, or with a higher harm to benefit ratio than a strategy with more harms, were considered "inefficient" and eliminated from the calculation; all other strategies were considered "efficient." Because there is no consensus on the appropriate metric to assess efficiency, results are also presented in terms of the incremental number of total screening tests per life-year gained and the incremental number of colposcopies per cervical cancer case averted.

Sensitivity Analyses

The effects of uncertainty and alternative assumptions on the results were also assessed. Data uncertainty included screening test characteristics, colposcopy and biopsy performance, and effectiveness of precancer treatment. Alternative screening scenarios included variations in follow-up of hrHPV-positive women, including cytology triage with a colposcopy referral threshold of low-grade squamous

Table 2. Cervical Cancer Screening Strategies[a]

Strategy		Screen 1			Screen 2			
No.	Name[b]	Test	Interval, y	Start Age, y	Test	Interval, y	Start Age, y	Triage Strategies
1	CYTO-3Y, 21[c]	Cytology	3	21				HPV for ASCUS
2	CYTO-3Y, 21/COTEST-5Y, 30[c]	Cytology	3	21	Cotest	5	30	Repeat cotest, 12 mo
3	CYTO-4Y, 21/HPV-3Y (16/18), 25	Cytology	4	21	HPV	3	25	HPV-16/18 genotype
4	CYTO-3Y, 21/HPV-3Y (16/18), 27	Cytology	3	21	HPV	3	27	
5	CYTO-3Y, 21/HPV-3Y (16/18), 30	Cytology	3	21	HPV	3	30	
6	CYTO-4Y, 21/HPV-5Y (16/18), 25	Cytology	4	21	HPV	5	25	
7	CYTO-3Y, 21/HPV-5Y (16/18), 27	Cytology	3	21	HPV	5	27	
8	CYTO-3Y, 21/HPV-5Y (16/18), 30	Cytology	3	21	HPV	5	30	
9	CYTO-4Y, 21/HPV-3Y (cyto), 25	Cytology	4	21	HPV	3	25	Cytology triage
10	CYTO-3Y, 21/HPV-3Y (cyto), 27	Cytology	3	21	HPV	3	27	
11	CYTO-3Y, 21/HPV-3Y (cyto), 30	Cytology	3	21	HPV	3	30	
12	CYTO-4Y, 21/HPV-5Y (cyto), 25	Cytology	4	21	HPV	5	25	
13	CYTO-3Y, 21/HPV-5Y (cyto), 27	Cytology	3	21	HPV	5	27	
14	CYTO-3Y, 21/HPV-5Y (cyto), 30	Cytology	3	21	HPV	5	30	
15	CYTO-4Y, 21/COTEST-3Y, 25	Cytology	4	21	Cotest	3	25	Repeat cotest, 12 mo
16	CYTO-3Y, 21/COTEST-3Y, 27	Cytology	3	21	Cotest	3	27	
17	CYTO-3Y, 21/COTEST-3Y, 30	Cytology	3	21	Cotest	3	30	
18	CYTO-4Y, 21/COTEST-5Y, 25	Cytology	4	21	Cotest	5	25	
19	CYTO-3Y, 21/COTEST-5Y, 27	Cytology	3	21	Cotest	5	27	

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

[a] Cotest strategies involve cytology and high-risk HPV (hrHPV) testing. Follow-up of women with abnormal screening results was assumed to follow clinical guidelines[2,23] and includes (1) for cytology testing, reflex hrHPV testing for women with ASCUS and referral to colposcopy for women with more severe abnormal results; (2) for cotesting, repeat cotesting in 12 months for women with cytology-negative, hrHPV-positive results; and (3) for hrHPV testing, 2 triage options—(A) "HPV (16/18)" strategies involving referral to colposcopy for women testing positive for HPV-16/18 genotype and cytology triage for women positive for other (non-16/18) hrHPV and (B) "HPV (cyto)" strategies involving cytology triage for all hrHPV-positive women. Analysis assumes screening end age of 65 years.

[b] Strategy name indicates SCREENING TEST 1–interval (years), start age (years)/SCREENING TEST 2–interval (years) (triage strategy for hrHPV-positive women), start age (years). For example, "CYTO-3Y, 21/COTEST-5Y, 30" indicates cytology alone every 3 years starting at age 21 years, with switch to cotesting every 5 years starting at age 30 years.

[c] Strategy currently recommended by the US Preventive Services Task Force and other guidelines-making organizations.[1-3]

intraepithelial lesion (base-case analyses assumed ASCUS), varying intervals for follow-up testing from 6 months to 24 months (base-case analyses assumed 12 months), and immediate colposcopy for all hrHPV-positive women. To reflect a low-risk population, screening of HPV-vaccinated women was evaluated, assuming that 100% of women were vaccinated with the 3-dose HPV-16/18 vaccine in preadolescence and that vaccination conferred 100% protection against HPV-16 and HPV-18 infections over the lifetime.

The model was programmed in C++, and model outputs were analyzed in R version 1.0.136 (R Project for Statistical Computing).

Results

In the absence of screening, estimated lifetime cervical cancer incidence was 1.9% and lifetime risk of cervical cancer mortality was 0.83%, resulting in a life expectancy of 63.9 years (**Table 3**) for 20-year-old women. Compared with no screening, all modeled cervical cancer screening strategies were estimated to result in substantial reductions in cervical cancer cases and deaths and gains in life-years. However, the effectiveness of screening across the different strategies was estimated to be similar, with primary hrHPV-based and alternative cotesting strategies having slightly higher effectiveness in terms of life-years gained and cancer cases and deaths averted than current guidelines-based cytology testing. For example, cervical cancer deaths associated with the guidelines-based strategies (strategies 1 and 2) ranged from 0.30 to 0.76 deaths per 1000 women, whereas the new strategies involving primary hrHPV testing or cotesting varying switch age, interval, and triage option (strategies 3-19) were associated with fewer cervical cancer deaths, ranging from 0.23 to 0.29 deaths per 1000 women (an improvement of 0.01 to 0.53 lives saved per 1000 women screened).

In terms of harms, more frequent rescreening interval (ie, 3-year vs 5-year) and cotesting strategies were generally associated with a greater number of lifetime total tests, whereas the age to switch from cytology to hrHPV testing or cotesting did not have much effect on the estimates. Using cytology triage for hrHPV-positive women was associated with slightly increased lifetime total testing (1%-2%), compared with 16/18 genotype triage. With cotesting, the number of lifetime total tests were 60% to 82% greater than with the analogous strategy involving hrHPV testing alone.

Cytology testing alone every 3 years from age 21 to age 65 years was associated with the lowest number of lifetime colposcopies (ie, 645 per 1000 women) but also the lowest number of CIN 2 or CIN 3 and CIN 3+ cases detected. All other strategies were associated with a higher number of colposcopies, especially for cotesting (strategies 2, 15-19), followed by primary hrHPV testing with 16/18 genotype triage (strategies 3-8). Primary hrHPV testing with 16/18 genotype triage was

Table 3. Outcomes for Cervical Cancer Screening Strategies Over the Lifetime of Screening[a]

Strategy		Per 1000 Women									
No.	Name[b]	Cytology Tests	HPV Tests	Total Tests[c]	No. of Colposcopies	CIN 2 or 3 Detected	CIN 3+ Detected[d]	False-Positives[e]	Cervical Cancer Cases	Cervical Cancer Deaths	Life-Years
0	No screening	0	0	0	0	0	0	0	18.86	8.34	63 921.34
1	CYTO-3Y, 21	13 877	786	14 662	645	160	46	484	2.34	0.76	64 181.89
2	CYTO-3Y, 21 /COTEST-5Y, 30	11 425	8380	19 806	1630	201	54	1429	1.08	0.30	64 192.97
3	CYTO-4Y, 21 /HPV-3Y (16/18), 25	1905	14 807	16 712	2530	218	57	2312	0.74	0.23	64 195.61
4	CYTO-3Y, 21 /HPV-3Y (16/18), 27	2876	13 772	16 648	2278	214	56	2063	0.83	0.25	64 195.08
5	CYTO-3Y, 21 /HPV-3Y (16/18), 30	3824	12 428	16 252	1978	205	54	1773	1.01	0.27	64 193.51
6	CYTO-4Y, 21 /HPV-5Y (16/18), 25	1706	10 065	11 771	2068	211	55	1857	0.79	0.25	64 195.39
7	CYTO-3Y, 21 /HPV-5Y (16/18), 27	2697	9290	11 987	1861	207	55	1655	0.89	0.28	64 194.69
8	CYTO-3Y, 21 /HPV-5Y (16/18), 30	3675	8476	12 151	1635	199	53	1435	1.05	0.29	64 193.38
9	CYTO-4Y, 21 /HPV-3Y (cyto), 25	2277	14 790	17 067	2209	217	56	1992	0.75	0.23	64 195.53
10	CYTO-3Y, 21 /HPV-3Y (cyto), 27	3205	13 738	16 943	1992	213	56	1779	0.85	0.25	64 194.82
11	CYTO-3Y, 21 /HPV-3Y (cyto), 30	4102	12 397	16 499	1734	203	54	1530	1.04	0.28	64 193.19
12	CYTO-4Y, 21 /HPV-5Y (cyto), 25	1993	10 049	12 042	1826	209	55	1617	0.81	0.25	64 195.35
13	CYTO-3Y, 21 /HPV-5Y (cyto), 27	2950	9273	12 223	1648	205	54	1443	0.91	0.28	64 194.44
14	CYTO-3Y, 21 /HPV-5Y (cyto), 30	3888	8459	12 348	1452	198	53	1254	1.08	0.29	64 193.07
15	CYTO-4Y, 21 /COTEST-3Y, 25	15 723	14 693	30 416	2535	223	57	2312	0.76	0.23	64 195.50
16	CYTO-3Y, 21 /COTEST-3Y, 27	15 765	13 723	29 488	2303	218	57	2084	0.83	0.25	64 194.75
17	CYTO-3Y, 21 /COTEST-3Y, 30	15 456	12 411	27 867	2021	209	55	1812	1.03	0.27	64 193.17
18	CYTO-4Y, 21 /COTEST-5Y, 25	10 944	9914	20 859	2029	213	55	1816	0.82	0.26	64 195.26
19	CYTO-3Y, 21 /COTEST-5Y, 27	11 275	9233	20 508	1846	209	55	1637	0.89	0.27	64 194.40

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN 3+, CIN 3 or worse; HPV, human papillomavirus.

[a] Outcomes calculated from age 20 to 100 years; analysis assumes screening end age of 65 years.

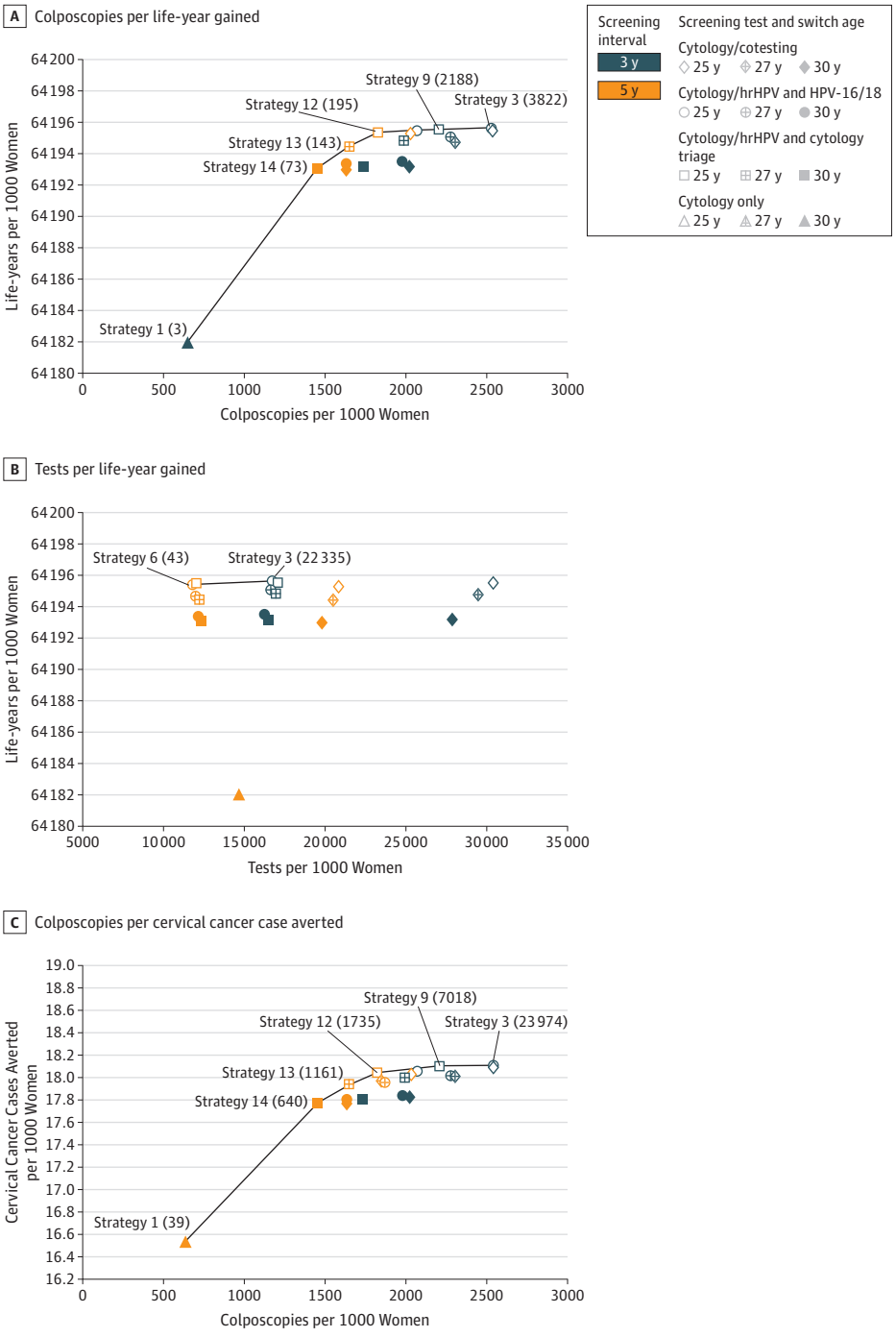
[b] See Table 2 footnote for description of nomenclature.

[c] Total number of tests, irrespective of primary, triage, or surveillance context; does not include colposcopies.

[d] Includes cases of CIN 3 and cervical cancers detected through screening (excludes clinically detected cancers).

[e] Total number of colposcopies that did not result in CIN 2, CIN 3, or cancer detection.

Figure 2. Results from the Efficiency Analysis: Colposcopies per Life-Year Gained, Tests per Life-Year Gained, and Colposcopies per Cervical Cancer Case Averted for All 19 Cervical Cancer Screening Strategies



Strategies varied in terms of primary screening test (cytology with a switch to cotesting; cytology with a switch to primary high-risk HPV [hrHPV] testing with HPV-16/18 genotype testing for triage of hrHPV-positive women; cytology with a switch to primary hrHPV testing with cytology triage of hrHPV-positive women; cytology only); screening interval (3 years, 5 years); and switch age from cytology to primary hrHPV testing or cotesting (25 years, 27 years, 30 years). The efficiency ratios (values in parentheses) were calculated as the additional number of harms (ie, colposcopies or tests) divided by the additional benefits (ie, life-years gained or cancer case averted) of a specific strategy compared with the strategy having the next fewer harms. Efficient strategies (ie, those that lie on the efficiency frontier [solid lines]) were those that yielded more benefit and less harm than another strategy, or a lower harm to benefit ratio than a strategy with less harms; all other strategies (ie, those that do not lie on the efficiency frontier) were considered "inefficient." All strategies assume cytology alone starting at age 21 years and a screening end age of 65 years. Tests include the total number of screening tests over the lifetime of screening, including both routine screening and any surveillance testing but not diagnostic (ie, colposcopy and biopsy) testing.

associated with 12% to 14% more colposcopies than hrHPV testing with cytology triage. Consistent with the trend of colposcopies, the number of false-positive results increased when switching from 3-year cytology testing to hrHPV testing or cotesting.

Relative Efficiency Analysis

Three different metrics were calculated to reflect different ways of capturing the harm-benefit trade-off (**Figure 2**).

Colposcopies per Life-Year Gained

The strategy with the lowest number of colposcopies per life-year gained was the current guidelines-based strategy of cytology testing alone every 3 years from ages 21 to 65 years (strategy 1), with 3 colposcopies per life-year gained compared with no screening (Figure 2A). By comparison, primary hrHPV and cotesting strategies were associated with both increased life-years and more colposcopies. Primary hrHPV testing with cytology triage every 5 years

at a switch age of 30 years (strategy 14) was associated with 73 colposcopies per life-year gained; at a switch age of 27 years (strategy 13), with 143 colposcopies per life-year gained; and at a switch age of 25 years (strategy 12), with 195 colposcopies per life-year gained. Increasing the frequency of screening to 3-year primary hrHPV testing and switching at age 25 years required a much greater number of colposcopies per life-year gained, ranging from 2188 (cytology triage, strategy 9) to 3822 (16/18 genotype triage, strategy 3). All other strategies, including cotesting (strategies 2, 15-19), were not efficient, given the similar gains in life-years but much higher numbers of colposcopy referrals.

Tests per Life-Year Gained

When the analysis was expressed in terms of tests (ie, cytology and hrHPV tests) per life-year gained, the only efficient strategies were primary hrHPV testing with 16/18 genotype triage at a switch age of 25 years (Figure 2B); the efficiency ratio was 43 tests per life-year gained for 5-year screening (strategy 6) and increased substantially to 22 335 tests per life-year gained for 3-year screening (strategy 3). Both cytology-only and cotesting strategies (strategies 1-2, 15-19) were either equally or less effective but were associated with higher numbers of tests than primary hrHPV testing strategies and were therefore not efficient.

Colposcopies per Cervical Cancer Case Averted

Efficient strategies were consistent with those identified in the analysis of colposcopies per life-year gained. Cytology-only screening every 3 years (strategy 1) had the lowest ratio of 39 colposcopies per cervical cancer case averted (Figure 2C). Switching from cytology to 5-year primary hrHPV testing at age 30 years (strategy 14) was associated with a ratio of 640 colposcopies per cancer case averted; earlier switch ages required a greater number of colposcopies per cancer case averted, ranging from 1161 for switch age 27 years (strategy 13) and 1735 for switch age 25 years (strategy 12). High-risk HPV testing every 3 years at a switch age of 25 years increased the ratio to 7018 colposcopies per cancer case averted (cytology triage, strategy 9) and 23 974 colposcopies per cancer case averted (16/18 genotype triage, strategy 3). As with colposcopies per life-year gained, cotesting strategies (strategies 2, 15-19) were not efficient, given the much higher rate of colposcopy referrals.

Sensitivity Analysis

When the age to end screening was extended to 70 or 75 years, the efficiency results were similar to the base-case analyses (ie, age to end screening at 65 years) for all 3 efficiency outcomes (eFigure 3 and eTables 2-4 in the Supplement). The corresponding ratios increased as the end age increased, indicating that when screening is continued to later ages, it becomes less efficient.

Sensitivity analyses assessed the effect of test performance characteristics on the main results (eTables 2-4 in the Supplement). When test sensitivity for cytology was increased to the upper-bound value (with a corresponding decrease in specificity), the efficient strategies remained the same for all 3 efficiency metrics, but the ratios generally increased (ie, became less efficient), given the increase in downstream colposcopies and tests. In contrast, when specificity for cytology was increased (with a decrease in sensitivity), the effectiveness of all strategies decreased—especially for screening with cytology alone—but given the corresponding decrease in colposcopies, the ratios using this measure decreased (became more efficient) for all strategies.

The lower-bound (worst-case) relative sensitivity of hrHPV testing was explored, affecting both hrHPV testing alone and cotesting. Despite a decrease in the effectiveness of the primary hrHPV testing strategies, these strategies were still associated with greater benefits compared with the current guidelines-based strategies. Since the decrease in effectiveness was also accompanied by a decrease in colposcopies, the ratios among efficient strategies improved and more strategies involving 3-year screening with hrHPV testing alone (strategies 3, 9, 10) became efficient, likely because of an offset from the lower sensitivity value.

In analyses that introduced error in the performance of colposcopy and biopsy in classifying a woman's true histologic status, or that assumed that the effectiveness of precancer treatment (eg, loop electrosurgical excisional procedure) was decreased to 82%, the base-case results of the efficiency analyses remained stable under both sensitivity analyses, with slight decreases in the ratios attributable to the relatively greater reductions in harms (ie, colposcopies and tests) than benefits (ie, life-years and cases averted).

Alternative follow-up algorithms based on protocols from empirical studies were examined, including for women who receive cytology triage, a more stringent cutoff of low-grade squamous intraepithelial lesion as the threshold for colposcopy referral (ie, ASCUS in the base case), as well as varying the time to repeat testing after a normal cytology triage result to 6 months or 24 months (ie, 12 months in the base case). Each of these sensitivity analyses resulted in similar efficient strategies as in the base-case analyses, and the ratios for the strategies across the different efficiency outcomes changed only marginally.

A third alternative triage option was evaluated in which all hrHPV-positive women were referred directly to colposcopy. The number of colposcopies and false-positive results was much greater, with only a small increase in effectiveness. For ratios that used colposcopies as a measure of harm, all strategies that referred hrHPV-positive women directly to colposcopy without further testing were not efficient.

For women assumed to be completely protected from HPV-16/18 infections over their lifetime because of vaccination, the same strategies were identified as efficient as in the base case; however, the harm to benefit ratios for these strategies became less favorable, given the considerably lower cervical cancer risk in HPV-vaccinated women.

Discussion

In this analysis, consistent with short-term evidence from clinical studies, the model projected that strategies involving primary hrHPV testing or cotesting were associated with greater health benefits compared with current guidelines-based cytology testing alone but come at a harm of more tests, colposcopies, and false-positive results. In all analyses, across 3 different efficiency measures, primary hrHPV testing strategies occurring at 5-year intervals were efficient, with the harm to benefit ratios decreasing (ie, becoming more efficient) as the switch age extended from 25 to 30 years. By comparison, strategies involving 3-year hrHPV

testing generally had much higher ratios. The efficiency of triage options for hrHPV-positive women depended on which outcome was used as a proxy for harm: cytology triage was more efficient than 16/18 genotype triage for the 2 efficiency metrics that used colposcopy as the proxy for harm (per life-year gained and per cervical cancer case averted); however, 16/18 genotype testing was the preferred triage option when using screening tests as the proxy for harm (per life-year gained).

Cytology alone every 3 years from ages 21 to 65 years had the lowest benefit in terms of life-years gained and cervical cancer cases averted, as well as the lowest number of colposcopies. When number of colposcopies was used as the measure of harm, cytology testing alone every 3 years was associated with very low (ie, efficient) ratios; however, when using total tests as the measure of harm, cytology testing was inefficient. Cotesting strategies, including one currently recommended in the United States (consisting of cytology testing every 3 years starting at age 21 years, switching at age 30 years to cotesting every 5 years [strategy 2]), were predominantly inefficient compared with strategies involving hrHPV testing alone across all analyses.

This analysis, used to inform the USPSTF recommendations for cervical cancer screening, extends the 2012 decision analysis, which primarily evaluated cytology-based strategies.[24] The current analysis focused specifically on hrHPV testing for primary screening and included variations in age to switch from cytology-only screening to hrHPV testing, the rescreening interval, and triage options for hrHPV-positive women. For strategies that overlapped in both reports, the results from the current analysis were similar to the findings from the previous analysis.

When extending age to end screening from 65 to 70 or 75 years (assuming no recent abnormal results), the model projected slight increases in each of the ratios attributable to decreased efficiency of screening in older ages. However, given the uncertainties regarding the natural history of HPV infection and screening effectiveness in older women—which were not extensively explored in the current analysis—the findings of screening end age should be viewed as exploratory and interpreted with caution.

When multiple strategies are identified as efficient, selecting the optimal strategy depends on a threshold ratio that would be considered a reasonable balance of harms and benefits. The desired thresholds for each of the 3 efficiency measures is not clear when using intermediate metrics such as colposcopies or tests as a proxy for harm, as it is difficult to directly compare against other (noncervical cancer) health interventions.

Limitations

This study has several limitations. First, the analysis was based on assumptions of perfect adherence to screening intervals and follow-up of screen-positive women; however, it is well documented that screening practice is not perfect and is quite variable across the United States. How loss to follow-up might differ across testing modalities, age, and interval is uncertain but could affect the overall effectiveness and relative efficiency of the screening strategies.

Second, although a number of unique strategies were analyzed, there may be other strategies that could lead to a more attractive balance of harms and benefits. For example, the rescreening interval was restricted to not extend beyond every 5 years, but extending intervals (eg, to 7 or 10 years) may be more efficient without compromising effectiveness.

Third, the analyses did not explore different assumptions regarding the natural history of HPV infection in older women, nor did they examine other strategies or criteria to determine when to stop screening. There is much uncertainty regarding the prevalence and clinical importance of a newly acquired HPV infection vs reactivation of a previously acquired infection in older ages, which may affect the optimal age at which to stop screening. Two studies have indicated that the incidence and mortality rates from cervical cancer are underestimated by the SEER program, given high rates of hysterectomies in US women, and suggest that the current recommendation for terminating screening may not be optimal.[25,26] The findings from the microsimulation model, which do correct for hysterectomy rates by age in the population, indicate efficiency and greater effectiveness by extending the screening end age to 70 or 75 years; however, other screening exit criteria and strategies should be further explored in analyses under various assumptions of disease risk and screening effect at older ages.

Fourth, issues regarding HPV-negative cancers and the implications for the relative effectiveness of hrHPV testing alone vs cytology alone or cotesting were not fully addressed.[27] The sensitivity analysis in which hrHPV relative test sensitivity (compared with cytology) was decreased to a lower bound estimate mimics a scenario of greater missed disease owing to hrHPV negativity; this scenario was the only one in which strategies involving 3-yearly hrHPV screening became more efficient, with ratios comparable to 5-yearly hrHPV screening in the base-case analyses.

Fifth, the results from the model represent average outcomes across the whole population and are intended to inform guidelines at the population level, not at an individual level. In assessing screening in a low-risk population, only 1 very specific subset of low-risk women was represented—those who receive protection against HPV-16/18 infection and disease from vaccination. Although other segments of the population are at low risk, this question will become increasingly more pertinent as vaccinated women enter screening age.

Conclusions

In this microsimulation modeling study, it was estimated that primary hrHPV screening may represent a reasonable balance of harms and benefits when performed every 5 years. Switching from cytology to hrHPV testing at age 30 years yielded the most efficient harm to benefit ratio when using colposcopy as a proxy for harms.

ARTICLE INFORMATION

Accepted for Publication: November 29, 2017.

Author Contributions: Dr Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Kim, Burger.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kim, Burger.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kim, Sy.
Obtained funding: Kim.
Administrative, technical, or material support: Kim, Burger, Regan.
Supervision: Kim.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This research was funded under contract HHSA-290-2012-00015-I, Task Order 6, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the USPSTF. Dr Kim, Dr Burger, Ms Regan, and Mr Sy were also supported in part by National Cancer Institute grant U01CA199334.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope and key questions for this analysis. AHRQ staff provided project oversight; reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project: the AHRQ staff, the Evidence-based Practice Center team, and the US Preventive Services Task Force members for comments on earlier versions of this research; Shalini Kulasingam, PhD, MPH, Emily A. Groene, MA, and Aanjaneya Shukla, MS (University of Minnesota), and the National Cancer Institute–funded Cancer Intervention and Surveillance Modeling Network (CISNET) cervical cancer working group for intellectual support and feedback throughout the project. Dr Kulasingam, Ms Groene, and Mr Shukla received salary support for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 3 content experts (Diana Petitti, MD, MPH, University of Arizona College of Medicine; Gillian Sanders Schmidler, PhD, Duke University; Alan Waxman, MD, MPH, University of New Mexico). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final report.

Editorial Disclaimer: This modeling study is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

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