JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Cervical cancer can be prevented with detection and treatment of precancerous cell changes caused primarily by high-risk types of human papillomavirus (hrHPV), the causative agents in more than 90% of cervical cancers.

OBJECTIVE To systematically review benefits and harms of cervical cancer screening for hrHPV to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, PsycINFO, and the Cochrane Collaboration Registry of Controlled Trials from January 2011 through February 15, 2017; surveillance through May 25, 2018.

STUDY SELECTION Randomized clinical trials (RCTs) and cohort studies comparing primary hrHPV screening alone or hrHPV cotesting (both hrHPV testing and cytology) with cytology (Papanicolaou [Pap] test) screening alone.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts and full-text articles and quality rated included studies; data were qualitatively synthesized.

MAIN OUTCOMES AND MEASURES Invasive cervical cancer; cervical intraepithelial neoplasia (CIN); false-positive, colposcopy, and biopsy rates; psychological harms.

RESULTS Eight RCTs (n = 410 556), 5 cohort studies (n = 402 615), and 1 individual participant data (IPD) meta-analysis (n = 176 464) were included. Trials were heterogeneous for screening interval, number of rounds, and protocol. For primary hrHPV screening, evidence was consistent across 4 trials demonstrating increased detection of CIN 3 or worse (CIN 3+) in round 1 (relative risk [RR] range, 1.61 [95% CI, 1.09-2.37] to 7.46 [95% CI, 1.02-54.66]). Among 4 hrHPV cotesting trials, first-round CIN 3+ detection was not significantly different between screening groups; RRs for cumulative CIN 3+ detection over 2 screening rounds ranged from 0.91 to 1.13. In first-round screening, false-positive rates for primary hrHPV screening ranged from 6.6% to 7.4%, compared with 2.6% to 6.5% for cytology. For cotesting, false-positives ranged from 5.8% to 19.9% in the first round of screening, compared with 2.6% to 10.9% for cytology. First-round colposcopy rates were also higher, ranging 1.2% to 7.9% for primary hrHPV testing, compared with 1.1% to 3.1% for cytology alone; colposcopy rates for cotesting ranged from 6.8% to 10.9%, compared with 3.3% to 5.2% for cytology alone. The IPD meta-analysis of data from 4 cotesting trials and 1 primary hrHPV screening trial found lower risk of invasive cervical cancer with any hrHPV screening compared with cytology alone (pooled RR, 0.60 [95% CI, 0.40-0.89]).

CONCLUSIONS AND RELEVANCE Primary hrHPV screening detected higher rates of CIN 3+ at first-round screening compared with cytology. Cotesting trials did not show initial increased CIN 3+ detection. Both hrHPV screening strategies had higher false-positive and colposcopy rates than cytology, which could lead to more treatments with potential harms.

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High-risk human papillomavirus (hrHPV) is readily transmitted through sexual contact[1,2] and is recognized as a causative agent in more than 90% of cervical cancers.[3] Persistent infection with hrHPV types 16 and 18 is responsible for most cases.[4,5] Although a high proportion of sexually active women become infected with some human papillomavirus type by age 25 years, most infections resolve spontaneously.[6] Effective screening and treatment for precancerous lesions are associated with low rates of cervical cancer mortality in the United States.[7] Annual age-adjusted cervical cancer incidence in the United States was 7.4 cases per 100 000 women and mortality was 2.3 deaths per 100 000 women (2011-2015), with the highest incidence among black (8.4 per 100 000) and Hispanic (8.9 per 100 000) women. Black women also had the highest mortality rate (3.7 deaths per 100 000 women).[8]

In 2012, the US Preventive Services Task Force (USPSTF) recommended screening women aged 21 to 65 years for cervical cancer with cytology (Papanicolaou [Pap] smear) every 3 years, with an option for women 30 years and older for hrHPV cotesting (cytology and cervical swab for hrHPV) every 5 years (A recommendation).[9] This systematic review, conducted to update evidence on cervical cancer screening, focused on the effectiveness of hrHPV screening strategies relative to cytology-based screening to support an updated USPSTF recommendation.

Methods

Scope of Review

Cytology is the foundation for long-standing cervical cancer screening recommendations, with well-established benefits and harms. The USPSTF commissioned this review to evaluate direct evidence from trials and large observational cohort studies on the comparative effectiveness of screening approaches that use hrHPV screening. Specifically, the 2 key questions (KQs) (**Figure 1**) aimed to identify the benefits (KQ1) and harms (KQ2) of cervical cancer screening using hrHPV screening alone as the initial test (primary screening) or paired with cytology (cotesting), compared with screening with cytology as the primary test. Additional methodological details regarding the review search strategies, including detailed study inclusion criteria, excluded studies, and description of data analyses, are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening2.

Data Sources and Searches

Comprehensive literature searches were performed for primary literature in MEDLINE, PubMed, PsycINFO, and the Cochrane Collaboration Registry of Controlled Trials from January 2011 through February 15, 2017, bridging from the dates of the previous USPSTF review.[11] Database searches were supplemented with experts' suggestions and by reviewing reference lists from other relevant systematic reviews. After February 2017, ongoing surveillance continued through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that could affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on May 25, 2018, and resulted in the addition of the initial results of the Compass trial.[12] The final results of the HPV FOCAL trial, published in *JAMA* in July 2018, have also been incorporated in this review.[13]

Study Selection

Two reviewers independently reviewed 2972 unique citations and 164 full-text articles against specified inclusion criteria (**Figure 2**). Discrepancies were resolved through consensus and consultation with a third investigator when required.

Eligible studies were rated as fair or good quality, published in English, and conducted in highly developed countries.[15] Quality assessment criteria are reported in eTable 1 in the Supplement. Studies had to be conducted in primary care or generalizable settings (eg, family planning clinics); studies based on laboratory results alone without an identified cohort were excluded. Randomized clinical trials (RCTs), individual participant data (IPD) meta-analyses, systematic reviews, and large ($\geq$ 10 000 women) longitudinal cohort studies that examined the benefits or harms of primary hrHPV screening or cotesting among average-risk women 21 years and older were included. Studies in women without a cervix, at high risk for cervical cancer, or who were pregnant were excluded. Studies evaluating hrHPV as a triage test after cytology compared with cytology alone were excluded. Cohort studies including fewer than 10 000 women were excluded, unless they addressed a subpopulation of interest (eg, underscreened women).

Invasive cervical cancer generally develops over years, preceded by progressive precancerous changes of the cervix, defined as cervical intraepithelial neoplasia (CIN) categorized as CIN 1, CIN 2, and CIN 3.[16] For KQ1, because invasive cervical cancer is a rare event in countries with organized screening programs such that even large trials did not have sufficient sample size or duration to detect changes in invasive cervical cancer incidence, CIN 3 or worse (CIN 3+) was chosen as the primary outcome. CIN 3+ was consistently reported because of broad consensus that detection and treatment of CIN 3 can prevent progression to invasive cervical cancer. For KQ2, studies were included if they reported false-positive CIN 2+ or false-negative invasive cervical cancer screening test results; biopsy rates, colposcopy rates, or both; or psychological harms (eg, labeling, stigma, distress, quality of life).

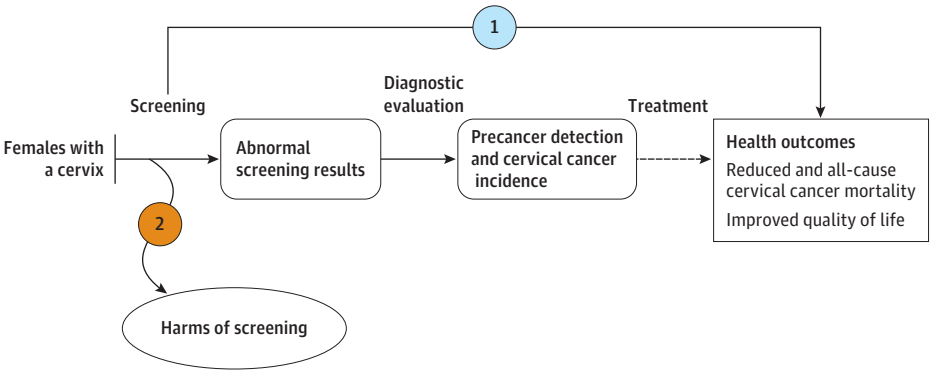
Data Extraction and Quality Assessment

Two investigators independently assessed the quality of included studies using USPSTF design-specific criteria for RCTs[17] and the Newcastle-Ottawa Scale for observational studies.[18] Each study was rated as good, fair, or poor (eTable 1 in the Supplement). Disagreements in quality ratings were resolved by consensus and by consultation with a third investigator if required. Poor-quality studies with major flaws (eg, attrition >40%, differential attrition >20%) or multiple important limitations that could invalidate the results were excluded. One investigator extracted study-level data (study design details, population and intervention characteristics, outcomes) into standardized evidence tables and a second investigator confirmed the accuracy of the data.

Data Synthesis and Analysis

Because of the heterogeneity of screening tests, screening protocols, follow-up protocols, and settings, results were qualitatively

Figure 1. Analytic Framework: Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing



Key questions

1 What is the effectiveness of human papillomavirus for high-risk HPV types (hrHPV) testing, with or without cytology, as a primary screening strategy for reducing cervical cancer mortality and incidence compared with currently recommended screening strategies for women in the United States?
a. Does the effectiveness of hrHPV testing to reduce cervical cancer outcomes vary by subpopulation (eg, age, race/ethnicity, screening history, hrHPV immunization status, and socioeconomic status)?
b. For each primary screening strategy, how does the rescreening interval relate to future cancer incidence or progression?
c. Does the appropriate rescreening interval for each primary screening strategy vary by subpopulation (eg, age, race/ethnicity, screening history, HPV immunization status, and socioeconomic status)?

2 What are the potential adverse effects of hrHPV testing, with or without cytology, as a primary screening strategy compared with currently recommended screening strategies for women in the United States?
a. Do the adverse effects vary by subpopulation (eg, age, race/ethnicity, and HPV immunization status)?
b. Do the adverse effects vary by screening strategy, including by rescreening interval?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Further details are available in the USPSTF procedure manual.[10]

synthesized. Summary tables of study design, population characteristics, protocols, and intervention and follow-up details for each round of screening were created. Results were synthesized by KQ and screening strategy, either primary hrHPV screening or cotesting. When possible, results were also stratified by age (<30-35 years vs ≥30-35 years) because of lower prevalence of hrHPV in women 30 years and older. Results were based on a "number of women screened" denominator, rather than intention-to-treat calculations using all women randomized. Relative risks (RRs) and 2-sided 95% confidence intervals were calculated when not reported in the study. Stata version 15.1 (StataCorp) was used for all analyses.

To estimate potential harms or burden of screening, test positivity, colposcopy rates, and false-positive rates were reported or calculated from available data. The false-positive rate was reported to quantify the extent to which women in a cervical cancer screening program experienced positive screening test results necessitating further follow-up (ie, triage testing, repeat screening, colposcopy, and biopsy) and were not found to have precancerous lesions or cervical cancer (ie, CIN 2+). This was calculated as the number with a positive screening test result without diagnosis of CIN 2+ as a proportion of women screened who were not diagnosed with CIN 2+. This pragmatic definition relies on colposcopy as a reference standard, recognizing that there is variability in the accuracy of colposcopy and biopsy.[19] False-negatives were defined as the proportion of invasive cervical cancer cases occurring among women with negative preceding screening results. Psychological harms, including adverse effects on anxiety, distress, and sexual satisfaction, were abstracted when reported.

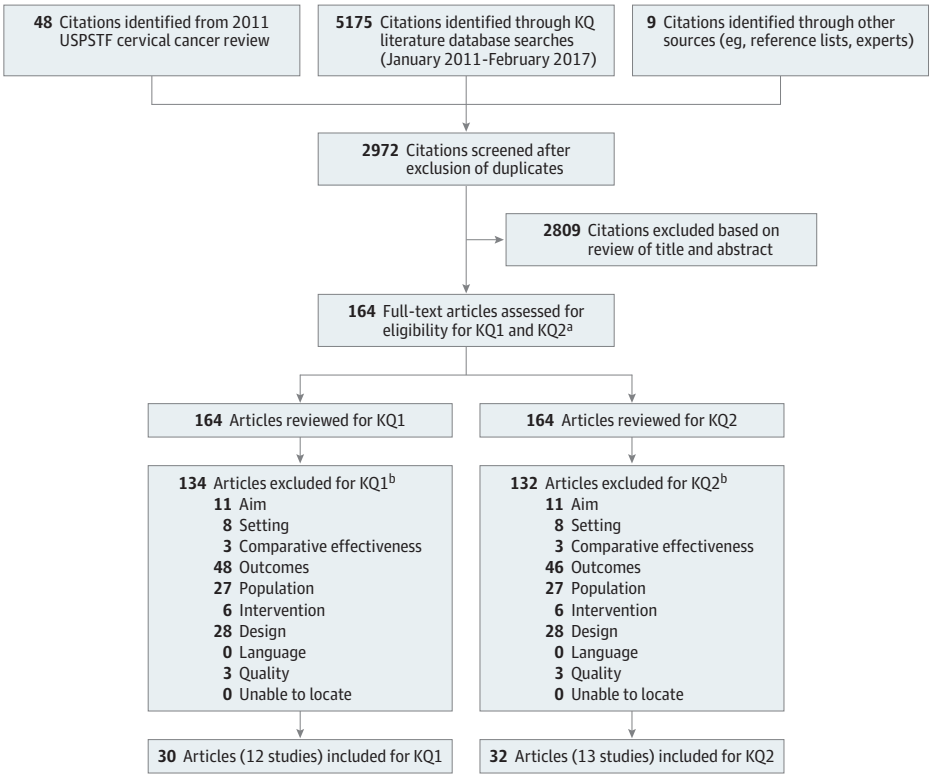
Results

Effectiveness of Screening

Key Question 1. What is the effectiveness of human papillomavirus for hrHPV testing, with or without cytology, as a primary screening strategy for reducing cervical cancer mortality and incidence compared with currently recommended screening strategies for women in the United States?

Four fair- or good-quality cervical cancer screening RCTs were identified that compared primary hrHPV screening with cytology (n = 282 838),[12-14,19-23] and 4 RCTs compared cotesting with cytology (n = 127 717) (**Table 1**).[14,25-35] One IPD meta-analysis combined 176 464 women from 1 primary hrHPV screening trial and 4 hrHPV cotesting trials to examine invasive cervical cancer incidence.[47] Four large cohort studies were included: 1 of primary hrHPV screening (n = 48 736),[24] 2 of cotesting (n = 351 613),[36-42,48,49] and 1 reporting on cotesting outcomes in 1832 unscreened women.[42] Trials varied in the number of reported screening rounds (1 or 2), the screening interval (3-5 years), consistency between screening rounds (eg, randomization maintained, cytology only or cotesting for both intervention and control groups in the second screening round), and the protocols for evaluation of abnormal screening results. For primary hrHPV screening, follow-up varied and included cytology triage from a specimen obtained at the time of initial screening and held, hrHPV genotyping with follow-up based on viral type, or immediate colposcopy (Table 1). Four RCTs offered consistent evidence that primary hrHPV screening will detect

Figure 2. Literature Search Flow Diagram: Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing



USPSTF indicates US Preventive Services Task Force.

[a] One publication (Ronco 2010[14]) includes 2 trials (NTCC Phase I and NTCC Phase II), so it is counted as 2 publications instead of 1.

[b] Reasons for exclusion: Aim: Study aim was not relevant. Setting: Study was not conducted in a country relevant to US practice or not conducted in, recruited from, or feasible for primary care or a health system. Comparative effectiveness: Active comparator (eg, liquid-based cytology vs conventional cytology alone). Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Population: Study was not conducted in an included population. Intervention: Intervention was out of scope. Design: Study did not use an included design. Language: Publication not in English. Quality: Study was poor quality. Unable to Locate: Review staff was unable to locate article.

higher rates of CIN 3+ at an initial screening round compared with cytology, while trials of cotesting did not show initial increased CIN 3+ detection at round 1. Data on mortality from cervical cancer were not reported in any included studies.

Primary hrHPV Compared With Cytology Screening

Across 4 trials with variable protocols and hrHPV test types, conducted in women aged 25 to 65 years, evidence was consistent in demonstrating that primary hrHPV screening led to a statistically significant increased detection of CIN 3+ in the initial round of screening (RR range, 1.61 [95% CI, 1.09-2.37]) to 7.46 [95% CI, 1.02-54.66]) (**Table 2**).[12,13,19,21,22] The New Technologies for Cervical Cancer (NTCC) Phase II trial of primary hrHPV screening (in which all women with a positive hrHPV test result were referred to colposcopy) had complete results from 2 rounds of screening, but the screening strategy was not maintained (at round 2 screening, all women received cytology testing).[14,20] In that study, CIN 3+ detection in round 1 was 3 times higher in the hrHPV screening group, with cumulative detection 1.8 times higher after the second round of screening. In the recently published 48 -month screening results of the HPV FOCAL trial, all women received cotesting at the second round of screening.[13] CIN 3+ detection in the hrHPV screening group was higher in round 1 (RR, 1.61 [95%CI, 1.09-2.37]) but significantly lower in round 2 (RR, 0.42 [95% CI, 0.25-0.69]). Results of a single-group cohort study of primary hrHPV screening at 3-year intervals were consistent with trial findings (eTable 2 in the Supplement).[24]

Cotesting Compared With Cytology Screening

Four cotesting trials followed up enrolled women aged 25 to 64 years through 2 rounds of screening, but only 1 trial (A Randomized Trial in Screening to Improve Cytology [ARTISTIC]) maintained the randomly assigned screening protocol in the second round (Table 1).[32-35] None of the trials demonstrated significantly higher detection of CIN 3+ with cotesting in the first round of screening, with the RR ranging from 0.96 (95% CI, 0.74-1.23) to 1.31 (95% CI, 0.92-1.87) (Table 2). By the second round of screening 3 to 5 years later, CIN 3+ detection in 2 trials was significantly lower, with RRs ranging from 0.53 (95% CI, 0.29-0.98)[30,31] to 0.73 (95% CI, 0.55-0.96).[27-29] Cumulative detection of CIN 3+ over 2 rounds was similar in all trials, with no RR significantly different than 1.0. Long-term follow-up was reported for 2 cotesting trials: the Swedescreen trial reported up to 13 years by tracking study participants in the National Quality Registry for Cervical Cancer Prevention,[31] and the Population-based Screening Study Amsterdam (POBASCAM) trial reported 14 years of follow-up tracked through the nationwide network and registry of histopathology and cytopathology.[29] In both studies, no statistical difference in cumulative CIN 3+ rates was detected between the intervention and control groups.

Two large single-group cohort studies of cotesting showed higher detection of CIN 3+ in the first screening round relative to a follow-up round (eTable 2 in the Supplement).[24,37,43,44] Long-term evaluation of the US-based cohort found that risk of CIN 3+ in women

Table 1. Study Characteristics of Randomized Clinical Trials and Cohort Studies of hrHPV Screening

Source	Study Design (Quality[a])	No. of Participants	Ages Recruited, y	Screening Strategy at Entry	No. of Screening Rounds (Screening Interval, y)	Criteria for Immediate Colposcopy	Protocol Changes Between Rounds	Follow-up Period, y[b]
hrHPV Primary Screening								
NTCC Phase II Ronco et al,[20] 2008 Ronco et al,[14] 2010 (Italy)	RCT (good)	49 196	25-60	hrHPV alone	2 (3)	hrHPV+	Screening with conventional cytology in round 2	7.0
				Conventional cytology	2 (3)	LSIL+ or ASCUS+[c]	NA	
2018 HPV FOCAL Ogilvie et al,[22] 2010 Cook et al,[19] 2015 Ogilvie et al,[21] 2017 Ogilvie et al,[13] 2018 (Canada)	RCT (fair)	19 009	25-65	hrHPV with LBC triage	2 (4)[d]	hrHPV+ and ASCUS+	Received cotesting at 4-y exit screen	4.0
				LBC with hrHPV triage	2 (4)[d]	ASCUS+ and hrHPV+ (or, for cytology only, ASC-H or LSIL+)	Received cotesting at 4-y exit screen	
FINNISH Leinonen et al,[23] 2012 (Finland)	RCT (fair)	203 425	25-65	hrHPV with conventional cytology triage	1 (5)	hrHPV+ and LSIL+	NA (single round)	5.0
				Conventional cytology	1 (5)	LSIL+	NA (single round)	
Compass Canfell et al,[12] 2017 (Australia)	RCT (fair)	4995	25-64	hrHPV with LBC triage[e]	1 (5)	HPV16/18+, other hrHPV+ with LSIL or ASC-H+ or p16/Ki-67+	NA (single round)	5.0
				LBC	1 (2.5)	ASC-H$^+$/HSIL+	NA (single round)	2.5
Zorzi et al,[24] 2017 (Italy)	Cohort (fair)	48 736	25-64	hrHPV with conventional cytology triage	2 (3)	hrHPV+ and ASCUS+	NA (single round)	6
hrHPV Cotesting With Cytology								
NTCC Phase I Ronco et al,[25] 2006 Ronco et al,[26] 2006 Ronco et al,[14] 2010 (Italy)	RCT (good)	45 174	25-60	hrHPV with conventional cytology	2 (3)	ASCUS+, hrHPV+, or both among women ≥35 y	Screening with conventional cytology in round 2	7.0
				Conventional cytology	2 (3)	LSIL+ or ASCUS+[c]	NA	
POBASCAM Bulkmans et al,[27] 2004 Rijkaart et al,[28] 2012 Dijkstra et al,[29] 2016 (The Netherlands)	RCT (good)	44 938	29-61	hrHPV with conventional cytology	2 (5)	HSIL+	None	9.0
				Conventional cytology	2 (5)	HSIL+	Screening with cotesting in round 2	
Swedescreen Naucler et al,[30] 2008 Elfström et al,[31] 2014 (Sweden)	RCT (fair)	12 527	32-38	hrHPV with conventional cytology	1 (3)	ASCUS+[c]	Unblinding of hrHPV status[f]; screening with conventional cytology in round 2	4.1[g]
				Conventional cytology	1 (3)	ASCUS+[c]	NA	
ARTISTIC Kitchener et al,[32] 2008 Kitchener et al,[33] 2009 Kitchener et al,[34] 2009 Kitchener et al,[35] 2014 (United Kingdom)	RCT (fair)	25 078	20-64	hrHPV with LBC	2 (3)	HSIL+	None	4.5
				LBC				

(continued)

Table 1. Study Characteristics of Randomized Clinical Trials and Cohort Studies of hrHPV Screening (continued)

Source	Study Design (Quality[a])	No. of Participants	Ages Recruited, y	Screening Strategy at Entry	No. of Screening Rounds (Screening Interval, y)	Criteria for Immediate Colposcopy	Protocol Changes Between Rounds	Follow-up Period, y[b]
KPNC Castle et al,[36] 2011 Katki et al,[37] 2011 Katki et al,[38] 2013 Katki et al,[39] 2013 Gage et al,[40] 2014 Gage et al,[41] 2015 (United States)	Cohort (fair)	331 818	≥30	hrHPV with conventional cytology	2 (3)	ASCUS/hrHPV+ or LSIL+	NA	6.0
Ibáñez et al,[42] 2014 (Spain)	Cohort (fair)	1832	40-88	hrHPV with conventional cytology	2 (3)	hrHPV+ or ASCUS+	NA	6.0
WOLPHSCREEN Petry et al,[43] 2013 Luyten et al,[44] 2014 (Germany)	Cohort (fair)	19 795	≥30	hrHPV with conventional cytology	2 (5)	hrHPV+, HSIL/ASC-H, or both	LBC with p16/Ki-67 dual staining introduced as a triage test Participants who changed health insurance provider excluded from round 2 (n = 6256)	10.0
McCaffery et al,[45] 2004 (United Kingdom)	Cross-sectional (fair)	428	20-61	hrHPV with conventional cytology	1 (NR)	ASCUS+, hrHPV+, or unsatisfactory smears	NA	NR

Abbreviations: ARTISTIC, A Randomized Trial in Screening to Improve Cytology; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; HPV FOCAL, Human Papillomavirus for Cervical Cancer Screening; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; KPNC, Kaiser Permanente Northern California; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; NA, not applicable; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; RCT, randomized clinical trial.

[a] Assessed using criteria from the US Preventive Services Task Force.[46]

[b] All time points are maximum follow-up, with the exception of the Swedescreen trial, which reported mean follow-up.

[c] Some differences between trial sites.

[d] HPV FOCAL had 2 randomized hrHPV groups: a safety group (screening every 2 years) and an intervention group (screening every 4 years). Only the latter is reported; results from the control group are reported at 4 years and include the 2-year screening round results.

[e] Triage could be performed via LBC or dual-stained cytology.

[f] Unblinding of human papillomavirus status 3 years after enrollment and 4 months after the completion of round 1.

[g] Range, less than 0.1 to 7.7 years.

Table 2. Effectiveness of hrHPV Screening for CIN 3+ and Invasive Cervical Cancer Incidence, Based on Randomized Clinical Trials (Key Question 1)

Source	Quality[a]	Screening Round (Planned Follow-up Period, y)	Screening Approach	CIN 3+ Absolute Detection (%)[b] Intervention	CIN 3+ Absolute Detection (%)[b] Control	CIN 3+ RR (95% CI)	Invasive Cervical Cancer, Absolute Detection (%)[b] Intervention	Invasive Cervical Cancer, Absolute Detection (%)[b] Control
hrHPV Primary Screening								
NTCC Phase II Ronco et al,[20] 2008 Ronco et al,[14] 2010	Good	1 (3.5)	hrHPV vs conventional cytology	97/24 661 (0.4)[c]	33/24 535 (0.1)[c]	2.92 (1.97-4.34)[d]	NR	NR
		2 (3.5)	Conventional cytology vs conventional cytology	5/23 978 (0.02)[c]	23/24 372 (0.09)[c]	0.22 (0.08-0.58)[d]		
		Cumulative (7)		102/24 661 (0.4)[c]	56/24 535 (0.2)[c]	1.81 (1.31-2.51)[d]		
HPV FOCAL Ogilvie et al,[22] 2010 Cook et al,[19] 2015 Ogilvie et al,[21] 2017 Ogilvie et al,[13]	Fair	1 (1)[e]	hrHPV with LBC triage vs LBC	67/9540 (0.7)	41/9408 (0.4)	1.61 (1.09-2.37)	NR	NR
		2 (4)[e,f]	Cotesting vs cotesting	22/9540 (0.2)	52/9408 (0.6)	0.42 (0.25-0.69)		
		Cumulative (4)[e,f]		89/9540 (0.9)	93/9408 (1.0)	0.94 (0.71-1.26)		
FINNISH Leinonen et al,[23] 2012	Fair	1 (5)	hrHPV with conventional cytology triage vs conventional cytology	195/66 410 (0.3)	118/65 784 (0.2)	1.64 (1.30-2.06)[d]	17/66 410 (0.03)	9/65 784 (0.01)
Compass Canfell et al,[12] 2017	Fair	1 (5)	hrHPV with LBC triage vs LBC[f]	30/4000 (0.8)	1/995 (0.1)	7.46 (1.02-54.66)	0/4000 (0)	0/995 (0)
hrHPV Cotesting With Cytology								
NTCC Phase I Ronco et al,[25] 2006 Ronco et al,[26] 2006 Ronco et al,[14] 2010	Good	1 (3.5)	Cotesting vs conventional cytology	75/22 708 (0.3)[c]	58/22 466 (0.3)[c]	1.28 (0.91-1.80)[d]	NR	NR
		2 (3.5)	Conventional cytology vs conventional cytology	13/22 093 (0.06)[c]	19/22 330 (0.08)[c]	0.96 (0.34-1.40)[d]		
		Cumulative (7)		88/22 708 (0.4)[c]	77/22 466 (0.3)[c]	1.13 (0.83-1.53)[d]		
POBASCAM Bulkmans et al,[27] 2004 Rijkaart et al,[28] 2012 Dijkstra et al,[29] 2016	Good	1 (4)	Cotesting vs conventional cytology	171/19 999 (0.9)	150/20 106 (0.7)	1.15 (0.92-1.43)	12/19 999 (0.06)	6/20 109 (0.03)
		2 (5)	Cotesting vs cotesting	88/19 579 (0.4)	122/19 731 (0.6)	0.73 (0.55-0.96)	4/19 579 (0.02)	14/19 731 (0.07)
		Cumulative (9)		259/19 999 (1.3)	272/20 106 (1.3)	0.96 (0.81-1.13)	16/19 999 (0.08)	20/20 106 (0.10)
Swedescreen Naucler et al,[30] 2008 Elfström et al,[31] 2014	Fair	1 (3)	Cotesting vs conventional cytology	72/6257 (1.2)	55/6270 (0.9)	1.31 (0.92-1.87)	NR	NR
		2 (NR)	Conventional cytology vs conventional cytology	16/6257 (0.3)	30/6270 (0.5)	0.53 (0.29-0.98)		
		Cumulative (4)		88/6257 (1.4)	85/6270 (1.4)	1.04 (0.77-1.39)[d]	1/6257 (0.02)	5/6270 (0.08)
ARTISTIC Kitchener et al,[32] 2008 Kitchener et al,[33] 2009 Kitchener et al,[34] 2009 Kitchener et al,[35] 2014	Fair	1 (2)	Cotesting vs LBC	233/18 386 (1.3)	81/6124 (1.3)	0.96 (0.74-1.23)[d]	5/18 386 (0.03)	4/6124 (0.07)
		2 (2)	Cotesting vs LBC	36/11 862 (0.3)[g]	17/3928 (0.4)[g]	0.76 (0.43-1.34)[d]	3/10 716 (0.03)[h]	0/3514 (0)[h]
		Cumulative (4.5)		269/18 386 (1.5)[g]	98/6124 (1.6)[g]	0.91 (0.73-1.15)[d]	8/18 386 (0.04)[h]	4/6124 (0.07)[h]

Abbreviations: ARTISTIC, A Randomized Trial in Screening to Improve Cytology; CIN, cervical intraepithelial neoplasia; CIN 3+, CIN 3 or worse; HPV FOCAL, Human Papillomavirus for Cervical Cancer Screening; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; RR, relative risk.

[a] Assessed using criteria from the US Preventive Services Task Force.[46]

[b] This table reports detection and relative risks for women of all ages included in the trial; see Supplement for results stratified by ages younger than 35 years vs 35 years and older.

[c] From author inquiry.

[d] Calculated (unadjusted).

[e] HPV FOCAL had 2 randomized hrHPV groups: a safety group (screening every 2 years) and an intervention group (screening every 4 years). Only the latter is reported; results from the control group are reported at 4 years and include the 2-year screening round results.

[f] The 4-year results compare 1 round of human papillomavirus screening in the intervention group with 2 rounds of cytology screening in the control group.

[g] Triage could be performed via LBC or dual-stained cytology.

[h] Preliminary or incomplete results.

cotesting negative was very low 3 and 5 years after testing (0.06% and 0.1%, respectively).[49]

To examine the effect of hrHPV screening on invasive cervical cancer in cervical cancer screening trials, Ronco et al conducted an IPD meta-analysis of 5 trials: 4 trials of cotesting and a single trial of primary hrHPV screening (NTCC Phase II).[47] Participant data were pooled, although these trials had distinctly different screening protocols, screening intervals, and hrHPV test types. The IPD meta-analysis included 176 464 women with 1 214 415 person-years of follow-up, with a total of 107 cases of invasive cervical cancer in a median follow-up period of 6.5 years. Cumulative detection of invasive cervical cancer was 46.7 per 100 000 in the hrHPV-screened women, compared with 93.6 per 100 000 women in the cytology groups. With a random-effects model, the overall pooled rate ratio for invasive cervical cancer in the hrHPV-screened women was 0.61 (95% CI, 0.41-0.91). The I^2 test for statistical heterogeneity was not significant (0.0%, $P = .52$).

Key Question 1a. Does the effectiveness of hrHPV testing to reduce cervical cancer outcomes vary by subpopulation (eg, age, race/ethnicity, screening history, hrHPV immunization status, and socioeconomic status)?

No trials provided data on race/ethnicity, screening history, or socioeconomic status for primary hrHPV screening. Several studies reported on outcomes by age group (eTables 3 and 4 in the Supplement), and 1 study reported on outcomes by age corresponding to the introduction of a population-based hrHPV immunization program.[12] One cohort study reported outcomes of a single round of cotesting in underscreened women.[42]

Primary hrHPV Compared With Cytology Screening Stratified by Age

In 4 trials of primary hrHPV screening, first-round CIN 3+ detection with hrHPV screening was consistently higher (range, 0.6%[14,20] to 2.4%[13,19,21,22]) among women younger than 35 years (eTable 4 in the Supplement) than for women older than 35 years (range, 0.2%[23] to 0.5%[13,19,21,22]) (eTable 3 in the Supplement). The RR for CIN 3+ detection between screening groups, however, was similar to the overall findings in both the younger (<30-35 years) and older (≥30-35 years) age groups. In the Compass trial,[12] participants were recruited from a population having 70% hrHPV vaccination coverage among women 33 years and younger. Primary hrHPV screening detected higher rates of CIN 3+ compared with cytology for both the younger (25-33 years) and older (34-64 years) age groups. Absolute detection rates were higher for women younger than 30 to 35 years, regardless of the screening test, in all primary hrHPV screening trials.

Cotesting Compared With Cytology Screening Stratified by Age

Three trials of cotesting reported outcomes by age group (eTables 3 and 4 in the Supplement). CIN 3+ detection was higher in women younger than 30 to 35 years compared with older women, but no trial found a significantly higher RR for cotesting compared with cytology among women younger than 30 to 35 years. Among women 35 years and older, only NTCC Phase I had a significantly higher RR for cotesting compared with cytology at round 1 (RR, 1.57 [95% CI, 1.02-2.43]). The effect estimates for CIN 3+ detection between screening groups were generally similar across age groups, with the exception of NTCC Phase I, with an RR of 0.89 (95% CI, 0.51-1.57) for women younger than 35 years and 1.57 (95% CI, 1.02-2.43) among women 35 years and older.

Gage et al published an age-stratified analysis of 1 313 128 women in a large US-based cohort who were screened for cervical cancer with cotesting from 2003 to 2013.[50] The 5-year risk of CIN 3+ was highest for women aged 25 to 29 years (1.23% [95% CI, 1.09%-1.39%]) and lowest for women aged 50 to 64 years (0.25% [95% CI, 0.22%-0.28%]).

In summary, while risks of hrHPV-positive results were consistently higher in women younger than 30 to 35 years, in most studies differences in CIN 3+ detection between screening methods were consistent across age groups.

Screening With hrHPV Cotesting in Underscreened Populations

A prospective single-cohort study from Spain described the outcomes of initial cotesting in a cohort of 1832 women older than 39 years with no documented cervical cancer screening in the previous 5 years.[42] No comparison group was included, and women older than 65 years were excluded after receiving negative initial cotesting results. Of 1494 remaining women, 767 (51.3%) completed follow-up. Nine women were diagnosed with CIN 3+, and 2 women had invasive cervical cancer (eTable 2 in the Supplement). Two women with CIN 3 were detected only by the hrHPV test.

Key Question 1b. For each primary screening strategy, how does the rescreening interval relate to future cancer incidence or progression?

Data were not adequate to compare outcomes of different rescreening intervals. One trial (HPV Testing for Cervical Cancer Screening [HPV FOCAL])[13,19,21,22] was designed to directly compare different rescreening intervals (2 years for cytology vs 4 years for primary hrHPV screening).[51] CIN 3+ detection was higher at initial screening in the hrHPV group compared with the cytology group (0.7% vs 0.4%; RR, 1.61 [95% CI, 1.09-2.37]) and lower at the 4-year exit-round screen compared with the cytology group (0.2% vs 0.6%; RR, 0.42 [95% CI, 0.25-0.69]) (Table 2).[13] The POBASCAM trial with 5-year screening intervals exhibited CIN 3+ detection and RRs for cotesting similar to those reported in cotesting trials with 3-year screening intervals.[27-29] In 13- to 14-year follow-up of the Swedescreen and POBASCAM trials, CIN 3+ risk remained persistently low in women who tested hrHPV-negative on initial screening, suggesting that 5-year intervals for hrHPV screening are no less effective than 3-year intervals over longer time frames.[29,31]

Recently published analyses of the large US-based cotesting cohort[48,49] evaluated the risk of CIN 3+ and invasive cervical cancer at 3 and 5 years after screening and found that after a negative hrHPV test result (regardless of the cytology result), risk of subsequent CIN 3+ was very low at 5 years (0.114% [95% CI, 0.106%-0.122%]) and only slightly lower at 3 years (0.085% [95% CI, 0.079%-0.092%]). Women with a negative cotesting result followed by a second negative hrHPV test result had risks of CIN 3+ of 0.04% (95% CI, 0.04%-0.05%) at 3 years and 0.06% (95% CI, 0.05%-0.07%) at 5 years. For each of 3 age groups (30-39, 40-49, and ≥50 years), each consecutive negative hrHPV test result was associated with progressively lower risk of CIN 3+. No cases of invasive cervical cancer were detected.[48]

Key Question 1c. Does the appropriate rescreening interval for each primary screening strategy vary by subpopulation (eg, age, race/ethnicity, screening history, hrHPV immunization status, socioeconomic status)?

No data were available to address rescreening intervals by subpopulation.

Harms of hrHPV Screening

Key Question 2. What are the potential adverse effects of hrHPV testing, with or without cytology, as a primary screening strategy compared with currently recommended screening strategies for women in the United States?

The same 8 RCTs,[12-14,19-23,25-35] IPD meta-analysis,[47] and 3 observational cohort studies described above[24,37,44] were included for harms, along with an additional cross-sectional study that assessed psychological harms among 428 women.[45] Studies reported screening test performance (ie, false-negative and false-positive results), procedures conducted to evaluate positive screening test results (ie, colposcopy and biopsy), and potential psychological harms (eg, quality of life, anxiety or distress, partner discord). Overall, screening with hrHPV primary or cotesting was associated with more false-positive results and higher colposcopy rates. Limited evidence suggested that positive hrHPV test results may be associated with greater psychological harm than abnormal cytology results. None of the included studies reported on harms occurring from the screening test, diagnostic testing, or treatments.

Primary hrHPV Screening

Trial differences in the protocol for follow-up of positive hrHPV screening test results affected colposcopy and false-positive rates. In the NTCC Phase II protocol, all hrHPV-positive results were referred directly to colposcopy.[14,20] Accordingly, the false-positive rate for CIN 2+ was higher with hrHPV screening (7.4% vs 3.2%), as was the colposcopy rate (7.9% vs 2.8%), than with cytology screening in the trial (**Table 3**). Most women referred to colposcopy underwent the procedure (93.6% in the intervention group, 90.6% in the control group), and more women in the hrHPV screening group underwent biopsy (3.2% vs 1.3% in the control group). The HPV FOCAL trial used a liquid-based cytology triage strategy for hrHPV-positive results.[13,19,21,22] In round 1 of screening, 5.7% of women in the hrHPV testing group were referred to colposcopy, compared with 3.1% in the cytology-only control group, and 94.1% of the trial participants referred to colposcopy attended.[13] Colposcopy referral rates in round 1 of the Compass trial for hrHPV screening compared with cytology screening were 3.8% vs 2.7%.[12] In the FINNISH trial,[23] primary hrHPV screening false-positive rates (7.2%) and colposcopy referral rates (1.2%) were similar to cytology screening false-positive (6.5%), and colposcopy referral (1.1%) rates. In 3 trials reporting age-stratified results, colposcopy referrals in round 1 of screening for women younger than 30 to 35 years ranged from 2.3% to 13.1% with hrHPV testing, compared with a range from 1.9% to 4.7% for cytology screening (eTable 7 in the Supplement). Among women older than 30 to 35 years, colposcopy referrals ranged from 0.9% to 5.8% for hrHPV testing, compared with 1.0% to 2.5% for cytology screening (eTable 6 in the Supplement).

False-negative results for invasive cervical cancer (based on interval detection) were uncommon. The NTCC Phase II trials reported no CIN 3 or invasive cervical cancer cases among screen-negative women in either group in follow-up after the first round of screening (3.5 years maximum).[14,20] The larger FINNISH trial reported invasive cervical cancer among screen-negative women in 0.01% (5/57 135) of the hrHPV testing intervention group participants and 0.003% (2/61 241) of the cytology control group participants after 1 round of screening with 5 years of follow-up.[23] Data on invasive cervical cancer among screen-negative women were not available for the HPV FOCAL or Compass trials.

No studies reported on the psychological effects of primary hrHPV screening.

hrHPV Cotesting

Colposcopy rates were reported in only 2 trials of cotesting (ARTISTIC and NTCC Phase I) (Table 3).[32-35] In the ARTISTIC trial, higher false-positive rates were observed with cotesting relative to the cytology screening control group at round 1 (19.9% vs 10.9%) and round 2 (11.2% vs 4.6%). Colposcopy rates in round 1 were 6.8% in the cotesting group and 5.2% in the cytology group.[32-35] The proportion of women attending colposcopy and undergoing biopsy was not reported. Only the NTCC Phase I trial reported age-stratified colposcopy and false-positive rates. In that trial, hrHPV-positive women 35 years and older and those with results positive for atypical squamous cells of undetermined significance were referred directly to colposcopy; colposcopy rates were 3 times higher for cotesting compared with cytology (10.6% vs 3.0%).[14,25,26] Of those referred, 94% in the intervention group and 91% in the control group received a colposcopy. For the Swedescreen trial,[30,31] colposcopies were not reported and false-positive rates could not be calculated. The POBASCAM[27-29] trial did not report colposcopy rates, but false-positive rates were twice as high with cotesting (5.8% vs 2.6%) at round 1 and similar at round 2, in which both the intervention group and the control group received cotesting (6.4% vs 6.5%).

The IPD meta-analysis obtained additional data from 5 trials (4 trials of cotesting and a single trial of primary hrHPV screening) and reported similar overall biopsy rates for women assigned to hrHPV cotesting or primary testing compared with cytology in analysis of the POBASCAM, Swedescreen, and ARTISTIC trials, which had a fixed-effects pooled rate ratio for biopsy of 1.02 (95% CI, 0.97-1.07; I^2 = 30.7%; P = .24). A pooled estimate calculated with the NTCC trial biopsy rate included had unacceptably high statistical heterogeneity (I^2 = 99.1%; P < .001). The rate ratio for biopsy from the NTCC trials was 2.24 (95% CI, 2.09-2.39) with hrHPV testing, likely because of the direct-to-colposcopy triage protocol.[47]

False-negative rates were difficult to estimate. No invasive cervical cancer cases were observed in screen-negative women in either screening group in 2 studies,[14,25,26,32-35] and 1 did not report rates of invasive cervical cancer among screen-negative women.[30,31] In the POBASCAM trial, 1 case of invasive cervical cancer was detected in a screen-negative woman in the control group and no cases in the intervention group, with 4 years follow-up on the first screening round.[27-29] In 14 years of long-term follow-up, there were no statistically significant differences in incidence of invasive cervical cancer among women in the intervention group who screened hrHPV-negative and cytology-normal at baseline and among those in the control group with normal cytology findings at baseline.[29] Findings of a large US-based cohort of women who received cotesting suggested that hrHPV testing has few false-negative cases of CIN 3+ detected by cytology: the 5-year risk of CIN 3+ was 0.12% (95% CI, 0.11%-0.12%) for women testing hrHPV-negative, compared with 0.10% (95% CI, 0.09%-0.10%) for women with negative cotesting results.[49]

Estimates of colposcopy rates from large observational cohort studies were similar to or lower than those observed in trials (eTable 5 in the Supplement). Just more than 6% of women were referred

Table 3. Colposcopy Referrals and False-Positive Rates as Harms of hrHPV Screening, Based on Randomized Clinical Trials (Key Question 2)

Source	Quality[a]	Screening Round (Planned Follow-up Period, y)[b]	Screening Approach	No./Total (%)					
				Test Positivity[c]		Colposcopy Referrals[d]		False-Positive Rate, No. Screened Positive Without CIN 2+/Total No. Screened Without CIN 2+ (%)[d]	
				Intervention	Control	Intervention	Control	Intervention	Control
hrHPV Primary Screening									
NTCC Phase II Ronco et al,[20] 2008 Ronco et al,[14] 2010	Good	1 (3.5)	hrHPV vs conventional cytology	hrHPV+: 1936/24 661 (7.9)	ASCUS+: 825/24 353 (3.4)	1936/24 661 (7.9)	679/25 435 (2.8)	1799/24 428 (7.4)	770/24 038 (3.2)
HPV FOCAL Ogilvie et al,[22] 2010 Cook et al,[19] 2015 Ogilvie et al,[21] 2017 Ogilvie et al,[13]	Fair	1 (1)[c]	hrHPV with LBC triage vs LBC	hrHPV+: 771/9540 (8.1)[d,e]	ASCUS+: 334/9408 (3.5)[d,e]	544/9540 (5.7)[e,g]	290/9408 (3.1)[e,g]	624/9393 (6.6)	244/9318 (2.6)
		2 (4)[c]	Cotesting vs cotesting[f]	hrHPV+: 469/8296 (5.7)	ASCUS+: 513/8078 (6.4)[d,e]	469/9540 (4.9)[e,g]	660/9408 (7.0)[e,g]	421/8248 (5.1)	413/7978 (5.2)
FINNISH Leinonen et al,[23] 2012	Fair	1 (5)	hrHPV with conventional cytology triage vs conventional cytology	hrHPV+: 4971/62 106 (8.0)[h]	ASCUS+: 4506/65 747 (6.9)[h]	796/66 410 (1.2)	755/65 784 (1.1)	4462/61 597 (7.2)	4239/65 480 (6.5)
Compass Canfell et al,[12] 2017	Fair	1 (5)	hrHPV with LBC triage vs LBC[i]	hrHPV+: 277/4000 (6.9)	ASCUS+: 67/995 (6.7)	154/4000 (3.8)	27/995 (2.7)	NR	NR
hrHPV Cotesting With Cytology									
NTCC Phase I Ronco et al,[25] 2006 Ronco et al,[26] 2006 Ronco et al,[14] 2010	Good	1 (3.5)	Cotesting vs conventional cytology	hrHPV+ or ASCUS+: 2830/22 708 (12.5)	ASCUS+: 855/22 466 (3.8)	2470/22 708 (10.9)[j]	738/22 466 (3.3)	2702/22 042 (12.3)	771/21 972 (3.5)
POBASCAM Bulkmans et al,[27] 2004 Rijkaart et al,[28] 2012 Dijkstra et al,[29] 2016	Good	1 (4)	Cotesting vs conventional cytology	hrHPV+ or ASCUS+: 1406/19 999 (7.0)	ASCUS+: 706/20 106 (3.5)	NR	NR	1149/19 742 (5.8)	513/19 913 (2.6)
		2 (5)	Cotesting vs cotesting	hrHPV+ or ASCUS+: 742/19 579 (3.8)	hrHPV+ or ASCUS+: 774/19 731 (3.9)	NR	NR	610/9572 (6.4)	612/9450 (6.5)
Swedescreen Naucler et al,[30] 2008 Elfström et al,[31] 2014	Fair	1 (3)	Cotesting vs conventional cytology	hrHPV+: 433/6257 (6.9) ASCUS+: 146/6257 (6.9)	ASCUS+: 150/6270 (2.4)	NR	NR	NR	72/6192 (1.2)
ARTISTIC Kitchener et al,[32] 2008 Kitchener et al,[33] 2009 Kitchener et al,[34] 2009 Kitchener et al,[35] 2014	Fair	1 (2)	Cotesting vs LBC	hrHPV+ or ASCUS+: 4019/18 386 (21.9)	ASCUS+: 786/6124 (12.8)	1247/18 386 (6.8)	320/6124 (5.2)	3566/17 933 (19.9)	653/5991 (10.9)
		2 (2)	Cotesting vs LBC	hrHPV+ or ASCUS+: 1258/11 862 (10.6)[k]	ASCUS+: 210/3928 (5.3)[k]	284/10 716 (2.7)[k]	74/3514 (2.1)[k]	1178/10 512 (11.2)[k]	176/3832 (4.6)[k]

Abbreviations: ARTISTIC, A Randomized Trial in Screening to Improve Cytology; ASCUS, atypical squamous cells of undetermined significance; CC, conventional cytology; CIN, cervical intraepithelial neoplasia; HPV FOCAL, Human Papillomavirus for Cervical Cancer Screening; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam.

[a] Assessed using criteria from the US Preventive Services Task Force.[46]

[b] With the exception POBASCAM and ARTISTIC, only results from round 1 were reported.

[c] Test positivity was defined based on trial protocol. Test findings that would lead to a clinical action based on the study protocol, such as colposcopy or more intensive follow-up, were considered test-positive. Thus, in some trials, the test positivity rate in the intervention group is simply the rate of hrHPV test positivity, whereas in others it is the rate of hrHPV+ with ASCUS+.

[d] This table reports harms for women of all ages included in the trial; see Supplement for age-stratified results.

[e] HPV FOCAL had 2 randomized hrHPV groups: a safety group (screening every 2 years) and an intervention group (screening every 4 years). Only the latter is reported; results from the control group are reported at 4 years and include the 2-year screening round results.

[f] Women with positive cotesting results on either hrHPV or cytology were referred for colposcopy.

[g] Percentage of women; converted from rate per 1000 participants.

[h] From author inquiry.

[i] Triage could be performed via LBC or dual-stained cytology.

[j] Estimated data from figure.

[k] Preliminary or incomplete results.

to colposcopy over 2 rounds of hrHPV primary screening in an Italian cohort study (n = 48 751).[24] In a German study of hrHPV cotesting (n = 19 795), 3.9% of women were referred to colposcopy at the first round of screening and 1% at a second round.[44]

Two included studies reported psychological effects of hrHPV cotesting.[32,45] In a substudy of the ARTISTIC trial,[45] samples of women aged 20 to 64 years were surveyed approximately 2 weeks after receiving screening results (n = 2508). Women assigned to the study intervention screening group who received hrHPV results in addition to their cytology screening results reported lower sexual satisfaction but similar levels of distress and anxiety in the short term. A smaller cross-sectional study (n = 428) by McCaffery et al[45] surveyed women 1 week after they received cervical cancer screening results and found that for women who underwent cotesting and had normal cytology findings, those with hrHPV-positive results were more distressed and anxious than women with hrHPV-negative results and had worse feelings about their current, past, and future sexual partners regardless of cytology results.

Key Question 2a. Do the adverse effects vary by subpopulation (eg, age, race/ethnicity, and hrHPV immunization status)?

Three primary hrHPV screening trials and 1 cotesting trial reported age-stratified colposcopy rates (eTables 6 and 7 in the Supplement). In all trials, women younger than 30 to 35 years screened with primary hrHPV testing or cotesting had higher referral rates for colposcopy (range, 2.3%-13.1%) than women screened with cytology (range, 1.9%-4.7%).[14,20,22,23] In the Compass trial of primary hrHPV screening, colposcopy referrals were higher with hrHPV screening among women aged 25 to 33 years (8.5% in the intervention group vs 4.7% in the control group) and lower for women aged 34 to 64 years (2.6% in the intervention group vs 2.2% in the control group) in both screening groups, despite expected vaccination rates in younger women of approximately 70%.[12]

Key Question 2b. Do adverse effects vary by screening strategy, including by rescreening interval?

The influence of screening interval and strategy on potential harms of missed cancer cases or possible overdetection could not be directly ascertained from available evidence because of lack of within-trial interval comparisons and variability of protocols across studies. Screening intervals of included trials ranged from 2 to 5 years, with the longest intervals from FINNISH[23] and POBASCAM.[27-29] The trials with longer intervals reported some invasive cervical cancer cases among women who had tested hrHPV-negative, but these trials (FINNISH and POBASCAM) also had larger samples and there were very few invasive cervical cancer cases overall, limiting inferences that can be drawn from between-study comparisons. After 2 negative cotesting results, rates of invasive cervical cancer in the US-based cohort were very low (0.003% [95% CI, 0.002%-0.006%]) and equal at 3- and 5-year screening intervals.[48]

Discussion

A summary of the evidence for this review is shown in **Table 4**. Four RCTs of primary hrHPV screening and 4 of cotesting (both hrHPV testing and cytology) compared the use of hrHPV screening for cervical cancer screening with cytology alone for the detection of CIN 3+ and invasive cervical cancer. The evidence was consistent across trials that primary hrHPV screening increased detection of CIN 3+ in the initial round of screening by as much as 2 to 3 times when compared with cytology. Evidence was mixed in cotesting trials; CIN 3+ detection in round 1 was not significantly higher for cotesting. No trials compared hrHPV primary testing with cotesting. Evidence on subgroups was limited to age and a single-cohort study focused on previously underscreened women. Women younger than 35 years had consistently higher rates of hrHPV positivity and of CIN 3+, but the RR of CIN 3+ detection with primary hrHPV screening or cotesting compared with cytology was similar between younger and older women.

False-positive rates were higher in the intervention group for both primary hrHPV screening and cotesting in the first screening round. Colposcopy referrals were often reported but biopsy rates were not, limiting estimation of the downstream harms of screening. In 3 primary hrHPV screening trials and all cotesting trials, rates of colposcopy referral were higher in the intervention group, indicating a greater relative burden with hrHPV screening and potential differences in downstream consequences of treatment compared with screening cytology. Harms of treatment of the cervix to remove precancerous cells were not reported in any of the included studies but include pain and bleeding, which on rare occasion requires vaginal packing or transfusion.[52,53] Harms related to subsequent pregnancy outcomes, particularly risk of second-trimester pregnancy loss and preterm birth, may occur after cold knife conization or loop electrosurgical excision procedure deeper than 10 mm.[54,55] Limited evidence suggested that, compared with abnormal cytology results, hrHPV test positivity may be associated with greater short-term psychological harm.[32-35]

Cervical cancer incidence and mortality have substantially decreased since the introduction of screening programs more than half a century ago; the lowest rates are found in countries with organized screening programs. All of the RCTs included in this review were conducted in countries with robust, organized screening programs. Organized screening programs are well-suited for comparative trials of screening strategies; however, the generalizability of findings from this review to women in the United States is limited by the lack of organized screening programs for the majority of US-based women. Most cervical cancer screening in the United States is opportunistic, without population-based registries or regular invitations to screening. More than 50% of women diagnosed with cervical cancer in the United States have not been screened in the prior 3 to 5 years.[56] The highest proportions of unscreened women are those without insurance (23.1%) or no regular clinician (25.5%).[57]

Cervical cancer predominantly affects underscreened women in the United States; thus, a substantial effect on cervical cancer incidence and mortality requires the identification of effective outreach strategies. Limited evidence from a single cohort study of poorly screened women in Spain suggests that the increased sensitivity of hrHPV screening may be particularly important for early detection among underscreened women.[42] Several systematic reviews summarize evidence that hrHPV screening via self-collection of samples may be a sufficiently accurate and acceptable strategy for reaching underscreened and unscreened populations.[10,58,59] Further research is needed to examine the effect of self-collection screening strategies on overall screening rates, adherence to follow-up, and health outcomes for women with limited access to health care or low rates of participation in screening programs.[60,61]

Table 4. Summary of Evidence by Key Question and hrHPV Screening Strategy

Screening Method	No. of Studies (Study Quality; No. of Observations)[a]	Summary of Findings by Outcome	Consistency and Precision	Body of Evidence Limitations (Includes Reporting Bias)	Applicability
KQ1: Effectiveness of hrHPV Screening or Cotesting vs Cytology Alone for Reducing Cervical Cancer Incidence and Mortality					
hrHPV primary screening	4 RCTs (1, good, 3 fair; n = 282 839) 1 cohort study (fair; n = 48 736)	In 4 RCTs reporting results over 1-2 rounds of screening spanning 4-7 y, hrHPV screening found more CIN 3+ in an initial screening round Overall CIN 3+ detection ranged from 0.3% to 0.8% across studies Invasive cancers reported in 1 RCT, but numbers were very small (less than 0.1%) Cohort study findings were consistent with RCTs Mortality data not reported	Reasonably consistent and precise for CIN 3+ detection Imprecise for invasive cervical cancer incidence	Randomization not maintained for more than 1-2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess invasive cervical cancer incidence and mortality Cohort study lacked a comparison group Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology	4 RCTs (2 good, 2 fair; n = 127 717) 2 cohort studies (fair; n = 351 613)	In 4 RCTs reporting results over 1-2 rounds of screening spanning 4.5-9 y, cotesting found similar rates of CIN 3+ vs cytology in round 1 and cumulatively Two of 4 trials had lower CIN 3+ rates in round 2 of screening Follow-up (13 y) in 1 trial did not detect a difference between groups Two large single-group cohort studies found CIN 3+ in 0.6%-0.7% of women at initial screening Among women who initially screened negative and were rescreened after 3 or 5 y, rates of CIN 3+ were very low (0.05%) Mortality data not reported	Reasonably consistent and precise for CIN 3+ Imprecise or NA for invasive cervical cancer incidence	Randomization not maintained for more than 1-2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess invasive cervical cancer incidence and mortality Two large cohort studies had no comparison groups Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
KQ1a: Subpopulation (ie, Age, Unscreened Women) Differences in Screening for Reducing Cervical Cancer Incidence and Mortality					
hrHPV primary screening in women aged <30-35 y	4 RCTs (1 good, 3 fair; n = 41 914) 1 cohort study (fair; n = 5103)	Four RCTs reported absolute detection of CIN 3+; Women <35 y had higher rates of cumulative CIN 3+ detection across studies, but relative detection rates between hrHPV screening and cytology were similar to overall results, including a small trial that included women vaccinated against hrHPV Across trials, CIN 3+ rates ranged from 0.2%-3.0% The cohort study found higher rates of CIN 2+ in women aged 25-29 y, consistent with the trials Mortality data not reported	Reasonably consistent and precise for CIN 3+ detection Imprecise for invasive cervical cancer incidence	Randomization not maintained for more than 1-2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess invasive cervical cancer incidence and mortality Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs

(continued)

Table 4. Summary of Evidence by Key Question and hrHPV Screening Strategy (continued)

Screening Method	No. of Studies (Study Quality; No. of Observations)[a]	Summary of Findings by Outcome	Consistency and Precision	Body of Evidence Limitations (Includes Reporting Bias)	Applicability
hrHPV cotesting with cytology in women aged <30-35 y	3 RCTs (2 good, 1 fair; n = 23 243)	Three RCTs reported on women <35 y CIN 3+ detection rates were comparable between the intervention and control groups for both rounds, with no significant differences in cumulative CIN 3+ detection Detection rates ranged from 0.1%-3.3% across trials Mortality data not reported	Reasonably consistent and precise for CIN 3+ detection over 1-2 rounds of screening Imprecise for invasive cervical cancer incidence	Randomization not maintained for more than 1-2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess invasive cervical cancer incidence and mortality Single-cohort study with no comparison group Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV primary screening in women ≥30-35 y	4 RCTs (1 good, 3 fair; n = 169 714) 1 cohort study (fair; n = 43 647)	Four RCTs reported on 1-2 rounds of screening in women >30-35 y CIN 3+ outcomes were similar to the overall group results CIN 3+ detection rates ranged from 0.2%-0.5% The cohort study found lower rates of CIN 2+ in women >29 y, consistent with the trials Mortality data not reported	Reasonably consistent and precise for CIN 3+ detection over 1-2 rounds of screening Imprecise for invasive cervical cancer incidence	Randomization not maintained for more than 1-2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess invasive cervical cancer incidence and mortality Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology in women ≥30-35 y	4 RCTs (2 good, 2 fair; n = 99 073)	Four RCTs reported findings from 1-2 rounds of screening CIN 3+ outcomes were similar to the overall group results, with no significant differences in cumulative CIN 3+ detection in any trial CIN 3+ detection rates ranged from 0.03%-1.4% Mortality data not reported	Reasonably consistent and precise for CIN 3+ detection over 1-2 rounds of screening Imprecise or NA for invasive cervical cancer incidence or mortality	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and follow-up tests and protocols; trials underpowered to assess cervical cancer incidence and mortality Single cohort study with no comparison group Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology in unscreened women	1 cohort study (fair; n = 1832)	One study of underscreened women suggested 1-time hrHPV cotesting would detect more CIN 3 and invasive cervical cancer; of 9 CIN 3+ cases, all were hrHPV+ and 6 had positive cytology findings	Consistency NA Imprecise	Lack of a comparison group, substantial loss to follow-up Reporting bias undetected	1 small single-group cohort study conducted in Spain
KQ1b and KQ1c: Relationship of Rescreening Intervals to Future Cancer Incidence or Progression					

(continued)

Table 4. Summary of Evidence by Key Question and hrHPV Screening Strategy (continued)

Screening Method	No. of Studies (Study Quality; No. of Observations)[a]	Summary of Findings by Outcome	Consistency and Precision	Body of Evidence Limitations (Includes Reporting Bias)	Applicability
hrHPV primary screening or cotesting compared with cytology	1 RCT (primary screening; quality NA; n = 19 009) 2 RCTs (long-term cotesting follow-up; quality NA; n = 57 465) 1 Cohort study (cotesting; quality NA; n = 331 818)	No trials compared different screening intervals for hrHPV testing Evidence from 1 primary screening trial, long-term follow-up from 2 cotesting trials, and 1 large US cotesting cohort supports that 4- to 5-year screening intervals for primary hrHPV testing or cotesting are as effective as shorter intervals	NA	NA	NA
KQ2: Adverse Effects of hrHPV Screening or Cotesting vs Cytology					
hrHPV primary screening	4 RCTs (1 good, 3 fair; n = 282 839) 1 cohort study (fair; n = 48 736)	In 2 trials reporting, false-positive results were higher in the hrHPV-screened group (intervention) All trials had higher rates of colposcopy in the intervention group False-positive results in the single-group cohort were approximately halved at round 2 Screen-negative invasive cervical cancer cases were not consistently reported No studies reported on adverse events associated with screening, diagnostic screening, or treatment of CIN	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols make it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology	4 RCTs (2 good, 2 fair; n = 127 717) 2 cohort studies (fair; n = 351 613)	False-positive results were consistently higher in the intervention group for 3 trials reporting on round 1 Round 2 results, reported only in 1 trial, were similar between groups German cohort data found that colposcopy referral rates declined from 3.9% after round 1 to 1.0% at round 2 No studies reported adverse events associated with screening, diagnostic screening, or treatment of CIN Two studies reported that positive hrHPV test results as part of cotesting were associated with higher anxiety and distress and with lower satisfaction with current and past sexual partnerships	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols make it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates Reporting bias undetected	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs Psychological harms were assessed in UK women enrolled in organized screening; findings may not be fully applicable to US women

(continued)

Table 4. Summary of Evidence by Key Question and hrHPV Screening Strategy (continued)

Screening Method	No. of Studies (Study Quality; No. of Observations)[a]	Summary of Findings by Outcome	Consistency and Precision	Body of Evidence Limitations (Includes Reporting Bias)	Applicability
KQ2a: Subpopulations (Adverse Effect Differences by Age)					
hrHPV primary screening in women aged <30-35 y	4 RCTs (1 good, 3 fair; n = 41 914)	False-positive results, reported in 1 trial, were higher in the intervention group Colposcopy referral rates were higher in the intervention group at round 1 screening One RCT reported colposcopy referrals for the youngest women (25-29 y), and these were the highest observed for any trial group (19.9% [95% CI, 17.9%-22.1%]) No studies reported adverse events associated with screening, diagnostic screening, or treatment of CIN by age No trials with >1 round of screening data available reported colposcopy rates at round 2 by age; invasive cervical cancer among screen-negative women and psychological harms by age were not reported	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols makes it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology in women aged <30-35 y	1 RCT (good; n = 11 810)	One RCT provided false-positive rates at round 1, with the largest differences seen among women <35 y Colposcopy rates were consistently higher in the intervention group for 4 RCTs No trials reported colposcopy rates at round 2 by age No studies reported adverse events associated with screening, diagnostic screening, or treatment of CIN by age False-negative invasive cervical cancer results and psychological harms by age were not reported	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols makes it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs

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Table 4. Summary of Evidence by Key Question and hrHPV Screening Strategy (continued)

Screening Method	No. of Studies (Study Quality; No. of Observations)[a]	Summary of Findings by Outcome	Consistency and Precision	Body of Evidence Limitations (Includes Reporting Bias)	Applicability
hrHPV primary screening in women ≥30-35 y	4 RCTs (1 good, 3 fair; n = 169 714)	One RCT reported false-positive rates by age, with higher rates in the intervention group 4 RCTs reported colposcopy referrals at round 1 Rates were higher in the intervention group but lower overall than in women <30-35 y No studies reported on harms associated with screening, diagnostic testing, or treatment of CIN by age No trials reported colposcopy rates at round 2 by age False-negative invasive cervical cancer results and psychological harms by age were not reported	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols makes it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
hrHPV cotesting with cytology in women ≥30-35 y	1 RCT (good; n = 33 364)	One RCT reported false-positive rates and colposcopy referrals and found higher rates for both in the intervention group but somewhat lower rates in women <30-35 y No trials reported colposcopy rates at round 2 by age False-negative results and psychological harms by age were not reported	Reasonably consistent Reasonably precise	Heterogeneity in screening follow-up protocols makes it difficult to draw conclusions about relative harms of different hrHPV screening strategies vs cytology alone Limited data on harms of screening and diagnostic procedures Not all trials reported colposcopy and biopsy rates	All trials conducted in organized screening programs in European countries with nationalized health systems Applicability lower for US women without access to organized screening programs and higher for US women with access to organized screening programs
KQ2b and KQ2c: Relationship of Rescreening Intervals to Future Cancer Incidence or Progression					
hrHPV primary screening or cotesting compared with cytology	0	No completed trials compared screening intervals with use of hrHPV screening Trials comparing hrHPV screening with cytology used 2- to 5-y intervals, but given variability of screening protocols, comparison between trials was not meaningful No evidence on subpopulations	NA	NA	NA

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN 3+, CIN 3 or worse; hrHPV, high-risk human papillomavirus; KQ, key question; NA, not applicable; RCT, randomized clinical trial.

[a] Study quality assessed using criteria from the US Preventive Services Task Force.[46]

Limitations

This review was limited by the quality and heterogeneity of the included studies. First, the quality of many of the included studies was rated as fair because of problems with attrition, protocol changes, and lack of blinding of outcome assessment. Second, the overall body of evidence was limited by trials having no more than 2 and often only 1 randomized round of screening available for comparisons. Only 1 trial (ARTISTIC) maintained the same strategy over 2 rounds of screening.[32-35] Third, outcome reporting on colposcopy and biopsy rates was inconsistent, and none of the trials reported on adverse events associated with the screening tests or with diagnostic and treatment procedures resulting from screening. Fourth, the trial evidence was supplemented with results of large cohort studies of primary hrHPV screening or cotesting over 2 screening rounds; however, none of the cohort studies had a comparison group screened with cytology only.

Conclusions

Primary hrHPV screening detected higher rates of CIN 3+ at first-round screening compared with cytology. Cotesting trials did not show initial increased CIN 3+ detection. Both hrHPV screening strategies had higher false-positive and colposcopy rates than cytology, which could lead to more treatments with potential harms.

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Concept and design: Melnikow, Henderson, Burda, Senger.
Acquisition, analysis, or interpretation of data: Melnikow, Henderson, Burda, Durbin, Weyrich.
Drafting of the manuscript: Melnikow, Henderson, Burda, Weyrich.
Critical revision of the manuscript for important intellectual content: Melnikow, Henderson, Burda, Senger, Durbin.
Statistical analysis: Burda.
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