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Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Importance: Cervical cancer can be prevented with early detection and treatment of precancerous lesions that are caused primarily by infection with high-risk strains of human papillomavirus (hrHPV). Current guidelines for screening in the United States focus on cytology screening with the Papanicolaou (Pap) test, with hrHPV cotesting as an option for women aged 30 to 65 years that allows for longer rescreening intervals. Evidence from large trials evaluating screening programs involving primary hrHPV testing (hrHPV alone as the initial test) and cotesting may inform new screening strategies. Evidence supporting cytology screening is well established, so this review evaluated screening with hrHPV testing alone or as cotesting with cytology compared to cytology to address whether these forms of screening provide better protection from cervical cancer and allow for longer rescreening intervals. Rates of cervical cancer are very low among routinely screened women in the United States, but not all women are routinely screened and there are significant racial and ethnic disparities in morbidity and mortality from cervical cancer.

Objective: To systematically review the benefits and harms of screening for cervical cancer using hrHPV testing as the screening strategy (with or without cytology).

Data Sources: MEDLINE, PubMed, PsychINFO, and Cochrane Collaboration Registry of Controlled Trials, and the Education Resources Information Center from January 2011 through February 15, 2017.

Study Selection: English-language trials of benefits or harms of screening for cervical cancer using HPV testing as the screening strategy (with or without cytology) in women aged 21 years or older. Cohort studies were also considered for inclusion to evaluate harms and screening performance in large, representative primary care populations and in underscreened women.

Data Extraction and Synthesis: Two investigators independently reviewed abstracts and full-text articles, and then extracted data from fair- and good-quality trials and cohort studies. Results were qualitatively synthesized.

Main Outcomes and Measures: Cervical cancer mortality, invasive cervical cancer (ICC) incidence, early detection of disease (i.e., cervical intraepithelial neoplasia (CIN) 3+), rates of false-positive and false-negative screening, colposcopy and biopsy rates, quality of life and other harms.

Results: We included seven randomized controlled trials (RCTs, n=405,561), five cohort studies (n=402,615), and one individual participant data (IPD) meta-analysis (n=176,464). Trials were heterogeneous with regard to type of cytology (conventional vs. liquid-based cytology), type of hrHPV test (DNA PCR enzyme immunoassay vs Hybrid Capture 2), screening interval (2 to 5 years), followup protocols for abnormal results, number of screening rounds (1 or 2), and consistency of screening protocols between rounds. Two fair-quality trials and one good-quality trial evaluated primary hrHPV screening (hrHPV testing alone) compared with cytology alone; two good- and two fair-quality trials compared hrHPV cotesting with cytology alone.

The evidence was generally consistent across three trials with variable protocols and hrHPV test types in demonstrating that primary hrHPV testing increased detection of CIN3+ in the initial round of screening by as much as 2- to 3-fold. Only the NTCC Phase II trial of primary hrHPV testing, where all women with a positive hrHPV test were referred to colposcopy, had complete results from two rounds of screening (at Round 2 screening all women received cytology testing).In that study, CIN3+ detection in Round 1 was 3-fold higher in the hrHPV testing arm. In the second screening round CIN3+ detection was significantly lower among women in the intervention group: RR 0.22 (95% CI, 0.08 to 0.58), and cumulative detection over both screening rounds was was 1.8-fold higher. Results of a large, single-arm fair-quality cohort study of primary hrHPV testing at three year intervals were consistent with trial findings. CIN3+ detection in the second screening round was significantly lower: the RR for CIN3+ detection at Round 2 compared to Round 1 was 0.14 (95% CI 0.06 to 0.32).

Among four trials of hrHPV cotesting, the first round CIN3+ detection was higher in the intervention group in two trials (though not significant) and equal in two trials. Cumulative CIN3+ detection over two rounds of screening ranged from 0.3 to 1.6 percent across studies. The RR for cumulative CIN3+ detection ranged from 0.91 to 1.13; none were significantly different from one. Long-term followup (13 year) in one trial showed similar results.

Evidence on subgroups was limited to age and a single cohort study focused on previously inadequately or unscreened women. Women under age 35 years had consistently higher rates of hrHPV positivity and of CIN3+. Outcomes of hrHPV primary testing or cotesting between screening strategies by age were not notably different from the results of the overall study populations. A small cohort study of cotesting among 1,832 Spanish women not screened in the previous five years found nine cases of CIN3+; of these three cases of CIN3 were detected by hrHPV testing but not by cytology. ICC incidence was very rare. An individual participant data meta-analysis pooled data from five heterogeneous trials (including primary hrHPV screening and cotesting). A total of 107 cases of ICC among 176,464 women were identified in the trials, with a pooled RR of 0.60 (95% CI, 0.40 to 0.89) for one or two rounds of hrHPV screening and 5 to 12 years of followup data. Each of these trials included different patient populations and screening test protocols, adding uncertainty to interpretation of pooled findings. No studies reported cervical cancer mortality.

The included trials did not report on potential adverse consequences of the screening tests, diagnostic procedures, or rates of treatments and associated harms. Screening test positivity, false-positive rates for CIN2+ detection, and colposcopy referrals tended to be higher in the intervention arms of the trials, particularly at Round 1 screening. False positive rates were twice as high in the intervention arm of one completed primary hrHPV trial and less discrepant in the other completed trial. In hrHPV cotesting trials, test positivity in the intervention arm ranged from 7 to 22 percent of screened women, and was approximately 2- to 3-fold higher than in the control group. False positive rates were also consistently higher in the intervention group at Round 1 for three cotesting trials reporting on this outcome, ranging from 6 to 20 percent, and nearly 2- to 3-fold higher than control group rates. Two cotesting trials reported test performance data from Round 2 screening; the false positive rate was similar between arms in one trial, but two times higher in the intervention arm in another. Three hrHPV primary screening trials and two cotesting trials reported referrals to colposcopy. One primary screening trial had more

referrals among women in the intervention group versus control group at Round 1 of screening (8% vs 3%). Two other trials of primary hrHPV screening had similar rates of referral to colposcopy at Round 1 in both trial arms (3% and 1%). Two hrHPV cotesting trials reported more referrals to colposcopy in the intervention group compared to the control group (11% vs 3% and 7% vs 5%). Round 2 colposcopy referral rates, reported only in one cotesting trial, were similar between treatment groups (IG 3% vs. CG: 2%). Biopsy rates were reported in the IPD meta-analysis; the pooled estimate had very high heterogeneity largely explained by the two-fold difference in biopsy rates between intervention and control arms in the two NTCC trials that referred all hrHPV+ women to colposcopy. Biopsy rates were similar between arms for the other trials. Data were too sparse to draw conclusions regarding the risk of missed cases of cervical cancer (false negatives) for different screening strategies, given very few cases of ICC. Limited evidence on psychological harms from one cross-sectional study (n=428) and a substudy of a cotesting trial (n = 2,508) suggested that women receiving hrHPV positive test results experienced increased anxiety and distress, and reduced satisfaction with sexual partnerships.

Conclusions and Relevance: Seven large randomized trials, three of primary testing and four of hrHPV cotesting contributed to the evidence comparing use of hrHPV testing as part of cervical cancer screening with cytology alone for detection of CIN3+. All trials were conducted in the context of organized screening programs, with heterogeneous screening strategies and followup protocols. Interpretation of trial findings was limited by the fact that after one round of screening, only one trial conducted further screening applying the assigned strategies in the control and intervention arms. In all other trials, both arms received the same test at Round 2 (either cytology testing or cotesting). hrHPV testing as a primary test increased detection of CIN3+ in the initial round of screening by as much as 2- to 3-fold. Only the NTCC Phase II trial of primary hrHPV testing, where all women with a positive hrHPV test were referred to colposcopy, had results from two rounds of screening.[1, 2] In that study, CIN3+ detection in Round 1 was 3-fold higher in the hrHPV testing arm, and cumulative detection was 1.8-fold higher after the second round of screening. Evidence was mixed in cotesting trials. No trial showed a significant increase in CIN 3+ detection in round one for cotesting. In two of four trials, CIN3+ detection was lower in round two in the hrHPV cotesting arm and higher in the cytology-only arm. Cumulative CIN3+ detection was similar between intervention and control study arms in all trials. Because no trial sustained the intervention and control group protocols beyond two screening rounds, evidence comparing the long-term outcomes of hrHPV primary testing or cotesting with cytology only was lacking.

In most trials and in a large U.S.-based observational study, women under age 30 to 35 years had higher rates of hrHPV positivity and CIN3+, accompanied by higher rates of colposcopy. No completed studies compared different screening intervals. An individual participant data meta-analysis suggested a lower rate of ICC with hrHPV screening strategies, but this analysis pooled data from trials with distinctly different screening strategies and hrHPV test types, adding uncertainty to interpretation of the findings. All of the RCTs on hrHPV screening were conducted in countries with organized screening programs, not available to most women in the United States. Rigorous comparative research is needed in United States screening settings to examine longer screening intervals, long term outcomes, and to identify effective strategies for outreach and screening of poorly screened and unscreened women. The higher sensitivity of hrHPV testing in a single round may have potential to improve outcomes in this high-risk

population.

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Chapter 1. Introduction

Condition Definition

Two primary histologic abnormalities account for the majority of cancer of the uterine cervix—squamous cell carcinoma (SCC) and adenocarcinoma. The majority of cervical cancer cases (70% or more) are SCC, which is thought to arise from the transformation zone of the cervix.[3] The transformation zone is the region at the junction between the squamous and columnar cells of the cervix (squamocolumnar junction), which migrates from the exocervix to the distal endocervical canal with advancing age.[4] Adenocarcinoma, which develops from the mucus-producing cells of the endocervix, accounts for approximately 18 percent of cervical carcinomas. Adenocarcinomas and their precursors (atypical glandular cells and adenocarcinoma in situ) are less likely to be detected by cytology than SCC. The remainder of cervical carcinomas are adenosquamous (4%) and other carcinomas (5%) or malignancies (1.5%).[4]

Invasive cervical cancer (ICC) generally develops over a period of years and is preceded by precancerous changes of the cervix. Historically, precancerous changes of the cervix have been histologically defined as cervical intraepithelial neoplasia (CIN), identified at varying levels of severity: CIN1, CIN2, and CIN3. The latter includes CIS (carcinoma in situ, a preinvasive carcinomatous change of the cervix).[5] The term CIN2+ is used to indicate CIN2 or worse (CIN2, CIN3, or cancer), and CIN3+ is used to indicate CIN3 or worse (CIN3 or cancer). All of the trials and cohort studies in this review used this terminology. In 2012, a consensus group of the American College of Colposcopists and the American Society for Colposcopy and Cervical Pathology recommended changes to this terminology as part of the Lower Anogenital Squamous Terminology (LAST) Standardization Project. In the revised terminology, the primary determination is Low grade squamous epithelial lesion (LSIL) or High grade squamous epithelial lesion (HSIL), concordant with the terminology for cytology described below. These designations may be further classified by the applicable cervical intraepithelial neoplasia (CIN) subcategorization.[6] In LAST terminology, CIN1 is considered LSIL, CIN3 is considered HSIL, and CIN2 is considered HSIL but with the qualification that there is less diagnostic certainty regarding this subclassification. Immunohistochemical staining for p16 is recommended to categorize CIN2 as LSIL versus HSIL when there is diagnostic uncertainty. The studies included in this systematic review did not apply this terminology, so the older (CIN 1, 2, 3) terminology as used by the included studies is found in this review.

Cervical cytology is a standard screening test for cervical cancer and precancerous changes. The terminology for reporting the spectrum of cervical cytologic abnormalities derives from the 2001 Bethesda Workshop[7] and is displayed in **Table 1**.[8] Atypical squamous cells of undetermined significance, or ASC-US, are the least reproducible of all the cytologic categories and emphasize that a specific diagnosis cannot be made. Atypical glandular cell (AGC) abnormalities (previously called AGUS) may be reported as endocervical, endometrial, or not otherwise specified. The percentage of AGC Pap tests associated with underlying higher-grade lesions or disease (CIN2 or worse) is higher than for ASC-US.[8] High-grade squamous or glandular lesions can be seen in 10 to 39 percent of cases of AGC.[8] The term LSIL, or low-grade squamous intraepithelial lesion, includes cellular hrHPV changes and corresponds to CIN1. The term HSIL,

or high-grade squamous intraepithelial lesion, encompasses moderate to severe neoplasia and carcinoma *in situ* (CIS)—a pre-invasive carcinomatous change of the cervix—and generally corresponds to CIN2 and CIN3. The term ASC-US+ is used to indicate ASC-US or worse cytology, LSIL+ to indicate LSIL or worse, and HSIL+ to indicate HSIL or worse. Cervical cytology results are not diagnostic of neoplasia or cancer; biopsy and *histologic* confirmation are required for diagnosis.

Etiology and Natural History

The recognition of high-risk human papillomavirus (hrHPV) as a causative agent in the over 90 percent of cervical cancers has revolutionized the approach to prevention and screening.[9] Progression from hrHPV infection to cervical cancer occurs over a series of three steps: 1) hrHPV transmission resulting in acute hrHPV infection, which may resolve or persist; 2) persistent hrHPV infection leading to precancerous changes, and 3) ICC.[10] Transmission of hrHPV to the anogenital region occurs primarily as a result of skin-to-skin or mucosa-to-mucosa sexual contact.[10,11]

A high proportion of sexually active women become infected with hrHPV, but most infections resolve spontaneously and only a small proportion persist. HPV infection of all types is most common among sexually active women under the age of 25 years, and incidence declines with increasing age.[12] The majority of cervical cancers are caused by persistent infection with certain hrHPV types, primarily hrHPV 16 and 18.[13, 14] A 2011 meta-analysis of hrHPV type-specific prevalence data reported hrHPV detection in 90 percent of cervical cancers worldwide.[15] The 12 most common hrHPV types identified, in order of decreasing prevalence, were hrHPV 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51 and 56[15], with hrHPV types 16 and 18 accounting for approximately 70 percent of cervical cancers.[15, 16] A recent U.S.-based study detected hrHPV in 91 percent of cervical cancers (51% hrHPV 16, 16% hrHPV 18, and 24% other oncogenic types).[17] Most hrHPV infections associated with low-grade lesions clear within 2 years of acquisition, and persistent infections are implicated in the development of invasive cancer.[18-20] Risks associated with hrHPV infection are type-specific, with types 16 and 18 conferring the highest risk for hrHPV persistence and progression to high-grade lesions, although even these types are likely to clear in young women. [21 22]

Regression of hrHPV infection is presumably due to a successfully mounted immune response,[23] and increased persistence of hrHPV infections is observed in immunocompromised populations.[24, 25] It is unknown whether viral infections resolve as a result of complete clearance of the virus or by maintenance of the virus in a latent state.[10] While cohort studies have demonstrated that a viral type can reappear even after it has been thought to have cleared,[26] incident hrHPV infections may not confer a great deal of risk given the high probability of clearance and the long time period between hrHPV infection and cancer development, particularly among older women.[27]

Regression of histologically diagnosed lesions also can occur subsequent to hrHPV infection-induced neoplasia. Regression rates are higher for CIN1 then for CIN3, while CIN2 is a less reproducible diagnosis, and is likely a mixture of CIN1 and CIN3. In an historical cohort of

about 20,000 Toronto women during a period when lesions were managed conservatively, less than 1 percent (0.3%) of CIN2 lesions progressed to ICC within 2 years, 0.7 percent progressed within 5 years, and 1.2 percent progressed within 10 years.[28] Rates of CIN3 progression to ICC were considerably higher (1.6% within 2 years, 2.6% within 5 years, and 9.9% within 10 years). Regression from CIN2 to a second normal test occurred in 6.9 percent within 2 years, 29.0 percent within 5 years, and 53.7 percent within 10 years.

Progression of neoplasia to ICC is slow. The rate of progression of CIN3 to cancer has recently been estimated as 31.3 percent in 30 years. This rate was determined using retrospective data from an unethical clinical study in New Zealand between 1965 and 1974 that left a number of women with CIN3 disease incompletely treated or untreated.[5] Other rough estimates from early studies of women with precancerous cell changes suggest a 20 to 30 percent risk of ICC over a 5- to 10-year time frame.[29, 30]

Using composite data from cytology, histology, or both to define CIN lesions, a review summarized studies published between 1950 and 1990 on persistence, regression, and progression of CIN.[31] Over followup from 1 to 25 years, regression was most common for CIN1 (57% regressed, 32% persisted, and 1% progressed). For CIN2, 43 percent regressed, 35 percent persisted, and 5 percent progressed to cancer. For CIN3, regression rates were 32 percent, persistence rates were 56 percent, and progression rates were greater than 12 percent. Available data on CIN progression and regression have not discussed treatment for CIN3 specifically, nor its effect on the results reported although factoring in treatment is clearly important. In the New Zealand study,[5] about 31.3 percent of women with CIN3 who were untreated or inadequately treated progressed to cancer within 30 years, compared with 0.7 percent in those with adequate treatment.

Newer data suggest that CIN1, due to HPV infection of a specific type, does not predict any meaningful risk of CIN3.[10, 32] In addition, CIN1 diagnoses in the United States are poorly reproduced,[10, 32] which has also been established recently for CIN2 diagnoses in the United States and other countries.[33, 34] Despite poor reproducibility, data from the ASC-US-LSIL Triage Study (ALTS) trial have been used to estimate that up to 40 percent of CIN2 detected through colposcopy referral after positive primary screening tests (cytology and hrHPV) in younger women may regress, particularly in the presence of less severe cytology such as ASC-US+, LSIL+, or hrHPV positive tests that are not hrHPV 16 positive.[35]

Prevalence and Burden of Cervical Cancer and hrHPV

Cervical cancer incidence and mortality have substantially decreased since the introduction of screening programs over half a century ago.[36] The age-adjusted incidence from 2009 to 2013 cumulatively was 7.5 cases per 100,000 women per year; the age-adjusted mortality rate over the same period was 2.3 deaths per 100,000 women per year.[36] There were an estimated 12,990 new cases of cervical cancer and 4,120 deaths in 2016.[13] In SEER data, the median age at diagnosis was 49 years[36] and the highest incidence rates were among women between aged 35 and 54 years (48.0%) (**Table 2**) and among black (8.9 cases per 100,000 persons) and Hispanic (9.4 cases per 100,000 persons) women (**Table 3**).[36] The highest mortality rates were among women aged 45 to

64 years (47.6%) (**Table 2**) and black (3.9 deaths per 100,000 women) and American Indian/Alaskan Native (3.2 deaths per 100,000 women) women (**Table 3**).[36] A recent analysis of National Center for Health Statistics data (2000-2012) that adjusted for differences in the hysterectomy rate by race and ethnicity found much higher mortality disparities than previously recognized.[37] For black women, the corrected mortality rate rose to 10.1 per 100,000 women (uncorrected rate 5.7 per 100,000 women). In contrast, the adjusted rate for white women was 4.7 per 100,000 women. The study demonstrated that without the correction for hysterectomy, the disparity in mortality between races was underestimated by 44 percent. Correction for hysterectomy also indicated increasing cervical cancer mortality rates with age, particularly for black women, with corrected mortality rates above 30 per 100,000 women for black women 80 years and older. [37]

Rates of incident cervical cancer in SEER 13 data have decreased from 7.9 to 6.8 per 100,000 between 2004 and 2014, while overall cervical cancer, mortality has declined only slightly in the same time frame, from 2.4 to 2.3 per 100,000 women.[36] The steady fatality rate primarily results from a large proportion of incident cases and deaths occurring with late presentation among unscreened women (i.e., those who have not been screened in the past 5 years), as well as those screened but being lost to followup, highlighting the continued importance of improving access to cervical cancer screening and followup.[31, 38-41] A recent age-adjusted analysis of national cancer mortality by county identified particularly high rates of cervical cancer mortality in the southern United States along the Mississippi River, in southern Alabama, and a few counties in South Carolina, Georgia, and in South Dakota.[42] Cervical cancer incidence rises with age, and is believed to arise from persistent hrHPV infections from exposures earlier in life[43]. Persistent early infection, later in life incident infections, and reactivation of earlier infections could contribute to cervical cancer, but interactions between hrHPV exposure timing, infections with multiple types, and aging are not fully understood.[44]

HPV is the most common sexually transmitted infection in the United States. The estimated prevalence of hrHPV among women in the United States aged 18 to 59 years of age was 20.4 percent based on data from the 2013 to 2014 National Health and Nutrition Examination Survey (NHANES).[45] The prevalence has been shown to vary by age, race/ethnicity, and sexual history (**Table 4**).[45, 46] HPV infections were most common among young women aged 18 to 24 years (56.1%), black women (63.2%), those with income-to-poverty ratios of less than 130 percent (55.3%), and those with a greater number of lifetime sexual partners (≥ 11 partners, 60.7%). Many infections regress within a few years; however, those that persist may lead to cervical cancer.[31]

The risk of acquiring hrHPV dramatically increases with the number of lifetime sexual partners.[13, 24, 46] Co-infection with other sexually transmitted agents such as chlamydia trachomatis may also be associated with risk of hrHPV infection.[47, 48]Additional independent risk factors for cervical pre-cancer and cancer include long-term use of oral contraception, high parity, and cigarette smoking.[13, 49-51] Smoking is significantly associated with an increased risk of SCC among current smokers compared with never-smokers, but not associated with the risk of cervical adenocarcinoma.[52] Geographic and racial/ethnic disparities remain, with Southern states having higher rates of cervical cancer and nonHispanic black and Hispanic women having higher cervical cancer incidence and mortality. Women with lower socioeconomic status have higher

rates of cervical cancer mortality.[53]

From 2004 to 2007, the estimated annual direct medical cost for routine cervical cancer screening was $5.4 billion, with an additional $1.2 billion in followup of abnormal results.[54] The estimated annual direct medical cost of cervical cancer treatment was $441 million.[54]

Screening Strategies

Screening for cancerous or pre-cancerous changes of the cervix in developed countries begins with two types of tests: cytology-based screening and hrHPV testing (**Appendix A**). Microscopic evaluation of cervical cells was the progenitor screening test, traditionally performed by scraping cells from the cervix and fixing them on a glass slide in a method developed by Georgios Papanicolaou. This test, commonly referred to as the Pap test, is used to identify abnormal cells (e.g., ASC-US, LSIL) immediately after collection. Liquid-based cytology (LBC), another cytology-based screening method;, differs from conventional cytology in sample preparation. The cervical cells are first suspended in a liquid fixative by swirling the collection device in the fixative (ThinPrep, Hologic, Inc., Bedford, MA)[55] or by placing the collection device in the fixative (SurePath, TriPath Imaging, Burlington, NC).[56] Cells are then suspended, collected by filtration, and transferred onto a monolayer for microscopic evaluation. Conventional cytology and LBC have similar test performance characteristics (e.g., sensitivity, specificity) for the detection of CIN2+ and CIN3+ .[57] The effectiveness of cytology for cervical cancer screening is well-established.[57]

This review addresses the benefits and harms of cervical cancer screening with hrHPV testing testing alone (primary screening) or as cotesting with cytology. Assay methods for detecting hrHPV include a variety of platforms used to detect hrHPV. Most use either signal or nucleic acid amplification methods.

The U.S. Food and Drug Administration (FDA) has approved five different hrHPV tests (Hybrid Capture 2 [HC2],[58] cobas hrHPV [Roche Molecular Systems, Inc., Pleasanton, CA],[59] APTIMA hrHPV Assay [Gen-Probe, Inc., San Diego, CA],[60] Cervista hrHPV 16/18[61] and Cervista high-risk hrHPV [Hologic, Inc., Bedford, MA])[62] for testing patients with abnormal cytology results to determine the need for colposcopy referral and for use in women aged 30 years or older in conjunction with cytology (cotesting) to assess absence or presence of high-risk hrHPV type. In 2014, the cobas hrHPV test was the first to be approved by the FDA as a primary cervical cancer screening test for women aged 25 years or older.[63] Randomized trials of cervical cancer screening have used the HC2 assay or the GP5+/6+ PCR enzyme immunoassay (not used in the United States). A recent systematic review compared these assays to newer hrHPV tests, including those listed above. Of tests approved in the United States, HC2 was considered a reference standard; similar test performance characteristics were found for the APTIMA and Cervista assays, but only cobas 4800 HPV was found to fully meet 2009 international expert committee equivalency criteria.[64]

Because of the high frequency of transient HPV infection in women under the age of 30 years leads to many positive hrHPV tests and subsequent diagnostic and treatment interventions (with

potential to cause harm) for infections that are likely to resolve spontaneously,[65] hrHPVcotesting has not been recommended for cervical cancer screening in women under age 30 years.[66, 67] However, the recent FDA approval of cobas hrHPV for primary screening in women aged 25 years and older prompted the American College of Obstetrics and Gynecology to add this option to their screening recommendations in 2016.[66]

Vaginal self-sampling—or self-collection—for hrHPV testing could improve screening rates among under- or unscreened women as it reduces some of the barriers to cervical cancer screening (e.g., discomfort, inconvenience, cost, and accessibility of a clinician visit). Self-collection has women collect cervical- or vaginal-material using swabs, brushes, tampons, or lavage devices and send their samples to a health care provider or laboratory for analysis. Clinical followup is required for abnormal results. This screening alternative has not been widely evaluated in the United States, and is not FDA-approved. Evidence from other settings has prompted interest in its potential to reach unscreened women if the test accuracy and followup on positive test results are comparable to office-based screening. Lower accuracy and followup adherence might be viewed as sufficient, however, if self-collection increases overall screening, followup, and treatment among high-risk, unscreened women who are not responsive to other screening opportunities.

Whatever screening test is used, protocols for followup of abnormal test results will influence the frequency of both benefits and harms of cervical cancer screening. For cervical cancer screening to make a difference, once abnormal screening results are identified, followup with surveillance and/or treatment are required. Followup may include triage or subsequent testing with cytology or HPV, identification of the specific hrHPV type, and colposcopy (visualization of the cervix under magnification) with biopsy. Protocols vary depending on the severity of the abnormal result, and algorithms have been published,[68] but there is no clear consensus across organizations on preferred diagnostic and followup strategies. Followup strategies employ repeat testing with hrHPV and/or cytology at variable intervals, and differ on at what point evaluation with colposcopy and biopsy is recommended.[69] Early or more frequent use of colposcopy and biopsy leads to higher CIN detection rates, but reduces opportunities for low grade CIN to regress without intervention, and may lead to higher rates of treatment with potential for associated harms.

Prevention of hrHPV Infection

HPV vaccination helps prevent disease by reducing individual- and population-level infection with high-risk hrHPV types. HPV vaccination is most effective when administered before exposure to hrHPV.[70, 71] Currently, three vaccines are approved in the United States that protect against hrHPV infection; however, as of late 2016 the GARDASIL® 9 vaccine was the only one being distributed.[72] Licensed in 2006, the quadrivalent HPV vaccine (4vHPV) GARDASIL® protects against hrHPV types 16 and 18, the cause of 70 percent of cervical cancers, and HPV types 6 and 11, which cause 90 percent of genital warts.[73-81] In 2009, the bivalent hrHPV vaccine (2vHPV) CERVARIX® was also licensed to protect against hrHPV types 16 and 18.[73] In 2014, the FDA approved GARDASIL® 9 (9vhrHPV), which provides coverage for two hrHPV vaccine types (16, 18) and HPV types 6 and 11 in 4vHPV, and five additional high-risk

oncogenic strains (31, 33, 45, 52, 58) that account for 15 percent of cervical cancers.[82]

Recommendations for routine vaccination against HPV have been issued by the Advisory Committee on Immunization Practices (ACIP), a subsidiary component of the Center for Disease Control and Prevention's national vaccine programs, which recommends routine HPV vaccination for both sexes starting at age 11 or 12 years.[72] Children as young as 9 years may receive the vaccine. Additionally, the ACIP recommends that females and males who were not adequately vaccinated previously receive the vaccine through Q000000 For children younger than 15 years, a two-dose schedule is now recommended based on evidence of sufficient immunogenicity for these ages with the second dose administered 6 to 12 months after the first dose. For individuals who initiate the vaccine after the age of 15 years, a three-dose schedule is still recommended, with the second dose administered 1 to 2 months after the first and the third dose administered 6 months after the first dose.[72] The recent introduction of a two-dose or alternative simplified dosing schedules increases convenience for providers, parents, and vaccine recipients, reduces costs, and facilitates implementation of vaccines (i.e., reduce logistical challenges, decrease resources).[83 84] The two-dose schedule is expected to result in an increased proportion of children under age 15 who have completed the recommended series.

In 2015, the first cohort of vaccinated women reached 21 years of age, and became eligible for cervical cancer screening. Low rates of vaccination uptake initially and the lead time needed to observe effects limit conclusions that can be drawn regarding the impact of vaccination on cervical cancer incidence in the United States, but recent studies documenting declines in hrHPV infection and high-risk lesions among vaccinated women are encouraging. [85 86 87, 88] A systematic review found that in countries with greater than 50 percent vaccination coverage, hrHPV type 16 and 18 infections decreased significantly by 68 percent (Relative risk [RR], 0.32 [95% CI, 0.19 to 0.52]) in girls 13 to 19 years of age between pre-vaccination and post-vaccination periods. There was also evidence of cross protection against other types with higher rates of vaccine uptake.[87] An Italian consensus conference recently addressed the potential need for changes to screening recommendation based on broad population coverage with the HPV vaccine, and recommended a tailored screening approach, with screening at age 30 years for women vaccinated by age 12 years.[89] Based on data from 2008 to 2012, HPV was estimated to cause more than 90 percent of cervical cancers and over 24,600 hrHPV-associated cancers (e.g., cervical cancer, oropharyngeal) occur among women in the United States each year.[90, 91] Since the HPV vaccine was recommended for females aged 11 to 12 years through 26 years in 2006, NHANES data (2009-2012) demonstrates that there has been a 64 percent decrease in 4vHPV-type prevalence among females 14 to 19 years of age and a 34 percent decrease among females 20 to 24 years of age.[92]

Uptake of the HPV vaccine in the United States has been slow. Results from the 2015 National Immunization Survey-Teen (NIS-Teen) revealed a steady increase in HPV vaccination coverage among adolescents since its introduction in 2006 for females and 2011 for males. Coverage with one or more doses of any HPV vaccine increased from 25.1 percent in 2007 to 62.8 percent in 2015 among adolescent girls, and from 8.3 percent in 2011 to 49.8 percent in 2015 among adolescent boys.[93, 94] Coverage with three or more doses increased from 5.9 percent in 2007 to 41.9 percent in 2015 among females, and from 1.3 percent in 2011 to 28.1 percent in 2015 among males.[93]

Current Clinical Practice in the United States

In 2012, the U.S. Preventive Services Task Force (USPSTF) recommended initiating cervical cancer screening at age 21 years, screening women every 3 years with cytology or, among women aged 30 to 65 years, cytology in combination with hrHPV testing every 5 years, and to stop screening women with a hysterectomy or over the age of 65 years with a history of regular screening with negative results. These recommendations applied to women at average risk of cervical cancer.[95] At the same time, similar recommendations were released in a joint guideline by the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Society for Clinical Pathology (ASCP), and the American Cancer Society (ACS). The recommendations of other organizations published since the 2012 USPSTF recommendation are in **Appendix B**; many endorse either the USPSTF recommendations or the joint recommendations by ASCCP/ASCP/ACS.

Interim guidance from an expert panel cosponsored by the Society of Gynecologic Oncology (SGO) and the ASCCP was published in 2015 for primary hrHPV screening, and discussed initiation of screening with hrHPV testing alone at 25 years of age; this option was also included in an interim update to an ACOG Practice Bulletin in 2016.[66, 69] Evidence supporting these revisions came from the Addressing the Need for Advanced hrHPV Diagnostics (ATHENA) study, where 30 percent of CIN3+ cases were identified in women aged 25 to 29 years, and 37 percent of cases were identified in women aged 30 to 39 years.[96] In that study, 44 percent of women between 25 and 29 years of age with CIN3+ had abnormal cytology and 57% had a positive a positive cobas HPV test,[96] however, the AGO/ASCCP panel issuing the interim guidance noted that progression to cancer is uncommon in this age group and detection of disease in the 25-to-29-years age group can be safely deferred until age 30 years and older.[69] Age to stop screening was not specifically addressed.

Although cervical cancer screening programs have reduced the incidence and mortality of cervical cancer over the past 50 years, most screening in the United States is opportunistic, without population-based registries or regular invitations to screening. Organized cervical cancer screening programs are not widely available to women in the United States, and a sizeable proportion of the U.S.-based female population is not routinely screened. An estimated 8 million (11.4%) women in the United States aged 21 to 65 years had not been screened in the previous 5 years based on data from the 2012 Behavioral Risk Factor Surveillance System; these rates varied by age, race/ethnicity, and health insurance status.[97] The highest proportions of unscreened women among screening-eligible women were in those at younger (aged 23 to 29 years) or older (aged 60 to 65 years) ages, Asian/Pacific Islander (19.7%) or American Indian/Alaska Native (16.5%) and those without insurance (23.1%) or no regular health care provider (25.5%). Among women diagnosed with ICC, less than half had received a Pap test in the 5 years before diagnosis even though they had the opportunity to be screened.[39] Reasons for not being screened include a lack of access to health care (e.g., lack of insurance) and other barriers (e.g., discomfort with the exam, cultural or religious beliefs, socioeconomic status limiting resources needed to access care).

Most disparities in cervical cancer incidence and mortality are postulated to be attributable to differential access to screening and inadequate followup after abnormal screening results.[98] In an

analysis of 10,000 women in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), 44 percent with low-grade abnormalities in the two sequential Pap tests were followed up with colposcopy, while 56 percent were followed up with a third Pap test or not at all.[98] American Indian or Alaska Native women had the highest percentages of a third Pap test, and non-Hispanic black women had a higher percentage of no followup.[98] Over half of the women studied were not followed up in accordance with established guidelines for management of abnormal cervical cytology.[98] Even for women with access to services, clinician adherence to recommended screening varies by provider specialty, geographic location, personal characteristics, and knowledge, and can also be influenced by patient expectations and preferences. [99-107]

Previous USPSTF Recommendations

As mentioned previously, in 2012 the USPSTF recommended screening for cervical cancer in women aged 21 to 65 years with cytology (Pap test) every 3 years or, screening with a combination of cytology and hrHPV testing every 5 years for women aged 30 to 65 years who want to lengthen the screening interval (A recommendation).[95] They also recommended against screening for cervical cancer with hrHPV testing, alone or in combination with cytology, in women younger than age 30 years (D recommendation); screening for cervical cancer in women younger than age 21 years (D recommendation); screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high-risk for cervical cancer (D recommendation); and, screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of high-grade precancerous lesion (CIN grade 2 or 3) or cervical cancer (D recommendation).

In 2003, the USPSTF strongly recommended screening for cervical cancer in women who have been sexually active and have a cervix (A recommendation).[108] It also recommended against routinely screening women older than age 65 years for cervical cancer if they have had adequate recent screening with a normal Pap test and are not otherwise at high-risk for cervical cancer (D recommendation), and routine screening in women who have had a total hysterectomy for benign disease (D recommendation). At the time, the evidence was insufficient to recommend for or against the routine use of new technologies (such as LBC or automated screening) to screen for cervical cancer (I statement) and to recommend for or against the routine use of hrHPV testing as a primary screening test for cervical cancer (I statement).

Chapter 2. Methods

Scope and Purpose

This systematic review evaluated the evidence for the benefits and harms of cervical cancer screening using hrHPV testing with cytology (cotesting) or alone (primary screening). The USPSTF will use this review to update the 2012 recommendation on cervical cancer screening focusing on use of a hrHPV test alone or with cotesting comparted to cytology as screening strategies.[95]

Key Questions and Analytic Framework

In consultation with the Agency for Healthcare Research and Quality (AHRQ) and members of the USPSTF, we developed an analytic framework (**Figure 1**) and two Key Questions (KQs) to guide our review.

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 (KQ 1.0) and incidence (KQ 1.1) 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 (e.g., 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 (e.g., age, race/ethnicity, screening history, hrHPV 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 (e.g., age, race/ethnicity, and hrHPV immunization status)?
    b. Do the adverse effects vary by screening strategy, including by rescreening interval?

Data Sources and Searches

In addition to evaluating all previously included studies for inclusion in the current review, we conducted an initial search of existing systematic reviews related to cervical cancer screening in the following databases: MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects, and the databases or websites of various organizations including the Agency for Healthcare Research and Quality, the Canadian Agency for Drugs and Technologies in Health, DynaMed, First Consult (via Clinical Key), Health

Technology Assessment, the Institute for Clinical Systems Improvement, the Institute of Medicine, the NHS Health Technology Assessment Programme, and the National Institute for Health and Clinical Excellence from January 2010 through February 25, 2015. The search strategies are listed in **Appendix A**.

We searched for newly published literature in the following databases: MEDLINE/PubMed, Cochrane Central Register of Controlled Trials, and PsycINFO from 2011 through February 15, 2017 bridging from the previous USPSTF review with a 1-year overlap. The search strategies are listed in **Appendix A**. We managed literature search results using EndNote™ version 7.3.1 (Thomson Reuters, New York, NY).

Study Selection

Two investigators independently reviewed titles/abstracts using an online platform (Abstrackr)[109] and full-text articles against pre-specified inclusion and exclusion criteria (**Appendix A Table 1**). Disagreements were resolved through discussion and consensus or consultation with the other investigators. A list of excluded studies after full-text review including the reasons for exclusion is available in **Appendix C**.

We included good and fair quality randomized controlled trials (RCTs), controlled clinical trials (CCTs), individual participant data meta-analyses and systematic reviews, and large cohort studies published in the English language that were conducted among women aged 21 years or older. Women under the age of 21 years were excluded on the basis that the current recommendation to screen for cervical cancer with cytology (Pap test) is among those aged 21 years or older. Women in high-risk populations (e.g., HIV-positive), those without a cervix or who have had a hysterectomy (including removal of the cervix), and pregnant women were excluded as these women may be managed differently with regards to cervical cancer screening. We also required studies to be conducted in primary care or other settings generalizable to primary care in countries categorized as "very high" on the 2014 Human Development Index[110] as defined by the United Nations Development Program for greater applicability to the current cervical cancer screening practices in the United States.

We required studies to evaluate hrHPV screening as a primary strategy using either the hrHPV test alone or in combination with cytology (cotesting or reflex cytology). Cervical cancer screening strategies that did not include a hrHPV test (e.g., primary cytology-based screening) or used a hrHPV test for a purpose other than primary screening (i.e., cytology with hrHPV triage of abnormal cytology) were excluded. For comparators, we included any cervical cancer screening test including cytology-based or other hrHPV screening strategies. Studies evaluating the comparative effectiveness of cytology-based screening strategies were excluded.

For KQ1, we included studies if they reported on at least one of the following health outcomes, as defined by USPSTF procedures for evaluating potential benefits of screening[111]: early detection of disease (CIN3+ or CIN2+), ICC, all-cause or cervical cancer mortality, and quality of life. Our focus on CIN3+ to define disease, in the absence of cervical cancer or mortality outcomes is based on natural history considerations discussed above. CIN can regress, regression

rates are higher for CIN1 and CIN2 lesions, and the risk of developing cancer associated with lower grade lesions are considerably lower for CIN1/CIN2 than for CIN3. Cervical cancer is rare in screened populations, and cervical cancer mortality even more rare in this group. Disease detection in this review focuses on detection of CIN3+ cases, which includes both cancer and the category of intraepitheilial neoplasia that is most likely to lead to cancer if left untreated, and have a lower chance of resolving without treatment.

For KQ1, we used the following hierarchy[112] of cervical cancer-related outcomes for data abstraction and analysis:

- Rank 1: Cervical cancer mortality
- Rank 2: Cervical cancer morbidity/stage IB+ incidence
- Rank 3: Cervical cancer incidence (including microinvasive)
- Rank 4: Reduced CIN3+ incidence or p16 immunohistochemistry-associated high-grade squamous intraepithelial lesion incidence[113]
- Rank 5: Increased detection of CIN3+ (or CIN2+)
  - More CIN3+ detection overall (cumulative CIN3+)
  - More CIN2+ detection followed by less CIN3+ detection at subsequent screening (note: CIN2+ detection may include overdiagnosis)
- Rank 6: Increased test positivity with increased, similar, or minimally reduced positive predictive value

For KQ2, we included studies if they reported on at least one of the following harms: rates of false positive or false negative screening tests for CIN or cancer; biopsy and/or colposcopy rates; partner discord and other psychological harms (e.g., labeling, stigma, distress, quality of life). The potential harms of treatment, following from screening results and diagnostic testing, are discussed, but these outcomes are not generally reported in cervical cancer screening trials.

We identified seven large RCTs evaluating population-based cervical cancer screening programs and reported on relevant outcomes, and we applied the following hierarchy to select study designs to answer our KQs: (1) RCTs, (2) comparative cohort studies that provide outcomes/analyses not represented in RCTs, and (3) single group cohorts that provide outcomes/analyses not represented in RCTs, with priority placed on studies generalizable to U.S.-based clinical practices and healthcare settings. We selected publications that reported on final results only (usually the most recent study publication); publications on interim and preliminary results were excluded (unless they provided detailed methodology).

Quality Assessment and Data Abstraction

Two investigators independently assessed the quality of included studies using criteria defined by the USPSTF[114] supplemented with the Newcastle-Ottawa Scale[115] for observational studies (**Appendix A Table 2**). Each study was assigned a final quality rating of good, fair, or poor after investigators resolved any disagreements through discussion. Studies with a single "fatal flaw" (e.g., attrition greater than 40%, differential attrition greater than 20%) or multiple important limitations that could invalidate the results were rated as poor quality and excluded. Studies rated

as good quality studies met all or most of the criteria for the study design (e.g., adequate randomization methods); quality ratings were downgraded if studies did not meet most of the study design-specific criteria but did not have a fatal flaw that could invalidate the results.[116]

One investigator abstracted data from all included studies into a Microsoft Access® database (Microsoft Corporation, Redmond, WA) and a second investigator checked the data for accuracy. We abstracted study design, population demographics, intervention characteristics, screening and round protocols, outcomes, and adverse effects. When necessary, we contacted study authors for data clarifications and requests for final data.

Data Synthesis and Analysis

Due to the heterogeneity of screening tests, screening protocols, settings, and followup protocols, we did not quantitatively pool results using meta-analysis. We instead conducted a narrative synthesis of the results by screening strategy and age. We generated summary tables and descriptive text detailing the populations, protocols, and the interventions and followup procedures at each round of screening for included studies. The pre-specified outcomes were abstracted from each study by KQ, and results were presented in groups defined by the intervention type, primary hrHPV screening or hrHPV cotesting, and when possible, by age. We highlighted the absence of relevant outcomes. We drew inferences when possible, but also highlighted limitations in the evidence.

Results from the included RCTs were generally based on a 'number of women screened' denominator, rather than intention-to-treat calculations using all women randomized. These denominators are appropriate since the relative merits of the screening strategies being compared, rather than overall merits of the screening program, are being evaluated. Some results reported in the evidence and summary tables were calculated from data provided in the articles or by authors, as indicated in table annotations.

When possible, we provided data stratified by age because the prevalence of hrHPV is much lower in women aged 30 years or older than in women under the age of 30 years.[36] Cotesting with hrHPV tests in conjunction with cytology is FDA approved in women aged 30 years or older.[63] We defined two age categories: women aged less than 30 to 35 years of age and women aged older than 30 to 35 years of age.

The definition of test positive for this review was defined based on the trial protocol (**Appendix F Table 2**). Test findings that would lead to a clinical action, based on the study protocol, such as colposcopy or more intensive followup (e.g., retest in 6 months) were defined as 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 ASC-US+. We used Bethesda system terminology throughout the review and converted cytological results reported in other terminology systems to the Bethesda system, though there is not exact equivalence (e.g. borderline or mild dyskaryosis is comparable to ASC-US) (**Table 1**).

For evaluating potential harms or burden of screening, the false positive rate (FPR) quantifies the

chance that a patient experiences a positive screening test result, but histology results are not indicative of precancerous lesions or cervical cancer that would necessitate treatment or active surveillance if detected (CIN2+). Differences in the false positive rates associated with different screening strategies were estimated by comparing the number of women who do not have histologically confirmed CIN2+ diagnosed prior to or in the screening round following a test positive result (as defined above). The false positive rate was defined as histologically confirmed CIN2+ because this degree of cervical intraepithelial neoplasia is usually acted upon clinically once detected. This definition of FPR is a pragmatic one and relies on colposcopy as a reference standard, however, there is variability in the accuracy of colposcopy and biopsy to detect CIN2+ based on colposcopist training and experience as well as the biopsy protocol.[116]

Differences in colposcopy rates for different screening strategies tested in trials are related to both the test positivity rate and the triage protocols used. Colposcopy is uncomfortable, anxiety provoking, and time consuming.While it is also a necessary step toward diagnosis and treatment, colposcopy due to a false positive screening test may be considered a harm. Colposcopy may lead to treatments, which are associated with an uncommon risk of serious harms. A screening protocol equally effective at identifying CIN3+ cases and preventing ICC, but with more colposcopies, would be evaluated as having greater potential harm.

The false negative rate was another test performance characteristic evaluated in our analysis of potential screening harms. False negative rates were defined in this review as the proportion of women with invasive cancer who had negative screening findings at a previous round of screening. Although this is a rare outcome, evidence of differences in the rate of missed cases among screened women is important to consider. Since trials do not generally conduct colposcopies in women with negative screening results, we are not able to accurately estimate the false negative rates of CIN2 or CIN3. At followup rounds of screening, it is not possible to distinguish between newly emerging CIN2/CIN3 versus cases that were missed. ICC generally evolves slowly, so identification of ICC after a negative screen likely reflects a false negative result. In addition, cancer registries can be used to identify missed cases.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each KQ. We adapted the Evidence-based Practice Center approach[117] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[118] Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth required domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there

is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

We graded the overall strength of evidence as high, moderate, or low. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from May 28, 2015 to June 28, 2015. The draft version of this report was reviewed by experts and USPSTF Federal Partners. Comments received during any period were reviewed, considered, and addressed as appropriate.

USPSTF Involvement

This systematic review was funded by AHRQ under contract to support the USPSTF. We consulted with USPSTF liaisons at key points in the review including the development of the research plan (i.e., KQs, analytic framework, and inclusion and exclusion criteria) and the finalization of the systematic review. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the review, and assisted with expert review and public comment on the research plan and draft review. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the systematic review.

Chapter 3. Results

Literature Search

We screened 2,972 abstracts and 163 full-text articles for inclusion (**Appendix A Figure 1**). We included 12 studies[1, 119-128]that reported results in 31 publications (**Appendix D**). Eleven studies[1, 119, 121-128] were included for the effectiveness of hrHPV testing as the primary screening strategy with or without cytology (KQ1) and 12 studies[1, 119-128] were included for harms (KQ2).

Results of Included Studies

KQ 1. What Is the Effectiveness of 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?

Summary

The primary outcome of KQ1 was cervical cancer mortality, but this is a rare outcome in countries with organized cervical cancer screening programs. Though large numbers of women were recruited, none of the seven included trials reported on or was powered to assess mortality. Trials were heterogeneous with regard to type of cytology (conventional vs. LBC), type of hrHPV test (PCR vs. HC2), screening interval (2 to 5 years), followup protocols for abnormal results, number of screening rounds, and protocols for screening beyond the first screening round. No trials directly compared primary hrHPV screening with hrHPV cotesting; in all cases comparisons were made to cytology screening. Trials reported outcomes after one or two rounds comparing alternative screening strategies.

The evidence was generally consistent across trials with variable protocols and hrHPV test types in demonstrating that primary hrHPV testing increased detection of CIN3+ in the initial round of screening by as much as 2- to 3-fold. Only the NTCC Phase II trial of primary hrHPV testing, where all women with a positive hrHPV test were referred to colposcopy, had complete results from two rounds of screening (at Round 2 screening all women received cytology testing).[1, 2] In that study, CIN3+ detection in Round 1 was 3-fold higher in the hrHPV testing arm, and cumulative detection was 1.8-fold higher after the second round of screening. Results of a large, single-arm fair-quality cohort study of primary hrHPV testing at three year intervals were consistent with trial findings. CIN3+ detection in the second screening round was significantly lower: the RR for CIN3+ detection at Round 2 compared to Round 1 was 0.14 (95% CI 0.06 to 0.32).

Evidence was mixed in cotesting trials; in two of four trials round one CIN3+ detection was 1.2- to 1.3-fold greater for cotesting. By the second round of screening 3 to 5 years later, CIN3+ detection was lower in the hrHPV cotesting arm and higher in the cytology-only arm, such that

cumulative CIN3+detection was similar between intervention and control study arms. Because no trial sustained the intervention and control group protocols beyond two screening rounds, evidence comparing the long-term outcomes of hrHPV primary testing or cotesting with cytology only is lacking.

The large single-group cohort studies of cotesting were consistent with the pattern of higher detection of CIN3+ in the first screening round relative to a followup round.[124, 128, 129] Without a comparison group it is unknown how these cohort study findings would compare with screening with cytology only.

Findings of the IPD meta-analysis suggested lower incidence of ICC in the hrHPV screening arms beyond the first 2.5 years from the initial screening round.[130] While this finding is encouraging, it was based on pooling studies using different test protocols and screening intervals with only a cumulative total of 107 ICC cases. Studies were relatively consistent in finding that hrHPV testing will identify more CIN3+ in an initial screening round, but there was less evidence that CIN3+ or ICC is reduced by hrHPV screening over time. Because studies reported on only one round or at most two rounds of screening in which intervention and control arm strategies were compared, the evidence was not sufficient to draw conclusions about the outcomes of strategies including hrHPV testing compared with strategies involving cytology repeated multiple times at regular intervals over the recommended screening age range.

Evidence on subpopulation outcomes from the RCTs and cohort studies described above focused on outcomes by age group. Studies reported variable age groups, with break points at age 25 years, 29 to 30 years, or 34 to 35 years. Women under age 35 years had consistently higher rates of hrHPV positivity and of CIN3+. Outcome differences between screening strategies by age group were not notably different from the results in the study populations overall. No included studies reported on outcomes by race/ethnicity, hrHPV immunization status, or socioeconomic status. Neither trials nor the Kaiser Permanente Northern California (KPNC) cohort study reported on outcomes related to screening history, but all but one included study were based in organized screening programs, suggesting that most subjects were offered regular screening prior to study participation. For underscreened women, a single cohort study of cotesting from Spain of women not screened in the previous 5 years, overall CIN3+ was detected in 0.5 percent of women (nine women), but loss to followup was nearly 50 percent. Three women with CIN3 were detected only through hrHPV testing.

Data from trials were not adequate to compare outcomes of different rescreening intervals, due to lack of direct comparisons of intervals or consistent application of initial screening strategies for more than one screening round. Similarly, no data were available to address rescreening intervals by subpopulation.

Description of Included Studies

We identified seven RCTs that used hrHPV testing as part of cervical cancer screening (**Table 5**): New Technologies for Cervical Cancer (NTCC) Phase I and Phase II trials conducted in Italy;[1, 2, 131, 132] HPV testing for Cervical Cancer Screening trial (HPV FOCAL), conducted in Canada;[127, 133-135] a cervical cancer screening trial in Finland (FINNISH);[126] a cervical cancer

screening trial in Sweden (SWEDESCREEN);[121, 136] a cervical cancer screening trial in the United Kingdom, A Randomised Trial in Screening to Improve Cytology (ARTISTIC);[119, 137-139] and the POpulation-BAsed SCreening study in AMsterdam (POBASCAM).[122, 140, 141] In all cases, study subjects were recruited through organized screening programs. Study recruitment years varied; overall recruitment across seven trials spanned 1997 to 2011. Subject age ranged from 20 to 65 years (**Appendix F Table 1**). Three studies evaluated primary hrHPV screening: one study evaluated primary hrHPV screening with referral to colposcopy for all positive tests (NTCC Phase II), and two studies evaluated hrHPV testing with cytology triage of positive tests (HPV FOCAL and FINNISH). Cotesting with hrHPV and cytology was evaluated in four studies (NTCC Phase I, SWEDESCREEN, ARTISTIC, and POBASCAM). In addition, we included an IPD meta-analysis of five of these trials (NTCC Phase I, NTCC Phase II, SWEDESCREEN, ARTISTIC, and POBASCAM) that reported pooled rates of ICC as an ancillary article to these included trials.[130] We also included four cohort studies. A large Italian single cohort study reported on two rounds of primary HPV testing,[128] a large U.S.-based single cohort observational study reported results of of hrHPV cotesting conducted in a health maintenance organization population,[124, 142-144] and a German cohort study reported results of hrHPV cotesting with a 5-year interval (WOLPHSCREEN).[125, 129] A single cohort study of hrHPV cotesting underscreened women in Spain was included as evidence on hrHPV screening of underscreened women.[123]

Most trials reported outcomes after a single round of screening comparing an intervention with a control group, with one or more subsequent rounds of screening in which both groups received the same screening strategy (either hrHPV cotesting or cytology only). Each trial had a distinct screening protocol, with different hrHPV and cytology test types, intervals, and followup protocols (**Appendix F Tables 2** and **3**). For this reason, we did not pool study outcomes with meta-analysis. We focused primarily on detection of CIN3+ as the outcome of interest; all included studies reported this outcome. Although reducing cervical cancer morbidity and mortality is the target of cervical cancer screening, ICC is a rare outcome in countries where most women are regularly screened for cervical cancer by any method. Although reported separately in some studies, these outcomes were too rare for meaningful comparisons. Cervical cancer mortality is even less frequent and was not reported in any trial. CIN3+ includes all ICC and in-situ precancerous changes with a high-risk of progression to invasive cancer over time.

Three of the included trials were rated good-quality (NTCC Phase I and Phase II, POBASCAM) and the other four were rated fair-quality. Problems with blinding of outcome assessors, adherence to study protocols and maintenance of the randomization scheme over multiple rounds of screening contributed to risk of bias in this evidence base. Attrition and changes to the screening protocol over time limited the extent to which results from later rounds of screening could inform the key questions of this review.

Screening With Primary hrHPV Testing

Ronco and colleagues compared primary hrHPV with HC2 to conventional cytology in the good-quality NTCC Phase II trial (**Tables 6–8**).[1, 2] This trial, conducted in Italy, randomized 49,196 women aged 25 to 60 years invited for routine screening to either hrHPV testing with HC2 or conventional cytology. Subjects were followed for a maximum of 7 years over two rounds of screening at 3-year intervals. The second round of screening for both intervention and control

groups was with cytology only. Women in the intervention group were referred to colposcopy for any positive hrHPV test. Women with CIN2+ were treated, while women with CIN1 were followed with repeat colposcopy according to standard protocols, and received annual hrHPV and cytology testing. Abnormal cytology results were managed according to standard center protocols. Over two rounds of screening, detection rates for CIN3+ were 0.4 percent in the intervention group and 0.2 percent in the control group, with a RR for CIN3+ detection of 1.81 (95% CI, 1.31 to 2.51) (**Table 6**). Detection of ICC was not recorded separately.

The fair-quality HPV FOCAL trial, conducted in Canada, evaluated HC2 hrHPV testing with liquid-based cytology triage.[127, 133, 134] This trial randomized 25,223 women aged 25 to 65 years who were eligible for routine screening determined by the centralized British Columbia cytology database. Women were randomized to three arms: a control group of 9,457 women screened with liquid-based cytology every 2 years with cotesting at the 4-year exit screen, an intervention group of 9,552 women screened with hrHPV testing (HC2) at entry and with cotesting 4 years later, and a safety arm of 6,214 women screened with hrHPV testing at entry and screened 2 years later with LBC. In the intervention arm, women who had hrHPV positive results then had liquid-based cytology done on the specimen and if cytology was abnormal they were referred for colposcopy. Women with normal cytology had repeat testing at 12 months. The control group received liquid-based cytology followup according to standard protocols, including triage of ASC-US cytology results with hrHPV testing.At two years the safety arm received followup according to the same protocols. At Round 1, CIN3+ detection was 0.8 percent in the intervention group and 0.5 percent in the control group. After 2 years, CIN3+ detection was 0.06 percent in the safety arm (screened in Round 1 with hrHPV) and 0.25 percent in the control arm.[145] Final results including cumulative CIN3+ detection rates over the full 4 years of the trial are pending publication (**Table 6**).

In the fair-quality FINNISH trial, Leinonen and colleagues randomized women in Finland aged 25 to 65 years invited to participate in population-based cervical cancer screening between 2003 and 2007 for a single round of primary HC2 hrHPV testing compared with conventional cytology.[7] Followup for a positive hrHPV screening test was with cytology. A total of 203,425 women were invited for screening, and of these about 65 percent attended screening in each arm: 66,410 women in the hrHPV arm and 65,785 women in the cytology group. hrHPV testing was conducted with HC2. Women with abnormal cytology other than ASC-US were referred for coloposcopy in both arms. Women with ASC-US and women with hrHPV+ test results were followed with rescreening at 12 to 24 months. After the single round of randomized screening, followup through population based registries (Mass Screening Registry, Finnish Cancer Registry) continued for a maximum of 5 years and ended in December 2008. The RR for detection of CIN3+ among women in the hrHPV group was 1.64 (95% CI, 1.30 to 2.06) with 195 (0.3 %) of women in the intervention group found to have CIN3+ compared with 118 (0.2%) in the group screened with conventional cytology (**Table 6**).

A large, single-arm fair-quality cohort study conducted in two population-based cervical cancer screening programs in Italy reported on the results of primary HPV testing with HC2 and cytology triage of positive HPV tests, with two rounds of screening at a 3-year interval (**Tables 9** and **10**).[128] The study included 93,381 women invited for screening; 48,751 participated with completion of 48,736 hrHPV tests. Conventional cytology smears were obtained simultaneously,

and processed only for positive test results. Among those with positive hrHPV screening results, women with abnormal cytology were referred to colposcopy; women with normal cytology had repeat hrHPV testing at one year. Women with negative hrHPV testing were invited for a second round of screening at three years. At the time of publication, 29,694 were invited to screening, 22,000 (74.5%) participated, and 21,827 completed HPV tests. At Round 1, detection rates including one year followup were: 215 CIN2+, 95 CIN3+, and 6 invasive cervical cancers (CIN3+ 0.2%). Detection rates at Round 2 including 1 year followup were: 23 CIN2+, 6 CIN3+, no cervical cancers (CIN3+ 0.03%) The RR for CIN3+ detection at Round 2 compared to Round 1 was 0.14 (95% CI 0.06 to 0.32).

The ATHENA study was a single cohort observational study of 47,208 women aged 21 years and older (no upper age or age range is given) recruited for a single cross-sectional screening with three hrHPV test types, the HPV Amplicor and Linear Array HPV genotyping test, Hybrid Capture II, and cobas HPV test.[96] Liquid-based cytology was also performed on all subjects. Although initial results from the cross-sectional sample were reported for women 25 years and older (41,995), 77 percent of these women had no further followup. Subsequent followup was reported only on women with abnormal cytology (ASC-US or worse), women positive for HPV with Amplicor or linear array, and the group of women with normal results who were randomly selected and agreed to colposcopy (total n=9353). Of the 9353 women who were invited to that initial colopsocopy, 2685 (35%) were lost to followup after the initial colposcopy. Due to exclusion of most of the study population after cross-sectional screening, as well as high loss to followup over 3 years, this study was rated as poor quality and not included in the review.

Screening With hrHPV Cotesting

The good-quality NTCC Phase I trial by Ronco and colleagues compared HC2 hrHPV and LBC cotesting to conventional cytology (**Tables 11–13**).[1, 131, 132] In this trial, 45,174 Italian women aged 25 to 60 years attending a routine cervical cancer screening visit from March 2002 through December 2004 were randomized to cotesting or conventional cytology. Data from Phase II which used hrHPV testing alone are reported separately in the section on primary hrHPV testing above. At the 3-year followup round, all participants were screened with conventional cytology. Maximum total followup was 7 years. Women were referred to colposcopy for ASC-US+ on cytology, and women aged 35 to 60 years with a hrHPV+ test were referred to colposcopy. Women aged 24 to 35 with an hrHPV+ test result were referred to colposcopy only if hrHPV remained positive at the 1-year followup testing. In Round 1 screening, 0.3 percent of 22,708 women had CIN3+ detected in the intervention group, compared with 0.3 percent of 22,466 women in the control group with an RR of 1.28 (95% CI, 0.91 to 1.80). In Round 2, CIN3+ detection was 0.06 percent of 22,093 women in the intervention group compared with 0.08 percent of 22,330 women in the control group, with an RR of 0.96 (95% CI, 0.34 to 1.40). Cumulatively, the RR for detection of CIN3+ was 1.13 (95% CI, 0.83 to 1.53) with 88 (0.4%) of 22,708 women in the intervention group compared with 77 (0.3%) of women in the comparison group found to have CIN3+ (**Table 11**).

The fair-quality SWEDESCREEN trial compared hrHPV cotesting using the GP5+/6+ PCR enzyme immunoassay combined with conventional cytology with conventional cytology alone in the first round of screening.[121, 136] All women received both tests at baseline, but hrHPV samples

were frozen for future testing in the control arm. A total of 12,527 Swedish women who were invited for routine cervical cancer screening agreed to randomization and were followed after the first round of screening for slightly more than 4 years through comprehensive registry data. Screening protocols for women negative in Round 1 were through usual care. After 3 years, blinding of hrHPV results was discontinued because of concerns about higher rates of CIN2 and 3 associated with positive hrHPV results; all women enrolled in the study were informed of their hrHPV results. According to study protocol, women with cytology results consistent with CIN2 or worse were referred to colposcopy in all communities, but followup for ASC-US and LSIL varied by community, with women either referred to colposcopy or undergoing a repeat Pap smear. Women with normal cytology and a hrHPV+ test result were invited to repeat cotesting at 12 months, and referred to colposcopy if the hrHPV test were still positive at that time. The Round 1 study-based screen detected CIN3+ in 1.2 percent of 6,257 women in the intervention group compared with 0.9 percent of 6,270 women in the control group with an RR of 1.31 (95% CI, 0.92 to 1.87). Registry followup of usual care screening identified CIN3+ in 0.3 percent of 6,257 women in the intervention group compared with 0.5 percent of 6,270 women in the control group. The RR for detection of CIN3+ was lower for the intervention group in the second round of screening at 0.53 (95% CI, 0.29 to 0.98). Cumulative detection of CIN3+ over one round of screening with subsequent usual care followup was similar between arms: 88 (1.4%) in the cotesting arm and 85 (1.4%) in the cytology group with a RR of 1.04 (95% CI, 0.77 to 1.39).

Long-term followup was reported at up to 13 years based on tracking study participants in the National Quality Registry for Cervical Cancer Prevention, a national Swedish registry including cervical cytology and biopsy results from all sources in Sweden (**Appendix F Table 4**).[136] No statistical difference remained in cumulative CIN3+ rates between the intervention and control arms of the study. Cumulative rates of CIN3+ were examined for both baseline test results for both the combined study arms (cytology, hrHPV and hrHPV/cytology combined); Among women in either group with negative cytology, CIN3+ rates were lowest for women with negative hrHPV tests at baseline in both the intervention and control arms and highest in women with negative cytology without consideration (ie, no knowledge) of hrHPV test results.

In the fair-quality ARTISTIC trial, Kitchener and colleagues compared hrHPV with liquid-based cytology among women aged 20 to 64 years invited for routine cervical cancer screening in the United Kingdom.[119, 137-139] A total of 25,078 women received LBC and hrHPV testing and were randomized in a 3-to-1 ratio to have both hrHPV and LBC results revealed to the patient and the investigator (18,386 women in the intervention group), or to only LBC results revealed (6,124 women in the control group). Liquid-based cytology was processed via a ThinPrep system; hrHPV testing was conducted with HC2. Two rounds of screening were conducted with the second round using the same screening protocol at a 3-year interval. Women with high-grade cytology (HSIL+) in either group were referred directly to colposcopy and biopsy. Women with low-grade cytology results (LSIL) in either group had repeat testing at 6 months and were referred to colposcopy if persistently positive. Women with borderline cytology in either group were retested at 6 and 12 months; if persistently positive they were referred to colposcopy. Women in the intervention group with a positive hrHPV test and normal cytology were retested at 12 months. If the positive hrHPV result persisted, they were offered colposcopy or repeat testing at 24 months. Women with positive hrHPV testing at 24 months were referred to colposcopy. Loss to followup before the second round of screening was 33.2 percent in the

intervention group and 34.2 percent in the control group. In Round 1, CIN3+ was detected in 1.3 percent of women in the intervention group and 1.3 percent of women in the control group. The Round 1 CIN3+ RR was 0.96 (95% CI, 0.74 to 1.23). Round 2 detection of CIN3+ was 0.3 percent of women in the intervention group and 0.4 percent of women in the control group with an RR of 0.76 (95% CI, 0.43 to 1.34). Cumulative detection of CIN3+ was 1.5 percent of women in the intervention group and 1.6 percent in the control group. The cumulative RR for CIN3+ after two rounds of screening was 0.91 (95% CI, 0.73 to 1.15) (**Table 11**). After the second round of screening, all results were revealed; under a revised consent and protocol a third round to testing was conducted. Due to loss of randomization, protocol changes, and further loss to followup those results were not included in this review.[138]

In the good-quality POBASCAM trial, Rijkaart and colleagues randomized 44,938 women aged 29 to 61 years to one round of cotesting with hrHPV with the GP5+/6+ PCR enzyme immunoassay testing and conventional cytology (19,999 women in the intervention group), or conventional cytology alone (20,106 women) with blinded hrHPV testing.[122, 140, 141] After this single round of screening, followup testing 4 to 6 years later included cotesting with hrHPV GP5+/6+ PCR enzyme immunoassay and conventional cytology tests for all women. Women who had normal cytology with a hrHPV+ test result had repeat testing at 6 and 18 months. Women with moderate dyskaryosis or worse (HSIL+) in either group were referred for colposcopy and biopsy. Women in the intervention group with less than HSIL on cytology underwent repeat cytology and hrHPV testing at 6 months. If hrHPV was positive they were referred to colposcopy and biopsy, if not, testing was repeated at 18 months. Overall loss to followup from all causes was 16.5 percent and was similar between arms. In Round 1 of screening, CIN3+ was detected in 0.9 percent of women in the intervention group compared with 0.7 percent of women in the control group. The RR was 1.15 (95% CI, 0.92 to 1.43). At Round 2, CIN3+ was detected in 0.4 percent of women in the intervention group compared with 0.6 percent of women in the control group with an RR of 0.73 (95% CI, 0.55 to 0.96). With 9 years of followup after the two rounds of screening, and the second round including hrHPV testing for all subjects, the RR for CIN3+ in the intervention group was 0.96 (95% CI, 0.81 to 1.13) (**Table 11**). Detection of CIN3+ was 259 (1.3%) in the intervention group compared with 272 (1.3%) women in the control group.

Additional followup data from the POBASCAM trial was recently published in a report by Dijkstra and colleagues.[141] Outcomes for initially hrHPV negative women (intervention group) and cytology negative women (control group) were reported after 14 years of followup, through the national network of cervical histology and cytology. At Round 3 of screening, participants in both groups were managed based on cytology results. The authors reported outcomes of analyses that were not prespecified, for women who were cytology negative and hrHPV negative, and cytology positive and hrHPV negative in the intervention group and compared them to cytology negative women in the control group; HPV negative women had lowest rates of CIN3+ (**Appendix F Table 4**). The relative risks for these subsets in the intervention versus control groups for CIN3+ were not significantly different from 1.0.

ICC is a rare outcome in screened populations, and the trials summarized above had so few cases that meaningful statistical comparisons between arms was not possible. To examine the impact of hrHPV testing on ICC incidence in cervical cancer screening trials, Ronco and colleagues

conducted an IPD meta-analysis of five trials: four trials of cotesting (NTCC Phase I, SWEDESCREEN, ARTISTIC, and POBASCAM) and single trial of primary hrHPV testing (NTCC Phase II).[130] Participant data were pooled although these trials had distinctly different screening protocols, screening intervals, and hrHPV test types. Cancer ascertainment was performed at the individual trial level with no additional case review. Followup duration ranged from 5 to 12 years. Details of included study results are shown in **Table 14**. A total of 176,464 women with 1,214,415 person-years of followup were included with 107 cases of ICC in a median followup period of 6.5 years. After 8 years of followup, cumulative detection of ICC was 46.7 per 100,000 in the hrHPV screened women compared with 93.6 per 100,000 women in the control groups. With a fixed effects model, the overall pooled rate ratio for ICC in the hrHPV screened women was 0.60 (95% CI, 0.40 to 0.89). The I^2 test for statistical heterogeneity was not significant (0.0%, p=0.52). A random effects model gave a similar estimate of 0.61 (95% CI, 0.41 to 0.91). When limited to women whose baseline (entry) screening test was negative, the rate ratio was 0.30 (95% CI, 0.15 to 0.60).

Numerous reports have been published on a cohort of women who received cotesting at Kaiser Permanente Northern California (KNPC), a large health maintenance organization (**Table 9; Appendix Tables 5** and **6**).[124, 142-144] The number of women included in the cohort varied depending on the research question, the continuity of the screened population, selected characteristics of participants, and the number of rounds of screening considered. A study on cotesting over time in the same cohort of women was included to add representation of the United States population, and a larger but less continuous KPNC cohort substudy provided age-stratified comparisons (presented below). The cohort had no comparison group, but this large, U.S.-based study did report outcomes on a group of 331,818 women aged 30 years and older who underwent initial cotesting with conventional cytology and HC2 hrHPV testing between 2003 and 2005 (prevalence screen) with cumulative outcomes up to 6 years from enrollment.[124] They reported incidence screening outcomes on a group of 195,975 women with initial negative cotesting results who underwent a second cotesting round 3 years later. Of the 331,818 women, 24,849 women (7.5%) had an hrHPV+ test result or abnormal cytology result. 2,310 (0.7%) cases of CIN3+ were detected including 87 (0.03%) cases of ICC (**Table 15**). Among the 195,975 women with initial negative cotesting who had repeat screening 3 years later, 102 (0.05%) cases of CIN3+ were detected including 13 (0.01%) cases of ICC. A subsequent report on women with hrHPV+ test results and negative cytology in the Kaiser cohort extended inclusion through 2010. In this group of 32,374 women who were followed for variable durations after testing, CIN3+ was detected in 753 (2.3%) women.[143]

A German prospective observational cohort study included 19,795 women who underwent cotesting with conventional cytology and HC2 testing with a 5-year screening interval.[125, 129] No comparison group was included. Women with abnormal cytology and negative hrHPV testing, and those with positive hrHPV testing and normal cytology underwent repeat cytology at 6 months and hrHPV testing at 12 months with referral to colposcopy for any abnormal results. The investigators reported interim outcomes of 4,067 women screened in the first and second rounds for the same time interval beyond screening. CIN3+ was detected in 0.87 percent of women in Round 1 compared with 0.05 percent of women in Round 2, suggesting a declining risk over cotesting screening rounds. However, without a cytology-only comparison group, the incremental benefit of cotesting could not be assessed.

KQ 1a. Does the Effectiveness of hrHPV Testing to Reduce Cervical Cancer Outcomes Vary by Subpopulation?

Age

Screening With Primary hrHPV Testing

In the trials of primary hrHPV screening, subjects were eligible to start screening at age 25 years. Screening ended at age 60 years for NTCC Phase II, and at age 65 for the HPV FOCAL and FINNISH trials (**Table 5**). Results for these trials were stratified by age for women older (**Table 7**) and younger than age 35 years (**Table 8**). The NTCC Phase II trial included 13,725 women under age 35 years, and 35,471 women 35 years or older who were followed over two rounds of screening at 3 year intervals for a maximum followup of 7 years.[1, 2] hrHPV test positivity rates were substantially higher in women under age 35 years (13.1%) compared with women 35 years or older (5.8%). In contrast, rates of abnormal cytology were more similar across age groups, though still higher in women under age 35 years (4% vs. 3.1%). Cumulative CIN3+ rates were also higher in women younger than 35 years (IG: 0.7%, CG: 0.3%) compared with women 35 years or older (IG: 0.3%, CG: 0.2%). Detection of CIN3+ was highest in the intervention group in Round 1, particularly for women under 35 years (RR, 4.00 [95% CI, 2.07 to 7.73]) (**Table 8**) compared with women 35 and older (RR, 2.37 [95% CI, 1.44 to 3.89]) (**Table 7**). In Round 2, it was similarly lower for the intervention group in both age groups, with a RR of 0.20 (95% CI, 0.05 to 0.93) for women under 35 years (**Table 8**) and RR of 0.23 (95% CI, 0.07 to 0.82) for women 35 and older (**Table 7**). Over both rounds of screening, the RR for CIN3+ was 2.19 (95% CI, 1.31 to 3.66) in women under age 35 years (**Table 8**), and 1.57 (95% CI, 1.03 to 2.40) for women over age 35 years (**Table 7**).

The HPV FOCAL trial has published results from the initial round of screening and from the safety arm at 24 months.[127, 133, 134] Among the 4,849 women under age 35 years, Round 1 CIN3+ detection rates were 2.4 percent in the intervention group, compared with 1.7 percent for women years in the control group (**Table 8**). Round 1 CIN3+ rates among women aged 25 to 29 years were 3.1 percent in the intervention group, the highest of all age groups within the HPV FOCAL trial, compared to 1.7 percent in the control group. No other trial reported specifically on this age group. Among the 20,394 women aged 35 years or older, CIN3+ detection rates were 0.5 percent in the intervention group compared with 0.3 percent in the control group (**Table 7**). When stratified by age, differences in Round 1 CIN3+ detection between the intervention group and control group were not statistically significant. At two years, cumulative CIN3+ detection rates for women aged 25 to 29 years were 3. percent and 1.4 percent for women aged 30 to 34 years in the safety arm compared to 2.7 percent for women aged 25 to 29 years and 1.7 percent for women aged 30 to 34 years in the control arm.[145] Rates among women aged 35 and older were 0.4 percent and 0.3 percent, respectively.

The FINNISH trial included 22,262 women under age 35 years and 109,932 women aged 35 to 65 years who were screened with one round of hrHPV testing with cytology triage compared with conventional cytology, and followed up for 5 years.[126] CIN3+ rates were higher in the intervention group for women younger than 35 years (2.3% vs 1.9%) (**Table 8**). The RR for CIN3+ detection in the intervention group for the younger age group was 1.83 (95% CI, 1.21 to

2.78). CIN3+ rates were much lower overall in women aged 35 years and older (less than 0.3% in both the intervention and control groups) but still more frequently detected in the intervention group (RR, 1.56 [95% CI, 1.18 to 2.04]) (**Table 7**).

No studies provided data on race/ethnicity, screening history, hrHPV immunization status, and socioeconomic status for primary hrHPV testing.

Screening With hrHPV Cotesting

Three trials of hrHPV cotesting reported on outcomes by age group (**Tables 12** and **13**). The SWEDESCREEN trial recruited only women aged 32 to 38 years; overall results of that trial are reported above.[121, 136] NTCC Phase I included 11,810 aged 25 to 34 years.[1, 131, 132] Over two rounds of screening, 17.4 percent of 6,002 women in the intervention group had an hrHPV+ or ASC-US+ test result compared with an ASC-US+ rate of 4.5 percent of 5,808 in the control group. Rates of CIN3+ were similar between groups in all rounds: 0.4 percent in Round 1 and 0.1 percent in Round 2 in both groups. Cumulative CIN3+ rates were 0.5 percent in the intervention group and 0.6 percent in the control group, with an RR for CIN3+ overall of 0.91 (95% CI, 0.56 to 1.48) (**Table 13**). Among the 33,364 women enrolled from aged 35 to 60 years, 17.1 percent of 16,706 women in the intervention group were hrHPV+ or ASC-US+ compared with 3.6 percent of 16,658 women having ASCUS+ in the control group. CIN3+ detection was slightly higher in the intervention group in Round 1 (0.3% compared with 0.2% in the control group) and lower in Round 2 (0.03% in the intervention group compared with 0.07% in the control group). Cumulative CIN3+ rates were 0.3 percent in both the intervention group and control group, with an RR of 1.30 (95% CI, 0.87 to 1.19) (**Table 12**).

The ARTISTIC trial reported outcomes of 5,166 women aged 20 to 29 years.[119, 137-139] Only results of Round 1 were reported by age group. CIN3+ detection was 3.0 percent of 3,879 in the intervention group compared with 3.3 percent in the control group. The CIN3+ RR for Round 1 in women aged 20 to 29 years was 0.92 (95% CI, 0.65 to 1.31) (**Table 13**). Among 19,344 women aged 30 to 64 years, 10.6 percent of 14,507 women in the intervention tested hrHPV positive. The Round 1 detection of CIN3+ was 0.8 percent of 14,507 women in the intervention group and 0.8 percent of 4,837 women in the control group, with an RR of 1.12 (95% CI, 0.71 to 1.47) (**Table 12**).

The POBASCAM trial reported outcomes for 6,267 women aged 29 to 33 years over two rounds of screening at 4- to 5-year intervals.[122, 140, 141] Of 3,139 women in the intervention group, 12 percent had a hrHPV+ test result. In Round 1, CIN3+ detection was 2.2 percent of 3,139 women in the intervention group compared with 1.9 percent of women in the control group. In Round 2, CIN3+ detection was 1.1 percent for women in the intervention group compared with 1.3 percent in the control group. Cumulative CIN3+ detection was 3.3 percent in the intervention group compared with 3.4 percent in the control group with an RR of 0.97 (95% CI, 0.74 to 1.27) (**Table 13**). Among 33,838 women aged 34 to 56 years, 4 percent of women in the intervention group were hrHPV+. CIN3+ was detected among 0.6 percent of 16,860 women in the intervention group compared with 0.5 percent of 16,978 women in the control group in Round 1. In Round 2, CIN3+ was detected in 0.3 percent of the intervention group compared with 0.5 percent in the control group. Cumulative CIN rates were 0.9 percent in the intervention group

compared with 1.0 percent in the control group with an RR of 0.95 (95% CI, 0.76 to 1.18) (**Table 12**).

A large (n = 1,307,528), age-stratified cohort of KPNC patients screened with hrHPV cotesting found 5-year CIN3+ risk was highest among women aged 35 to 39 years and 60 to 64 years[124] (**Table 16**). Gage and colleagues recently published an age-stratified analysis of 1,313,128 women at KPNC who were screened for cervical cancer from 2003 to 2013.[142] Women aged 21 to 29 years were screened with cervical cytology while women aged 30 to 64 years were screened with cotesting. Cumulative risks of CIN3+ were reported based on age and cytology finding (**Table 16**). Women with normal cytology and hrHPV+ test results had repeat cotesting at 12 months. The cumulative incidence of CIN3+ (including baseline screening results) was higher for women aged 21 to 29 years at 3 and 5 years (0.4%) compared to women aged 30 to 64 years (0.3%). The 5-year risk of CIN3+ was highest for women aged 25 to 29 years (1.23 [95% CI, 1.09 to 1.39]), and lowest for women aged 50 to 64 years (0.25 [95% CI, 0.22 to 0.28]).

Screening History

Screening history was not described for the RCT participants or the Italian or KPNC cohort studies. Only one study of unscreened women met inclusion criteria. A prospective single cohort study from Spain described the outcomes of initial cotesting with HC2 and cytology (primarily conventional) in a population of 1,832 women older than 39 years with no record of cervical cytology in the previous 5 years.[123] Women were referred to colposcopy if either test was positive. No comparison group was included. Followup continued over 5 years; 338 women over age 65 years with negative testing were excluded from further followup. Of 1,494 remaining women, 767 (51.3%) completed followup. Of the initial group, 101 women had a hrHPV+ test result at baseline and 40 women had abnormal cytology (16 of these also were hrHPV+) (**Table 17**). By the last followup, seven women were diagnosed with CIN3, and two women had been diagnosed with ICC (CIN3+ rate, 9/1,832 [0.5%]). All nine women had a hrHPV+ test result at baseline; six had abnormal cytology results at baseline, including both women with ICC. Forty-nine percent of women were lost to followup; loss to followup was greater among women who tested negative on initial screening ($p<0.05$).

No studies of cotesting provided data on race/ethnicity, hrHPV immunization status, and socioeconomic status.

KQ 1b. For Each Primary Screening Strategy, How Does the Rescreening Interval Relate to Future Cancer Incidence or Progression?

Data from trials are not adequate to address outcomes of different rescreening intervals, due to lack of data from direct comparisons of intervals or consistent application of initial screening strategies for more than one screening round. Only one trial (HPV FOCAL) directly compared different rescreening intervals (2 years for cytology or primary hrHPV testing versus 4 years for primary hrHPV testing), and findings of the interval comparisons have not yet been published. Rescreening intervals in the completed trials ranged from 2 to 4 years for primary hrHPV testing; in trials of cotesting, rescreening intervals were 3 years with the exception of POBASCAM, with

a rescreening interval of 5 years. CIN3+ outcomes in POBSCAM were within the range of outcomes from cotesting trials with 3 year screening intervals. No included trials had more than two rounds of screening. Only the ARTISTIC trial had two screening rounds using the assigned screening protocol for each group. All other trials did one round of randomized screening and at subsequent rounds women either all received cervical cytology or all received cotesting.

KQ 1c. Does the Appropriate Rescreening Interval for Each Primary Screening Strategy Vary by Subpopulation?

No data were available to address rescreening intervals by subpopulation.

KQ 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?

Summary

None of the included trials reported on or were adequately powered to assess uncommon harms that can occur as a result of biopsy of a positive screening result or treatments of cervical lesions, diagnosed after colposcopy. Colposcopy rates were at least twice as high with hrHPV testing, indicating a higher relative burden of testing, and potential differences in the downstream consequences of treatment. Similarly, the test positivity rates and false positive rates of different screening interventions can be an indication of the burden of screening and the risk of downstream harms of treatment. Because of the potential for CIN to regress, the concept of overdetection is relevant to cervical cancer screening.

Test positivity rates were higher in the intervention arm for both hrHPV primary and hrHPV cotesting, particularly for the prevalence screening round. The FPR was also higher in the intervention arm for the first screening round in the five trials reporting sufficient data for this comparison. The FPR at a second round of screening was similar between arms in one trial of cotesting, but remained higher in the IG for another cotesting trial (with high loss to followup). One trial of cotesting reported colposcopy referral rates for more than one round of screening, with higher rates in the intervention arm at Round 1, and more comparable rates at Round 2 (with high loss to followup). Two of the three trials that tested a hrHPV primary screening strategy had similar rates of colposcopy in the intervention and control arms, but in one hrHPV primary screening trial and all trials of cotesting, colposcopy referrals were higher for the intervention arm. None of the trials that tested a hrHPV primary screening strategy reported the test positivity or colposcopy rates for a second round of screening, and initial screening strategies were not maintained for a second round of testing. This limited comparative evaluation of harms beyond a prevalence screen. None of the included studies reported harms occurring from the screening test itself or the diagnostic testing that followed a positive screen.

There was evidence that a hrHPV positive screening result is associated with greater psychological harm than a positive cytology result, including increased anxiety and distress, and

lower satisfaction with past and current sexual partners.

The included studies did not provide evidence on differences in adverse effects by any patient characteristic or risk factor other than age. Test positivity and colposcopy rates were higher for younger women (less than 35 years old and less than 30 years old) with hrHPV screening strategies; the difference was even more pronounced in one trial reporting rates of colposcopy for women aged 25 to 29 years.

The available trial evidence did not address differences in adverse effects by rescreening interval because none of the included studies was designed to directly compare intervals, and the between-study differences in design, screening strategies, and followup protocols are too great to support inferences about the effects of interval on harms. We could not ascertain from the available evidence how the screening interval and the type of screening strategy related to the potential harms of missed cancer cases and overdetection.

Description of Included Studies

The same seven RCTs and three observational cohort studies described above[110,124, 125, 128] and included for KQ1 also reported harms outcomes included for KQ2 (**Tables 5** and **9**). An additional cross-sectional study on psychological harms was also included.[120] Harms or adverse events associated with hrHPV screening strategies were compared to those associated with cytology-only screening programs. We sought evidence on harms associated with the screening test itself, the test performance of screening (i.e., false negative and false positive results), and the procedures conducted as a result of screening (i.e., colposcopy and biopsy). Evidence on the psychological effects of screening was also included, such as potential harms of screening related to reduced quality of life, anxiety and distress, partner discord, stigma, and labeling.

As reported for KQ1, the quality of many of the included studies was rated as fair due to problems with attrition, protocol changes, and blinding of outcome assessors. In addition, the overall body of evidence has shortcomings for drawing conclusions due to the limited number of randomized rounds of screening available for comparisons. Several of the trials changed screening or followup protocols after the first round of screening, making it impossible to draw conclusions about harms of screening beyond the prevalence screen. Outcome reporting on colposcopy and biopsy rates was also inconsistent, and none of the trials reported on adverse events associated with the screening tests or the diagnostic and treatment procedures undertaken as a consequence of screening.

Test Positivity, False Positive Rate, Colposcopy, and Biopsy

Screening with primary hrHPV testing. In NTCC Phase II, any woman with an hrHPV+ test result in the intervention screening condition was referred to colposcopy, as were women in the cytology alone control condition with ASC-US+ or LSIL+, according to the study protocol.[1, 2] The test positivity rate at the first round of screening was 7.9 percent (1,936/24,661) for the hrHPV screening intervention arm. In the control condition 3.4 percent (825/24,353) had positive cytology results (ASC-US+) (**Table 6**).The FPR for CIN2+ was higher (IG: 7.4%, CG: 3.2%) (**Appendix F Table 7**). Accordingly, 7.9 percent of women in the intervention group were

referred to colposcopy, compared with 2.8 percent of women in the cytology arm (**Table 6; Appendix F Table 8**). The rate of referrals to colposcopy for the cytology arm was lower than would be expected per trial protocol but was not explained. Most women referred to colposcopy underwent the procedure (IG: 93.6%, CG: 90.6%). Biopsies were taken from 44 percent of hrHPV screening arm colposcopies and 52 percent of the cytology control group colposcopies. More women in the intervention arm had a biopsy based on the prevalence screen (IG: 3.2%, CG: 1.3%). At Round 2 both groups received conventional cytology alone and colposcopy rates were not reported; therefore, the NTCC Phase II trial does not provide evidence on hrHPV-related colposcopy and biopsy harms beyond one round of screening and followup.

The HPV FOCAL trial reported test positivity, colposcopy and biopsy rates over one round of screening with 4 years of followup data, providing a comparison between hrHPV primary screening and LBC primary screening.[127, 133-135] More women randomized to the hrHPV primary screening intervention had a positive initial test: 8.2 percent (1,290/15,744) had hrHPV+ results in the intervention, and 3.6 percent (334/9,408) had ASC-US+ results in the LBC comparison arm (**Table 6**). Nearly twice as many women in the intervention group were referred to colposcopy than the control group (5.9% vs. 3.1%) on the basis of initial results or hrHPV/LBC triage, and nearly all attended (IG: 97%, CG: 96%). The number of women undergoing a biopsy and the FPR for CIN2+ has not been reported for this trial (**Appendix F Table 8**).

In the FINNISH trial, hrHPV test positivity was 8 percent (4,971/62,106) in the intervention group and 7 percent (4506/65,747) for ASC-US+ in the cytology comparison group.[126] The FPR for CIN2+ was similar between the two study arms (IG: 7.2%, CG: 6.5%) (**Appendix F Table 7**). Of women screened, 1.2 percent (796/66,410) of those in the intervention arm were referred for colposcopy compared with 1.1 percent (755/65,784) in the cytology comparison group (**Table 6; Appendix F Table 8**). The number of colposcopies attended and biopsies conducted were not reported.

An Italian population-based cohort (n = 48,751) provides supplemental observational evidence on test positivity and colposcopy referrals for a primary hrHPV screening with cytology triage and a 3 year screening interval.[128] The results are qualitatively consistent with trial evidence, finding hrHPV test positivity was halved at the second round of screening overall (6.4% vs. 3.5%) (**Table 10**). Similarly, following ASC-US triage (with 1-year retesting for hrHPV+/cytology-), colposcopy referrals were halved from Round 1 to Round 2 (4.4% vs. 2.2%). The rural study setting was thought to account for the lower rates of hrHPV positivity in this study population.

Screening with hrHPV cotesting. Test positivity rates were higher in the hrHPV cotesting arms compared with cytology alone after one round of screening for all included trials testing this comparison (**Table 11**). The protocol for positive test results differed between trials such that different combinations of results from cotesting had different implications for followup (**Appendix F Table 2**). In ARTISTIC, for example, positive cytology resulted in immediate colposcopy for HSIL+ or retesting (ASC-US or LSIL), and hrHPV+ test results with normal cytology had a repeat hrHPV test at 12 months.[119, 137-139] In contrast, the SWEDESCREEN trial referred hrHPV+ with normal cytology to a repeat screen but referred ASC-USor LSIL to immediate colposcopy or a repeat screen at 12 months, depending on the community practice..[121,

All trials reported test positivity at the first round of screening, and two of the trials, ARTISTIC and POBASCAM, also reported test positivity at a second round of screening (**Table 11**). In the NTCC Phase I trial, 12.5% (2,830/22,708) of women in the intervention group tested positive (hrHPV+ or ASC-US+); 9 percent were hrHPV+ (2,021/22,708).[1, 131, 132] The test positivity rate (ASC-US+) in the control group was 4 percent (855/22,466) of screened women. The FPR for CIN2+ was higher in the intervention group (IG: 12.3%, CG: 3.5%) (**Appendix F Table 7**). In SWEDESCREEN, the test positivity (for hrHPV+) was 7 percent (433/6,257) in the intervention group and 2 percent (150/6,270) in the control group. The FPR in the control group was 1.2 percent, and was not calculable for the intervention group. In ARTISTIC, the test positivity rate in the intervention group was 22 percent (4,019/18,386), with 16 percent (2,860/18,386) testing hrHPV positive. In the control group, test positivity was 13 percent (786/6,124). At the second round of screening, after 3 years, 11 percent (1,258/11,862) tested positive in the intervention group, and 5 percent (210/3,928) screened positive in the control group. The FPR in ARTISTIC was also higher in the intervention arm at Round 1 (IG: 19.9%, CG: 10.9%) and at Round 2 (IG: 11.2%, CG: 4.6%) (**Appendix F Table 7**).

In POBASCAM, test positivity was 7 percent (1,406/19,999) in the intervention group and 4 percent (706/20,106) in the control group.[122, 140, 141] At Round 2, test positivity was the same for both study arms, at approximately 4 percent (IG: 3.8% 742/19,579; CG: 3.9% 774/19731) (**Table 11**). The FPR was higher in the intervention than the control arm at Round 1 (IG: 5.8%, CG: 2.6%), but similar at Round 2 screening, but slightly higher in magnitude than at Round 1 (IG: 6.4%, CG: 6.5%) (**Appendix F Table 7**).

In the NTCC Phase I trial, colposcopy referral rates were higher in the intervention arm than in the control cytology-only arm (IG: 10.9%, CG: 3.3%) (**Appendix F Table 8**).[1, 131, 132] Of those referred, 94 percent in the intervention and 91 percent in the control group received a colposcopy. In the ARTISTIC trial, referral to colposcopy was similar between study arms at Round 1 (IG: 6.8%, CG: 5.2%), and lower at Round 2 but similar between groups (IG: 2.7%, CG: 2.1%).[119, 137-139] The proportion of women attending colposcopy and undergoing biopsy was not reported (**Appendix F Table 8**). Colposcopies and biopsies were not reported in the SWEDESCREEN or POBASCAM trials.

The IPD meta-analysis obtained additional data from these cotesting trials suggests that the overall biopsy rates for all screened women were similar in the intervention and control groups (**Table 14**).[130] In the NTCC trials (combining Phase I and II results), however, biopsy rates were twice as high in the intervention arm where hrHPV+ results were referred directly to colposcopy. The IPD meta-analysis did not report colposcopy rates.

Data published on a cohort of women who received cotesting at KPNC provided United States estimates of screening test performance observed in population with access to coordinated health care (**Table 9**).[124, 142-144] They reported test positivity rates on a group of 195,975 women with initial negative cotesting results who underwent a second cotesting round 3 years later. Of the 331,818 women, 24,849 women (7.5%) had a hrHPV+ test result or abnormal cytology result, but the colposcopy rates for test positives were not reported (**Table 15**). A German prospective

observational cohort study included 19,795 women who underwent cotesting with conventional cytology and HC2 testing with a 5-year screening interval.[125, 129] No comparison group was included. Women with abnormal cytology and negative hrHPV testing, and those with positive hrHPV testing and normal cytology underwent repeat cytology at 6 months and hrHPV testing at 12 months with referral to colposcopy for any abnormal results. At the first round of screening, 4 percent (765/19,795) of women were referred to colposcopy and at Round 2, with a much diminished followup population, an additional 1 percent (41/4,067) of were referred to colposcopy (**Table 17**).

False Negative Rates

The occurrence of ICC among women who screened negative in earlier rounds of screening provides some indication of the extent to which a screening program might miss cases, owing to a host of factors that comprise the strategy, including the triage approach, rescreening intervals, and underlying features of the screened population (age, disease prevalence), as well as technical factors relating to test sensitivity and laboratory quality. Estimating false negative rates is a challenge since women with negative results from hrHPV and cytology screening do not undergo colposcopy. Future rounds of screening may detect ICC, otherwise identification of false negatives relies on registry data, with cases of cancer more likely to be captured after longer followup periods.

Screening with primary hrHPV testing. The incidence of ICC among women with negative screening test results was reported at each screening round for all included trials (**Appendix F Table 9**). In NTCC Phase II there were no ICC cases (and no CIN3) among screen negative women in either group in followup on the first round of screening (3.5 years maximum).[1, 2] The FINNISH trial reported ICC among screen negative women in 0.01 percent (5/57,135) of the intervention group and 0.003 percent (2/61,241) of the control group participants after one round of screening with 5 years of followup.[126] Data on ICC among screen negative women were not yet available for HPV FOCAL.

Screening with hrHPV cotesting. In NTCC Phase I, no ICC was observed among screen negative women in either screening arm after the first round of screening and 3.5 years of followup.[1, 131, 132] SWEDESCREEN did not report ICC rates among screen negative women.[121, 136] For ARTISTIC, with 3 years intervals, there were no cases of ICC among screen negatives in either trial arm for either round of screening.[119, 137-139] In POBASCAM, with longer screening intervals than ARTISTIC (5 years), there was one case of ICC detected in a screened negative woman in the control group and no cases in the intervention group during the trial.[122, 140, 141] Long-term followup data on ICC among screen negatives was available only from POBASCAM (**Appendix F Table 4**). With 14 years of followup, differences in the cumulative incidence of ICC among screen negative women were not statistically significant between study arms. The false negative rate for ICC was not reported for the control arm in the IPD meta-analysis, but eight of 19 cancers in the pooled intervention arms were hrHPV negative at baseline screening.[130]

Psychological Effects

We identified two studies that reported on the psychological effects of hrHPV cotesting (i.e., anxiety and distress).[120, 139] We did not identify any studies that addressed labeling, stigma, partner discord or quality of life. No studies reported on the psychological effects of primary hrHPV testing.

In ARTISTIC, samples of consecutive women aged 20 to 64 years received information leaflets and questionnaires approximately 2 weeks after receiving cervical screening results. Women randomized to the revealed arm (intervention) received their hrHPV and cytology results while women in the concealed arm (control group) only received their cytology results. Of 3,582 questionnaires sent, 2,508 (70.0%) were returned (1,904/2,700 in the intervention group and 604/882 in the control group). Measures collected were the General Health Questionnaire [GHQ-28] to measure psychological distress, the Sexual Rating Scale [SRS] to measure sexual satisfaction, and the Spielberger State-Trait Anxiety Inventory [STAI] to measure anxiety. The two groups did not differ in distress or anxiety after receiving their screening results (**Table 18**), however, women in the intervention group reported lower sexual satisfaction than the control group (p=0.042). There were also no differences between groups among women with ASC-US/LSIL cytology in anxiety, distress, or sexual satisfaction. Women with normal cytology who were hrHPV+ in the intervention group had lower sexual satisfaction ratings than women with normal cytology who were hrHPV+ (concealed) in the control group (p=0.003). Observational comparisons of women in the intervention arm showed hrHPV+ (revealed) women with normal cytology were at higher risk of psychological distress (Odds ratio [OR], 1.70 [95% CI, 1.33 to 2.17]) with higher GHQ scores (age-adjusted mean difference, 1.43 [95% CI, 0.75 to 2.10]) than women who were hrHPV- with normal cytology; they also reported higher scores for state (age adjusted mean difference, 2.90 [95% CI, 1.40 to 4.39]) and trait (age-adjusted mean difference, 1.53 [95% CI, 0.16 to 2.92]) anxiety than hrHPV- women with normal cytology. Women who were hrHPV+ with ASC-US/LSIL cytology reported lower sexual satisfaction ratings than women who were hrHPV- with ASC-US/LSIL cytology (age-adjusted mean difference, 8.66 [95% CI, 4.30 to 130.2]). Similar trends were seen between control group women who were hrHPV+ (concealed) and hrHPV- (data not shown).

A cross-sectional study by McCaffery and colleagues evaluated the psychological effects of hrHPV cotesting in 428 women aged 20 to 64 years.[120] All women were mailed the results of their tests and provided a self-report questionnaire one week after receiving test results to assess psychosocial outcomes including anxiety (STAI), distress (Cervical Screening Questionnaire), and feelings about sexual relationships. Three hundred and eleven (71%) returned the questionnaires and 271 (63%) were included in the analyses; 69 (25.5%) screened positive for hrHPV and 40 (14.8%) had an abnormal or unsatisfactory cytology smear. Among women with normal cytology, women who were hrHPV+ were significantly more distressed (p<0.0001) and anxious (p<0.0001) than women who were hrHPV- (**Table 19**). Among women with an abnormal or unsatisfactory cytology smear, women who were hrHPV+ were significantly more distressed (p=0.002) but similarly anxious (no significant difference between groups). Women who were hrHPV+ also tended to have worse feelings about their current, past and future sexual partners than women who were hrHPV- regardless of cytology result.

KQ 2a. Do Adverse Effects of hrHPV Compared to Cytology Screening Vary by Subpopulation?

Age

Test positivity rates were higher at younger ages for hrHPV primary and cotesting interventions, as described above in the results for KQ1. Age stratified data on colposcopy was available for all three primary hrHPV screening trials, but only one of the hrHPV cotesting trials.

In trials of primary hrHPV screening, differences in colposcopy referral between study arms were more pronounced among younger women. Among women aged 35 to 60 in the NTCC Phase II trial, 6 percent (1,029/17,724) of women in the hrHPV screening intervention and 3 percent (435/17,747) of women in the cytology alone control condition were referred to colposcopy at Round 1 screening (**Table 7**).[1, 2] In the younger age group (25 to 34 years) in the NTCC Phase II trial, referral to colposcopy was more likely, particularly in the hrHPV screening arm: 13 percent (970/6,937) of women in the intervention group and 4 percent (270/6,788) in the control group were referred to colposcopy (**Table 8**). The HPV FOCAL trial provided additional data on the youngest women, with colposcopy rates reported for women aged 25 to 29 years and aged 30 to 34 years.[127, 133-135] Rates of colposcopy were highest among the youngest women assigned to the intervention group (hrHPV with LBC triage) in HPV FOCAL (19.9% of women screened) compared to those aged 30 to 34 years (174/1,612; 10.8%) and aged 35 to 65 years (487/12,810; 3.8%). In the FINNISH trial, colposcopy referrals were not as disparate between study arms, possibly owing to the cytology triage protocol.[126] Two percent of women aged 25 to 34 years were referred to colposcopy (IG: 257/11,191 [2.3%], CG: 210/11,071 [1.9%]) and one percent of women aged 35 to 65 years were referred (IG: 506/55,219 [0.9%], CG: 544/54,713 [1.0%]). In the Italian cohort,[128] higher test positivity rates were observed at Round 1 among women aged 25 to 29 years (14.8%) compared to women aged 30 to 64 years (5.5%), and colposcopy referrals were not reported by age (**Table 9**). Over half of participants in both age groups and in both screening rounds were no longer hrHPV+ when retested at 1 year following an hrHPV+ result with negative triage cytology.

Among the trials of hrHPV cotesting screening strategies, colposcopy referrals were reported by age only in NTCC Phase I (estimated from a figure) and in that trial, only for Round 1 screening.[1, 131, 132] In the cotesting arm, 12 percent of women aged 25 to 34 years and 11 percent of women aged 35 to 60 years were referred to colposcopy, whereas in the cytology arm, 4 percent of women aged 25 to 34 years, and 3 percent of women aged 35 to 60 years were referred. Notably, in this trial detection rates were not significantly different between arms by Round 2, and for the younger age group, were also not significant at Round 1 screening.

No included studies provided data on adverse effects of screening with hrHPV primary or cotesting by race/ethnicity or hrHPV immunization status.

KQ 2b. Do Adverse Effects Vary by Screening Strategy, Including by Rescreening Interval?

The screening intervals of included trials ranged from 3 to 5 years, but none were designed to test differences in colposcopy rates or false negatives with shorter and longer intervals within a trial (Appendix F Table 9). The longest maximum screening intervals tested were in the FINNISH trial126 (5 years) and the POBASCAM trial122, 140, 141 (4 to 5 years). The shortest intervals were tested in the ARTISTIC trial with two screening rounds at approximately 3 year intervals.119, 137-139 There were no ICC cases among women who had screened negative at the previous round. The longer intervals trials did identify ICC cases among women who had tested negative, but attribution to the interval is not certain because these trials had larger samples than ARTISTIC, and there were very few ICC cases overall. Specifically, in the FINNISH trial, there were five ICC cases (of 57,135 screened) in the intervention group and two ICC cases (of 61,241 screened) in the control group after a negative screening result at the first round of screening and 5 years of followup (maximum). The POBASCAM trial reported 13 cases of ICC among women screened with normal cytology in the control arm, and two cases of ICC among women with normal cotesting results (i.e., cytology normal, hrHPV negative) over two rounds of screening. In 14 additional years of trial followup there were no statistical differences in ICC cumulative incidence among screen-negative women, but numbers were low with four ICC cases observed among women screened hrHPV negative in the intervention group.

Chapter 4. Discussion

Summary of Evidence

Seven large randomized trials, three of primary testing and four of hrHPV cotesting contributed to the evidence comparing use of hrHPV testing for cervical cancer screening to cytology alone for detection of CIN3+ (**Table 20**). All trials were conducted in the context of organized screening programs, with heterogeneous screening strategies and followup protocols. Interpretation of trial findings was limited by the fact that after one round of screening, only one trial (ARTISTIC) maintained the same strategy over two rounds of screening. The trial evidence was supplemented with results of large cohort studies of hrHPV primary testing or cotesting over two screening rounds, however, none of the cohort studies had a comparison group screened with cytology only.

The evidence was generally consistent across trials with variable protocols and hrHPV test types in demonstrating that primary hrHPV testing increased detection of CIN3+ in the initial round of screening by as much as 2- to 3-fold. Only the NTCC Phase II trial of primary hrHPV testing, where all women with a positive hrHPV test were referred to colposcopy, had complete results from two rounds of screening (at Round 2 screening all women received cytology testing).[1, 2] In that study, CIN3+ detection in Round 1 was 3-fold higher in the hrHPV testing arm, and cumulative detection was 1.8-fold higher after the second round of screening.

Evidence was mixed in cotesting trials; in two of four trials round one CIN3+ detection was 1.2- to 1.3-fold greater for cotesting. By the second round of screening 3 to 5 years later, CIN3+ detection was lower in the hrHPV cotesting arm and higher in the cytology-only arm, such that cumulative CIN3+detection was similar between intervention and control study arms. Because no trial sustained the intervention and control group protocols beyond two screening rounds, evidence comparing the long-term outcomes of hrHPV primary testing or cotesting with cytology only is lacking.

Evidence on subgroups was limited to age and a single cohort study focused on previously inadequately or unscreened women. Women under age 35 years had consistently higher rates of hrHPV positivity and of CIN3+. Outcomes of hrHPV primary testing or cotesting between screening strategies by age were not notably different from the results of the overall study populations. In the relatively small single-cohort study of hrHPV cotesting for women in Spain not screened for at least 5 years, CIN3+ was detected in nine women, all were hrHPV positive but three women with CIN3 on biopsy had normal cytology findings.

The primary purpose of screening for cervical cancer is to reduce ICC morbidity and mortality. Because ICC is a rare outcome in countries with organized screening programs, no trial had sufficient power to examine cervical cancer incidence rates, and no trials reported on cervical cancer mortality. The individual participant data meta-analysis performed by Ronco et al pooled patients from five trials (combining one primary and four cotesting trials) and found a 40 percent lower incidence of ICC among patients screened with some form of hrHPV screening compared to cytology screening.[130] Each of these trials included different patient populations, and

employed different screening test and followup protocols, adding uncertainty to interpretation of pooled findings.

The same three hrHPV primary screening trials and four trials of hrHPV cotesting were the primary source of evidence for the comparative harms of cervical cytology screening relative to hrHPV testing. Harms of cervical cancer screening include false negative results and false positive results. False negative rates (which lead to ICC which could have potentially been prevented had precursors of ICC been discovered sooner) are approximated by assessing the proportion of women with invasive cancer in the screening interval or at a subsequent screening rounds, given the usually slow progression of cervical intraepithelial neoplasia. No primary testing trials, and only one trial of cotesting sustained the same screening protocol beyond one round, limiting comparison of false negative rates over multiple screening rounds. Among the trials of primary hrHPV testing, only the FINNISH trial reported cases of ICC among screen negative women five years after one round of screening; event rates were too low to ascertain differences, but there were five cases in the intervention (0.01%) and two cases in the control (0.003%) groups. In the trials of cotesting, two trials did not have any false negative ICC cases and one did not report on this outcome. The POBASCAM trial reported 13 cases of ICC among women screened with normal cytology in the control arm, and two cases of ICC among women with normal cotesting results (i.e., cytology normal, hrHPV negative) over two rounds of screening. In 14 additional years of trial followup there were no statistical differences in ICC cumulative incidence among screen-negative women, but numbers were low with four ICC cases observed among women screened hrHPV negative in the intervention group. In IPD-meta analysis, rates of ICC after a negative test between the control and intervention arms were not compared.

False positive results lead to unnecessary investigations with colposcopy and biopsy, and can result in women with CIN1 changes undergoing treatments and risking associated complications when these might have regressed spontaneously. For primary hrHPV screening, false positive rates in Round 1 of screening were similar between arms in the FINNISH trial but 2- to 3-fold higher in NTCC Phase II. In three trials of hrHPV cotesting reporting this outcome, false positive rates were 2- to 3-fold higher in the intervention groups for Round 1 screening. No primary screening trials and only two trials of cotesting reported false positive results from the second round of screening; rates were similar for both arms in POBSCAM but remained elevated for the intervention arm in ARTISTIC, which maintained the initial screening strategy over two rounds.

The primary hrHPV testing trials to date have reported colposcopies only for the first round of screening. Two of the three trials that evaluated hrHPV primary screening had similar rates of colposcopy in the intervention and control arms. The NTCC II primary testing trial referred all hrHPV+ women to colposcopy, generating colposcopy rates nearly three-fold higher in the intervention arm. Of the four cotesting trials, only two reported colposcopy rates. Colposcopies were more than 3-fold higher in the NTCC I intervention arm compared to the cytology only control arm. ARTISTIC reported colposcopy rates over two rounds of screening. Rates in the intervention arm were higher in both rounds, nearly two-fold at Round 1 and higher, but less discrepant at Round 2 (1.2-fold). Rates of treatment or treatment harms were not reported in the screening trials.

Once CIN2 or higher cervical abnormalities are identified, treatment generally follows, although the level of CIN for which treatment is recommended and type of treatment may vary depending on the clinical setting. Recommendations for treatment from the ASCCP and ACOG outline management algorithms depending on screening test results and abnormalities detected.[67, 146] A simplified description of these management strategies identifies women as having low, moderate, or high levels of CIN2+ risk based on initial colposcopy results, hrHPV type test results, and patient age.[147] Generally, for women at low risk, retesting in 3 years is recommended; at moderate risk retesting in 12 months is recommended; and at high-risk, treatment is recommended. Harms resulting from overtreatment can also be a consequence of screening, but the studies included in the review did not report on subsequent treatments or treatment harms.

Screening and Treatment-Related Harms

Our review included evidence on comparative psychological harms of screening strategies from two studies. Findings of these studies suggested that women undergoing hrHPV screening strategies had lower sexual satisfaction and greater psychological distress related to positive hrHPV test results compared to abnormal cytology. It is possible that women find it more distressing to be informed that they have a sexually transmitted virus than to be told that they have abnormal cells on their cervix; the connection to an STI may not always be communicated or apparent to patients receiving cytology results. Increased education of patients about the cause of abnormal cytology could reduce the observed differences, but closer to the higher distress level observed for hrHPV test results. A recent systematic review on the psychological consequences of CIN diagnosis and treatment also reported worse psychological and sexual function outcomes for women with CIN diagnosis and treatment compared with women with normal test results and for longitudinal comparisons of women before and after diagnosis and treatment.[155]

Evidence on potential harms of test positivity, diagnosis, and treatment are important to consider when evaluating the differences in detection rates of hrHPV screening strategies. Overall, the evidence from seven large RCTs was consistent that hrHPV primary or cotesting will detect more CIN3+ in a single screening round compared to cytology, and a similar rate of CIN3+ is detected by by cotesting over two screening rounds. In most trials where these outcomes were reported, hrHPV primary or cotesting led to higher test positivity rates and higher false positive rates. The evidence on these outcomes is strengthened by the studies' high subject-enrollment numbers and randomized design. Although not fully documented, it is likely that hrHPV testing led to higher rates of diagnostic testing and subsequent treatments.

In the United States, there is clinical variation in the treatment of CIN2+ lesions, but excisional treatments are most common for CIN2 and 3, primarily with loop electrosurgical excision procedure (LEEP) to remove lesions and obtain biopsies during colposcopic examination. Ablative techniques, which use cryo- or laser-therapy may be used to treat persistent CIN1 or CIN2 lesions that are amenable to the technique because of their size and position. Harms of treatment include pain and bleeding, which rarely requires vaginal packing or transfusion,[148, 149] and harms related to subsequent pregnancies. Cold knife conization was common before LEEP became available and remains in practice, although to a lesser extent. This procedure has been most clearly associated with perinatal mortality, preterm birth, low birth weight, and higher

caesarean section rates.[150, 151] While LEEP treatment was not significantly associated with adverse pregnancy outcomes in one comprehensive systematic review, the possibility of an association was not ruled out.[152] A recent Cochrane systematic review that included 15 studies (n=2,223,592) analyzed the effects of CIN treatment on fertility and early pregnancy outcomes. This review did not find a statistically significant association between having had a treatment and problems with conception. There were, however, significant associations between CIN treatment and later second-trimester miscarriage (RR, 2.60 [95% CI, 1.45 to 4.67]), ectopic pregnancy (RR, 1.89 [95% CI, 1.50 to 2.39]), and elective terminations (RR, 1.71 [95% CI, 1.31 to 2.22]). Notably, the authors of the review rated the evidence available to estimate these relationships as very low or low quality.[153] Authors of another systematic review have suggested that women with a history of CIN have a greater risk of preterm birth regardless of treatment type.[154]

A recent population-based cohort study in Norway estimated rates of preterm birth and spontaneous abortion associated with prior excisional procedures for cervical lesions. Norway has nearly complete registry data available on specific treatments for cervical lesions and on birth outcomes.[150] In a cohort of women with at least one singleton birth between 1998 and 2014, (n=545,243; births=943,321), the majority of treatments were excisional (99%), in women less than 30 years old (72%), and performed for grade CIN2 or CIN3 (95%). Preterm birth was more common among women with a treatment before childbirth (9.7%) compared with those without a treatment (5.3%), with an adjusted hazard ratio of 1.8 (95% CI 1.7, 2.0). The HR for LEEP was 1.5 (95% CI, 1.3 to 1.7), and was higher for laser conization (HR, 2.3 [95% CI, 2.0 to 2.5]) and cold knife conization (HR, 2.6 [95% CI, 1.3 to 5.3]).

Ongoing research has led to modifications in cervical cancer screening guidelines. These shifts in recommendations may lead to confusion among both women and clinicians, resulting in potential harms from overuse of screening and diagnostic tests, or harms from failure to recognize and followup important abnormal findings.

Limitations of the Review and Included Studies

This review was restricted by protocol to studies from highly developed countries (to increase applicability to the United States population) and to studies published in English. All of the RCTs included in this review were conducted in countries with robust, organized screening programs. Although screening history was not provided in any of the trials, it is likely that women enrolled in the trials were previously regularly screened with cytology. 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 women in the United States. For women in the United States participating in organized screening programs, the findings of this review are applicable, however, over 50 percent of women diagnosed with cervical cancer in the United States have not been screened in the prior 3 to 5 years.[156] The higher detection of CIN3+ in an initial screening round with hrHPV testing may provide more a more important benefit to women not able to participate in organized screening programs, since without such programs women may be less likely to return at regular intervals for screening. Mortality from cervical cancer in the United States is highest among black women and women of low socioeconomic status.[53, 157]

Studies included in this review did not provide evidence on race-ethnicity or socioeconomic status of participants, so we were not able to examine any relevant subgroup effects other than those based on age.

Important limitations of the evidence include lack of data on the primary outcome of cervical cancer mortality and limited data on cervical cancer incidence. Since cervical cancer is generally slow to develop and progress, and mortality from cervical cancer is a very rare outcome in countries with organized screening, the required size and duration of trials to study this outcome are impractical. A cluster RCT conducted in India did find a reduction in cervical cancer mortality after a single round of hrHPV testing compared with cytology, visual inspection with acetic acid, or a nonscreening control group.[158] This trial was excluded from this review as it was not conducted in a highly developed country.

As cervical cancer screening has become more widespread, the proportion of adenocarcinoma of the cervix appears to have increased.[159, 160] Some have proposed that hrHPV testing may improve early detection of adenocarcinoma and its precursors,[160] which is suggested by a lower RR for adenocarcinoma in the IPD meta-analysis,[130] while others have suggested that cytology may be more effective.[161] Due to the low incidence of cervical cancer in the included studies, it was not possible to evaluate any differences in detection of squamous cell versus adenocarcinoma of the cervix. The overall incidence of adenocarcinoma and its relative proportion among cervical cancers has increased concurrently with the advent of more widespread cervical cancer screening.[162] Whether early detection of adenocarcinoma will be reduced by increased use of hrHPV testing for cervical cancer screening remains unclear.

Heterogeneity of trial screening strategies and followup protocols prevented quantitative synthesis of the trial outcomes including harms. In addition to screening strategies, followup protocols for abnormal results have important influence on rates of false positive results and colposcopies. Comparative studies are needed of alternative followup protocols for abnormal screening results, which may influence the frequency of false positive and false negative results from screening.

Because evidence on comparative outcomes of screening strategies over more than two rounds of screening is lacking, conclusions based on the existing trial data do not provide insight into the effects of regular hrHPV testing as an ongoing screening strategy on outcomes in women screened at consistent intervals over many years. Whether one-time or intermittent hrHPV testing as a supplement to cytology screening could improve CIN3+ detection and reduce overall false positive results and unnecessary followup testing is unknown. Additional data on extended followup from trials in which subjects returned to regular screening cytology at the end of the trial could help to inform this question.

Evidence on the effects of screening at longer intervals (5 or more years) is limited to a single trial (POBASCAM). Only the FOCAL trial directly compared screening outcomes of hrHPV testing at different screening intervals (2 vs 4 years), but final results of this trial have not been published. All other trials of primary screening or cotesting screened at 2 to 3 year intervals. CIN3+ rates in these trials were low (highest cumulative detection rate 1.6%), with marked declines in detection in the second round of screening, supporting the clinical consensus on

screening with hrHPV primary or cotesting range not more frequently than every 3-5 years. A modeling study conducted for the USPSTF provides additional information on projected outcomes based on screening tests used, screening age range, and screening intervals.[163]

All trials and cohort studies included in this review used either the HC2 hrHPV assay or the GP5+6/6+ PCR-EIA assay (not approved in the United States). Several currently FDA approved hrHPV assays in the United States have not been evaluated in randomized clinical trials and have only partially met 2009 international expert clinical equivalency criteria, limiting the applicability of review findings to current clinical use of those assays.[64]

Finally, none of the trials or cohort studies included in this review provided outcomes for subgroups of women who had previously received the HPV vaccine. Applicability of these studies is limited for well-vaccinated populations of women who have only recently entered the age group for screening. Limited data from comparative registry studies of younger women (who had the opportunity for vaccination) suggest lower rates of CIN2+ in women previously vaccinated.[164, 165]

Future Research Needs

How hrHPV testing alone or with cytology cotesting performs over multiple screening rounds is not clear. Research is needed to further define the use of hrHPV testing alone and as cotesting at longer screening intervals over several rounds of screening, and to evaluate the effectiveness of intermittent cotesting combined with regular cytology screening. A potential risk of hrHPV testing alone for cervical cancer screening is failure of early detection of HPV negative cancers.[166] Such cancers appear to be very rare, and a large observational study of women with negative hrHPV tests documented a lower risk of future cervical cancer compared to women who were cytology negative,[124] but ongoing research on the outcomes of hrHPV primary screening in large populations over multiple screening rounds will further clarify this risk. Modeling will also be useful to project outcomes of hrHPV screening strategies at varying intervals over longer time frames.

As new hrHPV tests become available, head-to-head comparisons with tests used in the large RCTs and cohort studies will be helpful for extrapolation of effectiveness. Additional research comparing alternative followup protocols is needed to define the followup protocols most effective for maximizing detection of high grade abnormalities while minimizing harms from unnecessary testing. More recently recommended biomarkers, including p16 staining of cervical biopsies to clarify the level of CIN, deserve evaluation in population-based screening studies.[6]

We found very limited evidence on how vaccination against specific hrHPV types is affecting outcomes of screening with hrHPV primary testing or cotesting in age groups recommended for screening. As HPV vaccination coverage increases, whether shifts in hrHPV type prevalence will occur over time is not yet known. Studies to date have not supported substitution of nonvaccine hrHPV types,[167] and newer vaccines cover additional hrHPV types. An overall reduction in hrHPV prevalence would affect the positive predictive value of hrHPV testing. Ongoing studies of hrHPV prevalence and outcomes of screening in vaccinated populations are needed. If

vaccination results in an overall lower incidence of cervical cancer precursors and incidence, studies will be needed of screening strategies that have been modified to maintain screening efficiency and reduce harms from investigation of false positive results.

Because of the predominance of cervical cancer among underscreened women, a substantial impact on cervical cancer incidence and mortality requires the identification of effective strategies to reach poorly screened and unscreened women in the United States. Very limited evidence from a single cohort study of poorly screened women in Spain suggests that the increased sensitivity of hrHPV testing may offer particular advantages in this population. Rigorous comparative studies are needed to evaluate both the impact of hrHPV testing in this population and to identify and disseminate effective strategies to increase screening coverage and followup of abnormal results. Such strategies could include population-based screening programs with registries, outreach programs, low- or no-cost access to screening and followup evaluation, and options for self-collected samples.

There is evidence that hrHPV testing via self-collection may be an acceptable and important strategy to reach under- and unscreened populations.[168, 169 170] Studies have evaluated whether the tests are accurate enough to substitute for in-clinic testing and whether a self-collection option increases rates of screening and treatment among women not attending routine screening. A 2014 meta-analysis of 36 studies comparing the accuracy of hrHPV testing via self-collected samples to clinician-collected samples suggested slightly lower sensitivity and specificity for self-collection regardless of threshold (CIN2+ or CIN3+), (Compared to clinician-collected sensitivity was 0.88 [95% CI, 0.85 to 0.91] for CIN2+ and 0.89 [95% CI, 0.83 to 0.96] for CIN3+); and specificity was (0.96 [95% CI, 0.95 to 0.97] for CIN2+ and 0.96 [95% CI, 0.93 to 0.99] for CIN3+).[171] The implications of slightly lower test performance, particularly for sensitivity, might be different for a self-collection option among underscreened women.

Several systematic reviews summarize evidence on the effects of self-collection on screening participation. Most trials to date have been conducted in European countries, and usually randomize women with persistent missed screening to a control condition, such as a mailed reminder letter or telephone call, or the intervention, a mailed self-collection kit. Self-collection kits in these settings are consistently associated with higher screening rates. A 2013 systematic review of 10 trials examined the use of hrHPV self-testing on cervical cancer screening participation compared to a clinician letter. The overall relative risk of participation in screening using self-testing was 2.14 (95% CI, 1.30 to 3.52), with substantial heterogeneity observed between the studies (I^2=99.5%); reported use of hrHPV self-testing ranged from 10.2 to 98.2 percent among those invited to hrHPV self-test.[169] Similar significant beneficial effects on screening compliance have been observed in trials published since the 2013 review.[172-180]

One trial (n=601) of self-sampling to increase screening has been completed in the United States. The trial focused on low-income, uninsured Latina immigrants and Haitian women, and had three study arms. The control condition was culturally tailored health education materials and this was compared with a visit with a community health worker that offered navigation to a cervical clinical screening visit or a third intervention where the community health worker also offered a self-collection option. Rates of screening were highest when self-collection was offered, and the involvement of community health workers strengthened linkages to followup of

abnormal self-collection screening results (>90%). At 6 month followup, the proportion of women presenting for screening significantly differed across the groups: 29 percent in the health education materials group, 38 percent in the health navigation only arm, and 73 percent in the health navigation with self-collection option. Studies are needed to examine the effect of self-collection on overall screening rates and on adherence to followup of abnormal screening results among underscreened women. A number of ongoing studies of hrHPV self-sampling were identified in clinicaltrials.gov (**Appendix E**).

Conclusions

Three RCTs offer consistent evidence that hrHPV primary testing will detect higher rates of CIN3+ at an initial screening round. Two of four RCTs of cotesting also found higher CIN3+ detection. This higher detection is accompanied by increased false positive results and higher colposcopy rates. These higher rates of investigation are likely to lead to more treatments, which are associated with harms. Over two rounds of screening with hrHPV cotesting, most trials show similar rates of CIN3+ detection between strategies. Whether additional rounds of screening would result in a subsequent decline of CIN3+ with hrHPV testing strategies is unclear as trials did not extend beyond two rounds of screening. In most trials and a large U.S.-based observational study, women under aged 30 to 35 years had higher rates of hrHPV positivity and CIN3+, accompanied by higher rates of colposcopy. No completed studies compared screening intervals. An individual participant data meta-analysis suggested a lower rate of ICC with hrHPV screening strategies, but this analysis pooled data from trials with distinctly different screening strategies and hrHPV test types, which contributed uncertainty to interpretation of the findings. All of the evidence from RCTs on hrHPV primary screening and cotesting is from countries with organized screening programs, not available to most women in the United States. Rigorous comparative research is needed in U.S.-based screening settings to examine longer term outcomes, screening intervals, and to identify effective strategies for outreach, screening, and followup of poorly screened and unscreened women. The higher sensitivity of hrHPV testing in a single round of screening may have particular potential to improve outcomes in this high-risk population

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Figure 1. Analytic Framework

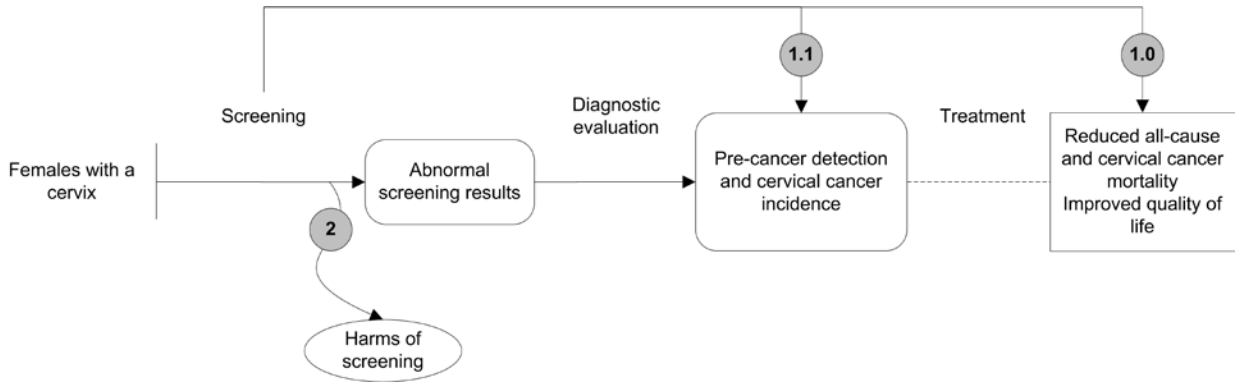

Table 1. Cytology Test Result Categories, the 2001 Bethesda System

Acronym	Description
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells – cannot exclude HSIL
LSIL	Low-grade Squamous Intraepithelial Lesion Includes human papillomavirus infection/mild dysplasia/CIN 1
HSIL	High-grade Squamous Intraepithelial Lesion Includes moderate and severe dysplasia, CIN2/3, and carcinoma *in situ*
AGC	Atypical Glandular Cells (specify endocervical or not otherwise specified [NOS])
---	Atypical Glandular Cells, favor neoplastic (specify endocervical or not otherwise specified [NOS])
AIS	Endocervical Adenocarcinoma In Situ
AdenoCa	Adenocarcinoma
SCC	Squamous Cell Carcinoma

Table 2. SEER Percent of Incident Cases and Deaths From Cervical Cancer by Age Group, 2010-2014

Age Group (years)	Incident Cases	Deaths
<20	0.1	0.0
20-34	13.9	5.2
35-44	23.8	13.4
45-54	23.8	23.3
55-64	18.7	23.9
65-74	11.2	16.5
75-84	5.8	11.2
>84	2.7	6.4

Table 3. SEER Average Age-Adjusted Annual Cervical Cancer Incidence and Mortality Rates per 100,000 Women by Race/Ethnicity, 2010-2014[36]

Race/Ethnicity	Incidence*	Mortality*
All Races	7.4	2.3
White	7.4	2.1
Black	8.7	3.8
American Indian / Alaska Native	7.7	2.8
Asian / Pacific Islander	6.1	1.7
Hispanic	9.1	2.6

*Rates not adjusted for hysterectomy status.

Table 4. Weighted Prevalence of HPV Among Females Aged 18 to 59 Years, National Health and Nutrition Examination Survey, 2007-2010[46] and 2013-2014[45]

Characteristic	Variable	Any HPV, %	High-risk[†] HPV (with or without low-risk HPV), %
All women[45]	--	39.9	20.4
Age, years[46]	18-24	56.1	--
	25-29	50.8	--
	30-34	40.1	--
	35-39	38.3	--
	40-44	34.5	--
	45-49	44.4	--
	50-54	33.4	--
	55-59	34.0	--
Race/ethnicity[45]	White, non-Hispanic	36.5	18.7
	Black, non-Hispanic	63.2	28.2
	Asian, non-Hispanic	23.2	11.6
	Hispanic	38.5	21.6
Education[46]	Less than high school	48.0	--
	High school graduate	47.5	--
	Some college	43.5	--
	≥ college graduate	31.4	--
Ratio of family income to poverty[46]	≥350%	33.3	--
	130-349%	43.0	--
	<130%	55.3	--
Total lifetime sexual partners[46]	0-1	14.8	--
	2-3	31.2	--
	4-5	45.8	--
	6-10	54.3	--
	11+	60.7	--
Total sexual partners within the past year[46]	0	33.7	--
	1	37.3	--
	2	74.8	--
	≥ 3	85.2	--

Note: 2007-2010 survey: n=3,738; 2013-2014 survey: n=NR.
[†]High-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

Abbreviations: HPV = human papillomavirus; NR = not reported

Table 5. Study Design Characteristics of Included Trials, Ordered by Screening Approach

Author, Year Quality	Country	N Rand	Inclusion Criteria	Exclusion Criteria	Recruitment	Followup (years)	HPV Screening Strategy	# of Rounds (Interval)
Ronco, 2010[1, 2] NTCC Phase II Good	Italy	49,196	Women aged 25-60 years attending for a new routine cervical cancer screening episode	Pregnant, had undergone a hysterectomy, been treated for CIN in the last 5 years	Population-based screening March 2002 to December 2004, two recruitment phases as part of nine population-based cervical cancer screening programs	7 (max)	HPV alone Hybrid Capture 2 (Digene)	2 (3 years)
Ogilivie, 2017[127, 133-135] HPV FOCAL Fair	Canada	25,223	Women aged 25-65 years, registered w/ Medical Services Plan in British Columbia, who receive care from a participating family physician for routine cervical screening	History of histologically confirmed proven CIN2+ requiring treatment in the last 5 years, history of histologically proven invasive cervical cancer, a Pap smear w/in the preceding 12 months, no cervix, pregnant at the time of enrollment, HIV positive or on immunosuppressive treatments	Population-based screening January 2008 - January 2011; women invited to participate when they present for cervical cancer screening and deemed eligible by family physician or pre-identified as being due for screening from the centralized provincial cytology database (invitation request woman schedule a cervical cancer screening appointment)	4 (max)	HPV w/ LBC triage Hybrid Capture 2 (Digene) and ThinPrep PreservCyt (Hologic Inc)	1 (2-4 years) 2 (2 year "safety round", 4 years)*
Leinonen, 2012[126] FINNISH Fair	Finland	203,425	Women aged 25-65 years invited for cervical cancer screening between 2003 and 2007 drawn from the Population Information System by birth year	NR	Population-based screening Women invited for screening btwn 2003 and 2007 from the Population Information System by personal letter; from eight municipalities	5 (max)	HPV w/ CC triage Hybrid Capture 2 (Digene) and CC	1 (5 years)
Ronco, 2010[1, 131, 132] NTCC Phase I Good	Italy	45,174	Women aged 25-60 years attending for a new routine cervical cancer screening episode	Pregnant, had undergone a hysterectomy, been treated for CIN in the last 5 years	Population-based screening March 2002 to December 2004, two recruitment phases as part of nine population-based cervical cancer screening programs	7 (max)	HPV cotesting Hybrid Capture 2 (Digene) and ThinPrep PreservCyt (Hologic Inc)	2 (3 years)

Table 5. Study Design Characteristics of Included Trials, Ordered by Screening Approach

Author, Year Quality	Country	N Rand	Inclusion Criteria	Exclusion Criteria	Recruitment	Followup (years)	HPV Screening Strategy	# of Rounds (Interval)
Naucler, 2007[121, 136] SWEDESCREEN Fair	Sweden	12,527	Women aged 32 to 38 years of age who participated in the screening program from May 1997 through November 2000 in five cities	Women who are recorded in cytologic-test registries as having had a recent Pap smear outside the screening program not invited to participate in the screening program	Population-based screening Screening program recruited women 23 to 50 years of age to undergo cervical-cancer screening at 3-year intervals and women 51 to 60 years of age to be screened at 5-year intervals; women chosen from the population registry which lists all women in Sweden	4.1	HPV cotesting PCR/GP5+/6+ and CC	1 (3 years)[†]
Kitchener, 2009[119, 137-139] ARTISTIC Fair	United Kingdom	25,078	Women aged 20 to 64 years undergoing routine cervical cancer screening in the NHS program in Greater Manchester	NR	Population-based screening Invitations to attend routine screening contained trial information leaflet; enrolled between July 2001 and September 2003	4.5 (max)	HPV cotesting Hybrid Capture 2 (Digene) and ThinPrep T3000 (Hologic Inc)	2 (3 years)
Rijkaart, 2012[122, 140, 141] POBASCAM Good	Netherlands	44,938	Women aged 30-60 years invited every 5 years to population-based screening program; eligible if they lived in a defined semi-urbanized region demarcated according to the District Health Authority SW of Amsterdam, having a uterus in situ	Women who had a history of CIN2+, had abnormal cytology in the preceding 2 years, or who had had a hysterectomy; women aged 57 years or older at baseline (not be routinely screened at second round); if HPV sample taken at baseline was lost	Population-based screening Enrolled btwn January 1999 and September 2002 as part of a nationwide screening program; women invited to screening every 5 years starting at age 30 years and ending at age 60 years. Invited by GP or directly by District Health Authority (if no GP)	9 (max)	HPV cotesting PCR/GP5+/6+ and CC	2 (5 years)

*****Results are preliminary; publication of 2nd round results are pending
[†]Registry followup in an organized screening program

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; btwn = between; CIN = cervical intraepithelial neoplasia; GP = general practitioner; HIV = human immunodeficiency virus; NHS = National Health Service; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; SW = southwest; w/ = with

Table 6. Results for Trials of hrHPV Primary Screening Strategies, All Participants

Parameter	Round	NTCC Phase II[1, 2]	HPV FOCAL[¶127, 133-135]	FINNISH[126]
Quality	--	Good	Fair	Fair
N Randomized	--	49,196	25,223	203,425
Ages Recruited	--	25-60 years	25-65 years	25-65 years
# of Rounds (Interval)	--	2 (3 years)	1 (2-4 years)[§]	1 (5 years)
Screening Approach (IG vs. CG)	1	hrHPV alone vs. CC	hrHPV w/ LBC triage vs. LBC w/ hrHPV triage	hrHPV w/ CC triage vs. CC
	2	CC vs. CC (both arms received same testing strategy)	LBC w/ hrHPV triage vs. LBC w/ hrHPV triage (both arms received same testing strategy)	--
Followup	1	3.5 years (maximum)	2-4 years (maximum)[§]	5 years (maximum) registry followup
	2	3.5 years (maximum)	2 years (maximum)[§]	--
	C	7 years (maximum)	4 years (maximum)	--
Test Positivity	1	IG (hrHPV+): 1,936/24,661 (7.9%) CG (ASC-US+): 825/24,353 (3.4%)	IG (hrHPV+): 1,290/15,744 (8.2%) CG (ASC-US+): 334/9,408 (3.6%)	IG (hrHPV+): 4,971/62,106 (8.0%)* CG (ASC-US+): 4,506/65,747 (6.9%)*
	2	NR	--	--
Colposcopy Referrals	1	IG: 1,936/24,661 (7.9%) CG: 679/25,435 (2.8%)	IG: 5.9% (95% CI, 5.5 to 6.3)[‖] CG: 3.1% (95% CI, 2.8 to 3.5)[‖]	IG: 796/66,410 (1.2%) CG: 755/65,784 (1.1%)
	2	NR	--	--
False Positive Rate for CIN2+	1	IG: 1,799/24,428 (7.4%) CG: 770/24,038 (3.2%)	NR	IG: 4,462/61,597 (7.2%) CG: 4,239/65,480 (6.5%)
	2	NR	--	--
Absolute Detection for CIN3+	1	IG: 97/24,661 (0.4%)* CG: 33/24,535 (0.1%)*	IG: 67/9,540 (0.7%) CG: 41/9,408 (0.4%)	IG: 195/66,410 (0.3%) CG: 118/65,784 (0.2%)
	2	IG: 5/23,978 (0.02%)* CG: 23/24,372 (0.09%)*	--	--
	C	IG: 102/24,661 (0.4%)* CG: 56/24,535 (0.2%)*	--	--
Relative Risk for CIN3+	1	2.92 (95% CI, 1.97 to 4.34)[†]	1.61 (95% CI, 1.09 to 2.37)	1.64 (95% CI, 1.30 to 2.06)[†]
	2	0.22 (95% CI, 0.08 to 0.58)[†]	--	--
	C	1.81 (95% CI, 1.31 to 2.51)[†]	--	--
Absolute Detection for CIN2+	1	IG: 218/24,661 (0.8%)* CG: 73/24,535 (0.3%)*	IG: 147/9,540 (1.5%) CG: 90/9,408 (1.0%)	IG: 540/66,410 (0.8%) CG: 319/65,784 (0.5%)
	2	IG: 12/23,978 (0.05%)* CG: 38/24,372 (0.2%)*	--	--
	C	IG: 230/24,661 (0.9%)* CG: 111/24,535 (0.5%)*	--	--
Relative Risk for CIN2+	1	2.97 (95% CI, 2.28 to 3.87)[†]	1.63 (95% CI, NR)[†]	1.68 (95% CI, 1.46 to 1.92)[†]
	2	0.32 (95% CI, 0.17 to 0.61)[†]	--	--
	C	2.06 (95% CI, 1.64 to 2.58)[†]	--	--
Invasive Cervical Cancer	1	NR	NR	IG: 17/66,410 (0.03%) CG: 9/65,784 (0.01%)
	2	NR	--	--
	C	NR	--	--

*From author inquiry

Table 6. Results for Trials of hrHPV Primary Screening Strategies, All Participants

[†]Calculated (unadjusted)
[§]HPV FOCAL had two randomized hrHPV arms: safety arm (screening every 2 years) and intervention arm (screening every 4 years); control arm screened every 2 years
[‖]Percent of women; converted from rate per 1,000 participants
[¶]Results are preliminary; publication of 2nd round results are pending

Abbreviations: C = cumulative; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV = high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening

Table 7. Results for Trials of hrHPV Primary Screening Strategies, Women Aged ≥35 Years

Parameter	Round	NTCC Phase II[1, 2]	HPV FOCAL[¶127, 133-135]	FINNISH[126]
Quality	--	Good	Fair	Fair
N Randomized	--	35,471	20,394	109,932
Ages Recruited	--	35-60 years	35-65 years	35-65 years
# of Rounds (Interval)	--	2 (3 years)	1 (2-4 years)§	1 (5 years)
Screening Approach (IG vs. CG)	1	hrHPV alone vs. CC	hrHPV w/ LBC triage vs. LBC w/ hrHPV triage	hrHPV w/ CC triage vs. CC
	2	CC vs. CC (both arms received same testing strategy)	LBC w/ hrHPV triage vs. LBC w/ hrHPV triage (both arms received same testing strategy)	--
Followup	1	3.5 years (maximum)	2-4 years (maximum)§	5 years (maximum) registry followup
	2	3.5 years (maximum)	2 years (maximum)§	--
	C	7 years (maximum)	4 years (maximum)	--
Test Positivity	1	IG (hrHPV+): 1,029/17,724 (5.8%) CG (ASC-US+): 555/17,747 (3.1%)	NR	NR
	2	NR	--	--
Colposcopy Referrals	1	IG: 1,029/17,724 (5.8%) CG: 435/17,747 (2.5%)	IG: 3.8 (95% CI, 3.5 to 4.2)‖ CG: 2.1 (95% CI, 1.8 to 2.4)‖	IG: 506/55,219 (0.9%) CG: 544/54,713 (1.0%)
	2	NR	--	--
False Positive Rate for CIN2+	1	IG: 960/17,655 (5.4%) CG: 519/17,711 (2.9%)	NR	NR
	2	NR	--	--
Absolute Detection for CIN3+	1	IG: 52/17,724 (0.3%)* CG: 22/17,747 (0.1%)*	IG: 47/8,714 (0.5%) CG: 27/8,580 (0.3%)	IG: 132/55,219 (0.2%) CG: 84/54,713 (0.2%)
	2	IG: 3/17,401 (0.02%)* CG: 13/17,658 (0.07%)*	--	--
	C	IG: 55/17,724 (0.3%)* CG: 35/17,747 (0.2%)*	--	--
Relative Risk for CIN3+	1	2.37 (95% CI, 1.44 to 3.89)*	1.71 (95% CI, 1.07 to 2.75)†	1.56 (95% CI, 1.18 to 2.04)†
	2	0.23 (95% CI, 0.07 to 0.82)*	--	--
	C	1.57 (95% CI, 1.03 to 2.40)*	--	--
Absolute Detection for CIN2+	1	IG: 102/17,724 (0.6%)* CG: 48/17,747 (0.3%)*	IG: 102/8,714 (1.2%) CG: 64/8,580 (0.8%)	IG: 322/55,219 (0.6%) CG: 200/54,713 (0.4%)
	2	IG: 5/17,401 (0.03%)* CG: 20/17,658 (0.1%)*	--	--
	C	IG: 107/17,724 (0.6%)* CG: 68/17,747 (0.4%)*	--	--
Relative Risk for CIN2+	1	2.13 (95% CI, 1.51 to 3.00)*	1.57 (95% CI, 1.15 to 2.14)†	1.59 (95% CI, 1.34 to 1.90)†
	2	0.25 (95% CI, 0.10 to 0.68)*	--	--
	C	1.58 (95% CI, 1.16 to 2.13)*	--	--
Invasive Cervical Cancer	1	NR	NR	IG: 16/55,219 (0.03%) CG: 7/54,713 (0.01%)
	2	NR	--	--
	C	NR	--	--

*From author inquiry

Table 7. Results for Trials of hrHPV Primary Screening Strategies, Women Aged ≥35 Years

†Calculated (unadjusted)
§HPV FOCAL had two randomized hrHPV arms: safety arm (screening every 2 years) and intervention arm (screening every 4 years); control arm screened every 2 years. Results above are from the safety and control arms.
‖Percent of women; converted from rate per 1,000 participants
¶Results are preliminary; publication of 2nd round results are pending

Abbreviations: CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV = high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening

Table 8. Results for Trials of hrHPV Primary Screening Strategies, Women Aged <35 Years

Parameter	Round	NTCC Phase II[1, 2]	HPV FOCAL[¶127, 133-135]	FINNISH[126]
Quality	--	Good	Fair	Fair
N Randomized	--	13,725	4,849 25-29 years: 2,188 30-34 years: 2,661	22,262
Ages Recruited	--	25-34 years	25-34 years	25-34 years
# of Rounds (Interval)	--	2 (3 years)	1 (2-4 years)§	1 (5 years)
Screening Approach (IG vs. CG)	1	hrHPV alone vs. CC	hrHPV w/ LBC triage vs. LBC w/ hrHPV triage	hrHPV w/ CC triage vs. CC
	2	CC vs. CC (both arms received same testing strategy)	LBC w/ hrHPV triage vs. LBC w/ hrHPV triage (both arms received same testing strategy)	--
Followup	1	3.5 years (maximum)	2-4 years (maximum)§	5 years (maximum) registry followup
	2	3.5 years (maximum)	2 years (maximum)§	--
	C	7 years (maximum)	4 years (maximum)	--
Test Positivity	1	IG (hrHPV+): 907/6,937 (13.1%) CG (ASC-US+): 270/6,788 (4.0%)	NR	NR
	2	NR	--	--
Colposcopy Referrals	1	IG: 970/6,937 (13.1%) CG: 244/6,788 (3.6%)	25-29 years: IG: 19.9 (95% CI, 17.9 to 22.1)‖ CG: 8.1 (95% CI, 6.4 to 10.2)‖ 30-34 years: IG: 10.8 (95% CI, 9.3 to 12.4)‖ CG: 6.2 (95% CI, 4.9 to 7.9)‖	IG: 290/11,191 (2.3%) CG: 211/11,071 (1.9%)
	2	NR	--	--
False Positive Rate for CIN2+	1	IG: 839/6,869 (12.2%) CG: 251/6,769 (3.7%)	NR	NR
	2	NR	--	--
Absolute Detection for CIN3+	1	IG: 45/6,937 (0.6%)* CG: 11/6,788 (0.2%)*	IG: 20/826 (2.4%) CG: 14/828 (1.7%)	IG: 63/11,191 (0.6%) CG: 34/11,071 (0.3%)
	2	IG: 2/6,577 (0.03%)* CG: 10/6,714 (0.15%)*	--	--
	C	IG: 47/6,937 (0.7%)* CG: 21/6,788 (0.3%)*	--	--
Relative Risk for CIN3+	1	4.00 (95% CI, 2.07 to 7.73)*	1.43 (95% CI, 0.73 to 2.82)†	1.83 (95% CI, 1.21 to 2.78)†
	2	0.20 (95% CI, 0.05 to 0.93)*	--	--
	C	2.19 (95% CI, 1.31 to 3.66)*	--	--
Absolute Detection for CIN2+	1	IG: 116/6,937 (1.7%)* CG: 25/6,788 (0.4%)*	IG: 45/826 (5.5%) CG: 26/828 (3.1%)	IG: 218/11,191 (1.9%) CG: 119/11,071 (1.1%)
	2	IG: 7/6,577 (0.1%)* CG: 18/6,714 (0.3%)*	--	--
	C	IG: 123/6,937 (1.8%)* CG: 43/6,788 (0.6%)*	--	--

Table 8. Results for Trials of hrHPV Primary Screening Strategies, Women Aged <35 Years

Parameter	Round	NTCC Phase II[1, 2]	HPV FOCAL[¶127, 133-135]	FINNISH[126]
Relative Risk for CIN2+	1	4.54 (95% CI, 2.95 to 6.99)*	1.73 (95% CI, 1.08 to 2.78)†	1.81 (95% CI, 1.45 to 2.26)†
	2	0.40 (95% CI, 0.17 to 0.95)*	--	--
	C	2.80 (95% CI, 1.98 to 3.95)*	--	--
Invasive Cervical Cancer	1	NR	NR	IG: 1/11,191 (0.01%) CG: 2/11,071 (0.02%)
	2	NR	--	--
	C	NR	--	--

*From author inquiry
†Calculated (unadjusted)
‖Percent of women; converted from rate per 1,000 participants
§HPV FOCAL had two randomized hrHPV arms: safety arm (screening every 2 years) and intervention arm (screening every 4 years); control arm screened every 2 years. Results shown above are safety arm and control arm.
¶Results are preliminary; publication of 2nd round results are pending

Abbreviations: CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV =high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NSD = no significant difference; NTCC = New Technologies for Cervical Cancer Screening

Table 9. Study Design Characteristics of Included Observational Studies

Author, Year & Quality	Design	Country	N	Inclusion Criteria	Exclusion Criteria	Recruitment
Katki, 2011[124, 143, 144, 181-183] KPNC Fair	Prospective Single Group Cohort	United States	331,818	Women aged ≥ 30 years	NR	Primary Care Women enrolled in KP between 2003 and 2005
Ibanez, 2014[123] Fair	Prospective Single Group Cohort	Spain	1832	Women aged > 39 years who had no evidence of cervical cytology in the public primary health registries in the previous 5 years	NR	Population-based screening Women identified in eight public primary health areas of Catalonia during 2007 and 2008
Luyten, 2014[125, 129] WOLPHSCREEN Fair	Prospective Comparative Cohort	Germany	19,795	Women aged ≥ 30 years who were voluntarily attending routine cervical cancer screening at one of the gynecological partners in private practice	History of hysterectomy	Population-based screening Between February 2006 and January 2011, female members of the Deutsche BKK aged ≥ 30 years who were voluntarily attending routine cervical cancer screening at one of the gynecological partners in private practice invited to participate
McCaffery, 2004[120] Fair	Cross-sectional study	United Kingdom	428	Women attended a NHS well-woman clinic for routine cervical cancer screening	NR	Primary care Women attended a NHS well-woman clinic for routine cervical cancer screening
Zorzi, 2017[128] Fair	Prospective Single Group Cohort	Italy	Round 1: 48,736 Round 2: 21,827	Women aged 25-64 years living in two areas of the Veneto region.	NR	Population-based screening Women living in the two areas of interested were invited to screening from April 2009 to April 2011.

Abbreviations: btwn = between; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; KP = Kaiser Permanente; NHS = National Health Service; NR = not reported

Table 10. Results for Italian Population-Based Cohort of Primary hrHPV Testing Over Two Rounds at a 3-Year Interval,[128] All Participants and Results by Age

Parameter	Round	All Participants	Women Aged 25-29	Women Aged 30-64
N Analyzed	--	48,736	5103	43,647
Ages Recruited	--	25-64	--	--
# of Rounds (Interval)	--	2 (3 years)	--	--
Screening Approach*	--	hrHPV Primary (HC2)	--	--
Test Positivity	1	3133/48,736 (6.4%)	754/5103 (14.8%)	2379/43,647 (5.5%)
	2	777/21827 (3.5%)	140/1723 (8.1%)	637/20104 (3.1%)
	C	3910/48,736 (8.0%)	894/5103 (17.5%)	3016/43,647 (6.9%)
Colposcopy Referrals	1	2136/48,736 (4.4%)	--	--
	2	472/21,827 (2.2%)	--	--
	C	2608/48,736 (5.4%)	--	--
Absolute Detection for CIN3+	1	95/48,736 (0.2%)	--	--
	2	6/21,827 (0.03%)	--	--
	C	101/48,736 (0.2%)	--	--
Relative Risk for CIN3+ (Round 2 vs. Round 1)	1	--	--	--
	2	0.14 (95% CI 0.06 to 0.32)	--	--
Absolute Detection for CIN2+	1	215/48,736 (0.4%)	53/5103 (1.0%)	162/43,647 (0.4%)
	2	23/21,827 (0.1%)	7/1723 (0.4%)	16/20,104 (0.1%)
	C	238/48,736 (0.5%)	60/5103 (1.2%)	178/43,647 (0.4%)
Relative Risk for CIN2+ (Round 2 vs. Round 1)	1	--	--	--
	2	0.24 (95% CI 0.16 to 0.37)	0.39 (95% CI 0.18 to 0.86)	0.21 (95% CI 0.13 to 0.36)

*Women with +hrHPV had conventional cytology triage: ASC-US+ were referred to colposcopy; normal cytology were rescreened at 1 year (those who remained HPV+ were referred to colposcopy); HPV- were rescreened at 3 years

Abbreviations: C = cumulative; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; Vs = versus

Table 11. Results for Trials of hrHPV Cotesting, All Participants

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Quality	--	Good	Good	Fair	Fair
N Randomized	--	45,174	44,938	12,527	25,078
Ages Recruited	--	25-60 years	29-61 years	32-38 years	20-64 years
Number of Rounds (Interval)	--	2 (3 years)	2 (5 years)	1 (3 years) Registry followup in organized screening program	2 (3 years)
Screening Approach (IG vs. CG)	1	hrHPV cotesting vs. CC	hrHPV cotesting vs. CC	hrHPV cotesting vs. CC	hrHPV cotesting vs. LBC
	2	CC vs. CC (both arms received same testing strategy)	hrHPV cotesting vs. hrHPV cotesting (both arms received same testing strategy)	CC vs. CC (both arms received same testing strategy in organized screening program)	hrHPV cotesting vs. LBC
Followup	1	3.5 years (maximum)	4 years (maximum)	3 years (maximum)	2.2 years (maximum)
	2	3.5 years (maximum)	5 years (maximum)	NR	2.3 years (maximum)
	C	7 years (maximum)	9 years (maximum)	4.1 years (average)	4.5 years (maximum)
Test Positivity	1	IG (hrHPV+ or ASC-US+): 2,830/22,708 (12.5%) CG (ASC-US+): 855/22,466 (3.8%)	IG (hrHPV+ or ASC-US+): 1,406/19,999 (7.0%) CG (ASC-US+): 706/20,106 (3.5%)	IG (hrHPV+)433/6,257 (6.9%): IG (ASC-US+): 146/6,257 (6.9%) CG (ASC-US+): 150/6,270 (2.4%)	IG (hrHPV+ or ASC-US+): 4,019/18,386 (21.9%) CG (ASC-US+): 786/6,124 (12.8%)
	2	NR	IG (hrHPV+ or ASC-US+): 742/19,579 (3.8%) CG (hrHPV+ or ASC-US+): 774/19,731 (3.9%)	NR	IG (hrHPV+ or ASC-US+): 1,258/11,862 (10.6%)‡ CG (ASC-US+): 210/3,928 (5.3%)‡
Colposcopy Referrals	1	IG: 2,470/22,708 (10.9%)§ CG: 738/22,466 (3.3%)	NR	NR	IG: 1,247/18,386 (6.8%) CG: 320/6,124 (5.2%)
	2	NR	NR	NR	IG: 284/10,716 (2.7%)‡ CG: 74/3,514 (2.1%)‡
False Positive Rate for CIN2+	1	IG: 2,702/22,042 (12.3%) CG: 771/21,972 (3.5%)	IG: 1,149/19,742 (5.8%) CG: 513/19,913 (2.6%)	IG: NR CG: 72/6,192 (1.2%)	IG: 3,566/17,933 (19.9%) CG: 653/5,991 (10.9%)
	2	NR	IG: 610/9,572 (6.4%) CG: 612/9,450 (6.5%)	NR	IG: 1,178/10,512 (11.2%)‡ CG: 176/3,832 (4.6%)‡
Absolute Detection for CIN3+	1	IG: 75/22,708 (0.3%)* CG: 58/22,466 (0.3%)*	IG: 171/19,999 (0.9%) CG: 150/20,106 (0.7%)	IG: 72/6,257 (1.2%) CG: 55/6,270 (0.9%)	IG: 233/18,386 (1.3%) CG: 81/6,124 (1.3%)
	2	IG: 13/22,093 (0.06%)* CG: 19/22,330 (0.08%)*	IG: 88/19,579 (0.4%) CG: 122/19,731 (0.6%)	IG: 16/6,257 (0.3%) CG: 30/6,270 (0.5%)	IG: 36/11,862 (0.3%)‡ CG: 17/3,928 (0.4%)‡
	C	IG: 88/22,708 (0.4%)* CG: 77/22,466 (0.3%)*	IG: 259/19,999 (1.3%) CG: 272/20,106 (1.3%)	IG: 88/6,257 (1.4%) CG: 85/6,270 (1.4%)	IG: 269/18,386 (1.5%)‡ CG: 98/6,124 (1.6%)‡
Relative Risk for CIN3+	1	1.28 (95% CI, 0.91 to 1.80)†	1.15 (95% CI, 0.92 to 1.43)	1.31 (95% CI, 0.92 to 1.87)	0.96 (95% CI, 0.74 to 1.23)†
	2	0.96 (95% CI, 0.34 to 1.40)†	0.73 (95% CI, 0.55 to 0.96)	0.53 (95% CI, 0.29 to 0.98)	0.76 (95% CI, 0.43 to 1.34)†
	C	1.13 (95% CI, 0.83 to 1.53)†	0.96 (95% CI, 0.81 to 1.13)	1.04 (95% CI, 0.77 to 1.39)†	0.91 (95% CI, 0.73 to 1.15)†

Table 11. Results for Trials of hrHPV Cotesting, All Participants

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Absolute Detection for CIN2+	1	IG: 187/22,708 (0.8%)* CG: 99/22,466 (0.4%)*	IG: 267/19,999 (1.3%) CG: 215/20,106 (1.1%)	IG: 144/6,257 (1.8%) CG: 76/6,270 (1.2%)	IG: 453/18,386 (2.5%) CG: 134/6,124 (2.2%)
	2	IG: 22/22,093 (0.1%)* CG: 34/22,330 (0.1%)*	IG: 160/19,579 (0.8%) CG: 184/19,731 (0.9%)	IG: 25/6,257 (0.4%) CG: 43/6,270 (0.7%)	IG: 88/11,862 (0.7%)‡ CG: 35/3,928 (0.9%)‡
	C	IG: 209/22,708 (0.9%)* CG: 133/22,466 (0.6%)*	IG: 427/19,999 (2.1%) CG: 399/20,106 (2.0%)	IG: 139/6,257 (2.2%) CG: 119/6,270 (1.9%)	IG: 541/18,386 (2.9%)‡ CG: 169/6,124 (2.8%)‡
Relative Risk for CIN2+	1	1.87 (95% CI, 1.46 to 2.38)†	1.25 (95% CI, 1.05 to 1.50)	1.51 (95% CI, 1.13 to 2.02)	1.34 (95% CI, 1.11 to 1.62)†
	2	0.65 (95% CI, 0.38 to 1.12)†	0.88 (95% CI, 0.71 to 1.08)	0.58 (95% CI, 0.36 to 0.96)	0.83 (95% CI, 0.56 to 1.23)†
	C	1.55 (95% CI, 1.25 to 1.93)†	1.08 (95% CI, 0.94 to 1.24)	1.17 (95% CI, 0.92 to 1.49)†	1.07 (95% CI, 0.90 to 1.26)†
Invasive Cervical Cancer	1	NR	IG: 12/19,999 (0.06%) CG: 6/20,109 (0.03%)	NR	IG: 5/18,386 (0.03%) CG: 4/6,124 (0.07%)
	2	NR	IG: 4/19,579 (0.02%) CG: 14/19,731 (0.07%)	NR	IG: 3/10,716 (0.03%)‡ CG: 0/3,514 (0%)‡
	C	NR	IG: 16/19,999 (0.08%) CG: 20/20,106 (0.10%)	IG: 1/6,257 (0.02%) CG: 5/6,270 (0.08%)	IG: 8/18,386 (0.04%)‡ CG: 4/6,124 (0.07%)‡

*From author inquiry
†Calculated (unadjusted)
‡Preliminary or incomplete results
§Estimated data from figure

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = Atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV = high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

Table 12. Results for Trials of hrHPV Cotesting, Women Aged ≥30-35 Years

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Quality	--	Good	Good	Fair	Fair
N Randomized	--	33,364	33,838	12,527	19,344
Ages Recruited	--	35-60 years	34-56 years	32-38 years	30-64 years
Number of Rounds (Interval)	--	2 (3 years)	2 (5 years)	1 (3 years) Registry followup in organized screening program	2 (3 years)
Screening Approach (IG vs. CG)	1	hrHPV cotesting vs. CC	hrHPV cotesting vs. CC	hrHPV cotesting vs. CC	hrHPV cotesting vs. LBC
	2	CC vs. CC (both arms received same testing strategy)	hrHPV cotesting vs. hrHPV cotesting (both arms received same testing strategy)	CC vs. CC (both arms received same testing strategy in organized screening program)	hrHPV cotesting vs. LBC
Followup	1	3.5 years (maximum)	4 years (maximum)	3 years (maximum)	2.2 years (maximum)
	2	3.5 years (maximum)	5 years (maximum)	NR	2.3 years (maximum)
	C	7 years (maximum)	9 years (maximum)	4.1 years (average)	4.5 years (maximum)
Test Positivity	1	IG (hrHPV+ or ASC-US+): 1,783/16,706 (10.7%) CG (ASC-US+): 594/16,658 (3.6%)	IG (hrHPV+) 684/16,860 (4%) CG: NR	IG (hrHPV+ or ASC-US+): NR CG (ASC-US+): 150/6,270 (2.4%)	IG (hrHPV+ or ASC-US+): 2,465/14,507 (17.0%) CG (ASC-US+): 508/4,837 (10.5%)
	2	NR	NR	NR	NR
Colposcopy Referrals	1	IG: 1,773/16,706 (10.6%)§ CG: 501/16,658 (3.0%)	NR	NR	NR
	2	NR	NR	NR	NR
False Positive Rate for CIN2+	1	IG: 1,704/16,335 (10.4%) CG: 543/16,607 (3.3%)	NR	IG: NR CG: 72/6,192 (1.2%)	NR
	2	NR	NR	NR	NR
Absolute Detection for CIN3+	1	IG: 52/16,706 (0.3%)* CG: 33/16,658 (0.2%)*	IG: 102/16,860 (0.6%)* CG: 90/16,978 (0.5%)*	IG: 72/6,257 (1.2%) CG: 55/6,270 (0.9%)	IG: 116/14,507 (0.8%) CG: 38/4,837 (0.8%)
	2	IG: 5/16,332 (0.03%)* CG: 11/16,561 (0.07%)*	IG: 55/16,545 (0.3%)* CG: 77/16,699 (0.5%)*	IG: 16/6,257 (0.3%) CG: 30/6,270 (0.5%)	NR
	C	IG: 57/16,706 (0.3%)* CG: 44/16,658 (0.3%)*	IG: 157/16,860 (0.9%) CG: 167/16,978 (1.0%)	IG: 88/6,257 (1.4%) CG: 85/6,270 (85%)	NR
Relative Risk for CIN3+	1	1.57 (95% CI, 1.02 to 2.43)*	1.14 (95% CI, 0.86 to 1.51)†	1.31 (95% CI, 0.92 to 1.87)	1.12 (95% CI, 0.71 to 1.47)†
	2	0.46 (95% CI, 0.16 to 1.33)*	0.72 (95% CI, 0.51 to 1.02)†	0.53 (95% CI, 0.29 to 0.98)	NR
	C	1.30 (95% CI, 0.87 to 1.91)*	0.95 (95% CI, 0.76 to 1.18)	1.04 (95% CI, 0.77 to 1.39)†	NR
Absolute Detection for CIN2+	1	IG: 109/16,706 (0.6%)* CG: 61/16,658 (0.4%)*	IG: 166/16,860 (1.0%)* CG: 127/16,978 (0.7%)*	IG: 144/6,257 (1.8%) CG: 76/6,270 (1.2%)	IG: 217/14,507 (1.5%) CG: 60/4,837 (1.2%)
	2	IG: 11/16,332 (0.07%)* CG: 19/16,561 (0.1%)*	IG: 108/16,545 (0.6%)* CG: 121/16,699 (0.7%)*	IG: 25/6,257 (0.4%) CG: 43/6,270 (0.7%)	NR
	C	IG: 120/16,706 (0.7%)* CG: 80/16,658 (0.5%)*	IG: 274/16,860 (1.6%) CG: 248/16,978 (1.5%)	IG: 139/6,257 (2.2%) CG: 119/6,270 (1.9%)	NR
Relative Risk for CIN2+	1	1.78 (95% CI, 1.30 to 2.44)*	1.32 (95% CI, 1.05 to 1.66)†	1.51 (95% CI, 1.13 to 2.02)	1.21 (95% CI, 0.91 to 1.60)†
	2	0.59 (95% CI, 0.28 to 1.24)*	0.90 (95% CI, 0.70 to 1.17)†	0.58 (95% CI, 0.36 to 0.96)	NR
	C	1.50 (95% CI, 1.13 to 1.98)*	1.11 (95% CI, 0.94 to 1.32)	1.17 (95% CI, 0.92 to 1.49)†	NR

Table 12. Results for Trials of hrHPV Cotesting, Women Aged ≥30-35 Years

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Invasive Cervical Cancer	1	NR	IG: 10/16,860 (0.06%)* CG: 4/16,978 (0.02%)*	NR	IG: 5/14,507 (0.03%) CG: 3/4,837 (0.06%)
	2	NR	IG: 4/16,545 (0.02%)* CG: 9/16,699 (0.05%)*	NR	IG: 2/9,037 (0.02%)‡ CG: 0/2,965 (0%)‡
	C	NR	IG: 14/16,860 (0.08%)* CG: 13/16,978 (0.08%)§	IG: 1/6,257 (0.02%) CG: 5/6,270 (0.08%)	IG: 7/14,507 (0.05%)‡ CG: 3/4,837 (0.06%)‡

*From author inquiry
†Calculated (unadjusted)
‡Preliminary or incomplete results
§Estimated data from figure

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = Atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV = high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

Table 13. Results for Trials of hrHPV Cotesting, Women Aged <30-35 Years

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Quality	--	Good	Good	Fair	Fair
N Randomized	--	11,810	6,267		5,166
Ages Recruited	--	25-34 years	29-33 years		20-29 years
# of Rounds (Interval)	--	2 (3 years)	2 (5 years)		2 (3 years)
Screening Approach (IG vs. CG)	1	hrHPV cotesting vs. CC	hrHPV cotesting vs. CC		hrHPV cotesting vs. LBC
	2	CC vs. CC (both arms received same testing strategy)	hrHPV cotesting vs. hrHPV cotesting (both arms received same testing strategy)		hrHPV cotesting vs. LBC
Followup	1	3.5 years (maximum)	4 years (maximum)		2.2 years (maximum)
	2	3.5 years (maximum)	5 years (maximum)		2.3 years (maximum)
	C	7 years (maximum)	9 years (maximum)		4.5 years (maximum)
Test Positivity	1	IG (hrHPV+ or ASC-US+): 1,047/6,002 (17.4%) CG (ASC-US+): 261/5,808 (4.5%)	IG (hrHPV+): 373/3,139 (12.0%) CG NR		IG (hrHPV+ or ASC-US+): 1,554/3,879 (40.1%) CG (ASC-US+): 278/1,287 (21.6%)
	2	NR	NR		NR
Colposcopy Referrals	1	IG: 697/6,002 (11.6%) CG: 237/5,808 (4.1%)	NR		NR
	2	NR	NR		NR
False Positive Rate for CIN2+	1	IG: 998/4,980 (20.0%) CG: 228/5,775 (3.9%)			NR
	2	NR			NR
Absolute Detection for CIN3+	1	IG: 23/6,002 (0.4%)* CG: 25/5,808 (0.4%)*	IG: 69/3,139 (2.2%)* CG: 60/3,128 (1.9%)*		IG: 117/3,879 (3.0%) CG: 42/1,287 (3.3%)
	2	IG: 8/5,761 (0.1%)* CG: 8/5,769 (0.1%)*	IG: 33/3,034 (1.1%)* CG: 45/3,032 (1.3%)*		NR
	C	IG: 31/6,002 (0.5%)* CG: 33/5,808 (0.6%)*	IG: 102/3,139 (3.3%) CG: 105/3,128 (3.4%)		NR
Relative Risk for CIN3+	1	0.89 (95% CI, 0.51 to 1.57)*	1.15 (95% CI, 0.81 to 1.61)†		0.92 (95% CI, 0.65 to 1.31)†
	2	1.00 (95% CI, 0.38 to 2.67)*	0.73 (95% CI, 0.47 to 1.15)†		NR
	C	0.91 (95% CI, 0.56 to 1.48)*	0.97 (95% CI, 0.74 to 1.27)		NR
Absolute Detection for CIN2+	1	IG: 78/6,002 (1.3%)* CG: 38/5,808 (0.6%)*	IG: 101/3,139 (3.2%)* CG: 88/3,128 (2.8%)*		IG: 236/3,879 (6.1%) CG: 73/1,287 (5.7%)
	2	IG: 11/5,761 (0.2%)* CG: 15/5,769 (0.3%)*	IG: 52/3,034 (1.7%)* CG: 63/3,032 (2.1%)*		NR
	C	IG: 89/6,002 (1.5%)* CG: 53/5,808 (0.9%)*	IG: 153/3,139 (4.9%) CG: 151/3,128 (4.8%)		NR
Relative Risk for CIN2+	1	1.99 (95% CI, 1.35 to 2.92)*	1.14 (95% CI, 0.86 to 1.52)†		1.07 (95% CI, 0.83 to 1.38)†
	2	0.73 (95% CI, 0.34 to 1.60)*	0.82 (95% CI, 0.57 to 1.19)†		NR
	C	1.63 (95% CI, 1.16 to 2.28)*	1.01 (95% CI, 0.81 to 1.26)		NR

Table 13. Results for Trials of hrHPV Cotesting, Women Aged <30-35 Years

Parameter	Round	NTCC Phase I[1, 131, 132]	POBASCAM[122, 140, 141]	SWEDESCREEN[121, 136]	ARTISTIC[119, 137-139]
Invasive Cervical Cancer	1	NR	IG: 2/3,139 (0.06%)* CG: 2/3,128 (0.06%)*		IG: 0/3,879 (0%) CG: 1/1,287 (0.08%)
	2	NR	IG: 0/3,034 (0%)* CG: 5/3,032 (0.16%)*		IG: 1/1,679 (0.06%)‡ CG: 0/549 (0%)‡
	C	NR	IG: 2/3,139 (0.06%)* CG: 7/3,128 (0.22%)§		IG: 1/3,879 (0.03%)‡ CG: 1/1,287 (0.08%)‡

*From author inquiry
†Calculated (unadjusted)
‡Preliminary or incomplete results
§Estimated data from figure

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = Atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; CG = control group; hrHPV = high risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

Table 14. Results of an Included Individual Participant Data Meta-Analysis of hrHPV-Based Screening Trials[130]

	NTCC Phases I and II	POBASCAM	SWEDESCREEN	ARTISTIC	Pooled Analysis
N Randomized	IG: 47,369 CG: 47,001	IG: 22,197 CG: 22,292	IG: 6,257 CG: 6,270	IG: 18,816 CG: 6,262	IG: 94,639 CG: 81,825
N Analyzed	IG: 47,369 CG: 47,001	IG: 21,996 CG: 22,106	IG: 6,257 CG: 6,270	IG: 18,386 CG: 6,124	IG: 94,008 CG: 81,411
Median followup, years	5.1	9.0	12.0	7.5	6.5
Invasive cervical cancer	IG: 9 (0.02%) CG: 24 (0.05%)	IG: 20 (0.09%) CG: 28 (0.13%)	IG: 5 (0.08%) CG: 7 (0.11%)	IG: 10 (0.05%) CG: 4 (0.07%)	IG: 44 (0.05%) CG: 63 (0.08%)
Detection rate of invasive cervical cancer	0.37 (95% CI, 0.17 to 0.80)	0.72 (95% CI, 0.40 to 1.27)	0.71 (95% CI, 0.23 to 2.25)	0.83 (95% CI, 0.26 to 2.66)	0.60 (95% CI, 0.40 to 0.89) I^2=0.0%, p=0.52
Biopsy procedures	IG: 2,538 (5%) CG: 1,127 (2%)	IG: 1,535 (7%) CG: 1,533 (7%)	IG: 675 (11%) CG: 701 (11%)	IG: 1,716 (9%) CG: 528 (9%)	IG: 6,464 (6.9%) CG: 3,889 (4.8%)
Rate ratio for biopsy procedures	2.24 (95% CI, 2.09 to 2.39)	1.01 (95% CI, 0.94 to 1.08)	0.97 (95% CI, 0.87 to 1.07)	1.08 (95% CI, 0.97 to 1.19)	1.35 (95% CI, 1.30 to 1.40) I^2=99.1, p<0.0001*

*Sensitivity analysis excluding the NTCC Phase I and Phase II trials: Rate ratio, 1.02 (95% CI, 0.97 to 1.07), I^2=30.7%, p=0.236

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CG = control group; CI = confidence interval; IG = intervention group; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

Table 15. Results From the KPNC Cotesting Observational Study, All Participants

Parameter	Round	KPNC[124]
N Analyzed	--	331,818
Ages Recruited	--	≥ 30 years
Number of Rounds (Interval)	--	2 (3 years)
Screening Approach	--	hrHPV cotesting (HC2 and CC)
Followup	1	NR
	2	2.9 years
	C	6 years
Test Positivity	--	hrHPV+ or ASC-US+: 24,849/331,818 (7.5%)
Colposcopy Referrals	--	NR
Absolute Detection for CIN3+	1	NR
	2	102/195,975 (0.05%)
	C	834/331,818 (0.3%)
Absolute Detection for CIN2+	1	NR
	2	346/195,975 (0.2%)
	C	2,310/331,818 (0.7%)
Invasive Cervical Cancer	1	NR
	2	13/195,975 (0.01%)
	C	87/331,818 (0.03%)

*Among women undergoing a colposcopy

Abbreviations: ASC-US = Atypical squamous cells of undetermined significance; C = cumulative; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papillomavirus; KPNC = Kaiser Permanente Northern California; LBC = liquid-based cytology; NR = not reported

Table 16. Cases and 3- and 5-Year Risk of CIN in the KPNC Cotesting Observational Study[124, 144]

		All Women*	Aged 21-29 Years	Aged 30-64 Years	HSIL	LSIL	ASC-US	hrHPV+ and ASC-US	hrHPV- and ASC-US	ASC-US-
N	--	1,307,528	284,940	1,022,588	2,771	19,096	53,107	25,336	26,191	1,232,554
CIN2+	3 yrs	9,689 (0.7%)	3,233 (1.1%)	6,456 (0.6%)	1,881 (67.9%)	2,081 (10.9%)	3,453 (6.5%)	3,241 (12.8%)	149 (0.6%)	2,274 (0.2%)
	5 yrs	11,569 (0.1%)	3,544 (1.2%)	8,025 (0.8%)	1,891 (68.2%)	2,184 (11.4%)	3,707 (7.0%)	3,446 (13.6%)	198 (0.8%)	3,787 (0.3%)
	3-year risk	1.12 (1.10 to 1.14)	2.29 (2.22 to 2.37)	1.05 (1.03 to 1.07)	71.4 (69.6 to 73.3)	13.71 (13.17 to 14.27)	7.86 (7.62 to 8.10)	15.69 (15.21 to 16.18)	0.97 (0.85 to 1.10)	0.47 (0.45 to 0.48)
	5-year risk	1.52 (1.49 to 1.54)	3.20 (3.08 to 3.32)	1.40 (1.37 to 1.43)	74.0 (71.9 to 76.1)	16.37 (15.66 to 17.11)	9.46 (9.16 to 9.78)	18.93 (18.30 to 19.57)	1.49 (1.31 to 1.70)	0.79 (0.77 to 0.82)
CIN3+	3 yrs	3,804 (0.3%)	986 (0.4%)	2,818 (0.3%)	1,162 (41.9%)	611 (3.2%)	1,130 (2.1%)	1,060 (4.2%)	48 (0.2%)	901 (0.1%)
	5 yrs	4,502 (0.3%)	1,084 (0.4%)	3,418 (0.3%)	1,168 (42.1%)	644 (3.4%)	1,240 (2.3%)	1,154 (4.6%)	64 (0.2%)	1,449 (0.1%)
	3-year risk	0.44 (0.42 to 0.45)	0.77 (0.73 to 0.82)	0.46 (0.44 to 0.47)	47.5 (45.2 to 49.9)	4.35 (4.02 to 4.91)	2.71 (2.57 to 2.87)	5.60 (5.29 to 5.92)	0.31 (0.24 to 0.39)	0.18 (0.17 to 0.19)
	5-year risk	0.29 (0.57 to 0.64)	1.12 (1.05 to 1.19)	0.59 (0.57 to 0.61)	50.4 (47.6 to 53.3)	5.36 (4.91 to 5.85)	3.39 (3.20 to 3.59)	7.12 (6.69 to 7.58)	0.49 (0.39 to 0.61)	0.30 (0.29 to 0.32)

*Excludes 5,600 women with other high-grade non-normal result

Abbreviations: ASC-US = Atypical squamous cells of undetermined significance; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; hrHPV = high-risk human papillomavirus; IG = intervention group; KPNC = Kaiser Permanente Northern California; LSIL = low-grade squamous intraepithelial lesion; NR = not reported; yrs = years

Table 17. Test Positivity, Histological Results, and Referrals to Colposcopy of Other Included Observational Studies of hrHPV Cotesting

Author, Year & Quality	Outcome	Subgroup	Round or Followup	N	Results
Ibanez, 2014[123] (Unscreened women) Fair	ASC-US+ (including 1 case of suspected adenocarcinoma)	All participants	Baseline	1832	40 (2.2)
	hrHPV+	All participants	Baseline	1832	123 (6.7)
	hrHPV+/ASC-US+	All participants	Baseline	1832	139 (7.6)
Luyten, 2014[125, 129] WOLPHSCREEN Fair	hrHPV+	All participants	1	19795	1232 (6.2)
		All participants	2	4067	146 (3.6)
	ASC-US+	All participants	1	19795	446 (2.2)
		All participants	2	4067	46 (1.1)
	hrHPV+/ASC-US+	All participants	1	19795	201 (1.0)
		All participants	2	4067	7 (0.2)
	Referred to colposcopy	All participants, stratified by cotesting results	1	19795	All participants: 765 (3.9)
			2	4067	All participants: 41 (1.0)
			1	201	hrHPV+/ASC-US+: 201 (100)
			1	1031	hrHPV+/ASC-US-: 536 (52.0)
			1	245	hrHPV-/ASC-US+: 28 (11.4)
			1	18318	hrHPV-/ASC-US-: 19 (0.1)
			1	1232	hrHPV+: 737 (59.8)
			1	446	ASC-US+: 229 (51.3)
	Colposcopy compliance	All participants, stratified by cotesting results	1	765	712 (93.1)
			2	41	38 (92.7)
			1	201	hrHPV+/ASC-US+: 192 (95.5)
			1	536	hrHPV+/ASC-US-: 506 (94.4)
			1	28	hrHPV-/ASC-US+: 14 (50)

Table 17. Test Positivity, Histological Results, and Referrals to Colposcopy of Other Included Observational Studies of hrHPV Cotesting

Author, Year & Quality	Outcome	Subgroup	Round or Followup	N	Results
			1	NR	hrHPV-/ASC-US-: NR (NR)
			1	737	hrHPV+: 698 (94.7)
			1	229	ASC-US+: 206 (90.0)
	CIN2+	All participants	1	19795	309 (1.6)
	CIN3+	All participants	1	19795	172 (0.87)
			2	4067	2 (0.05)
	Adenocarcinoma in situ	All participants	1	19795	13 (0.07)
	ICC	All participants	1	19795	20 (0.1)

Abbreviations: ASC-US = atypical squamous cells of undetermined significance CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papillomavirus; ICC = invasive cervical cancer; NR = not reported

Table 18. Psychological Harms Reported in the ARTISTIC Trial

Author, Year Quality	Outcome	Subgroup	IG n	IG Results	CG n	CG Results	Odds Ratio or Age-Adjusted Mean Difference (95% CI)	P-Value
Kitchener, 2009[119, 139] ARTISTIC Fair	GHQ ≥ 4, n (%)	All responders	1872	717.0 (38.3)	593	222.9 (37.6)	1.00 (0.82 to 1.23)	0.982
		hrHPV-/ASC-US-	972	286 (29.4)	331	106 (32.0)	NR	NR
		hrHPV-/ASC-US+	292	115 (39.4)	91	36 (39.6)	NR	NR
		hrHPV+/ASC-US-	407	170 (41.8)	103	36 (35.0)	1.33 (0.85 to 2.09)	0.213
		hrHPV+/ASC-US+	201	84 (41.8)	68	32 (47.1)	0.80 (0.46 to 1.40)	0.437
	GHQ, mean (SD)	All responders	1872	4.26 (5.73)	593	4.18 (5.71)	-0.01 (-0.65 to 0.60)	0.968
		hrHPV-/ASC-US-	972	3.31 (5.18)	331	3.22 (4.80)	NR	NR
		hrHPV-/ASC-US+	292	4.22 (5.63)	91	4.29 (5.83)	NR	NR
		hrHPV+/ASC-US-	407	4.77 (6.21)	103	4.02 (5.77)	0.74 (-0.63 to 1.91)	0.220
		hrHPV+/ASC-US+	201	4.57 (5.44)	68	5.75 (6.50)	-1.19 (-2.98 to 0.40)	0.121
	SRS, mean (SD)	All responders	1520	53.32 (23.02)	483	54.90 (23.00)	-2.40 (-4.91 to 0.16)	0.042
		hrHPV-/ASC-US-	803	51.28 (20.89)	271	50.81 (22.50)	NR	NR
		hrHPV-/ASC-US+	255	48.73 (23.34)	82	50.53 (21.26)	NR	NR
		hrHPV+/ASC-US-	311	55.32 (22.95)	76	61.10 (23.74)	-7.28 (-12.74 to -1.52)	0.007
		hrHPV+/ASC-US+	151	62.67 (23.00)	54	62.46 (22.97)	0.15 (-6.44 to 6.74)	0.965
	STAI-STATE, mean (SD)	All responders	1875	38.10 (12.64)	594	38.27 (12.61)	-0.31 (-1.62 to 0.92)	0.618
		hrHPV-/ASC-US-	971	35.85 (11.92)	331	36.00 (11.49)	NR	NR
		hrHPV-/ASC-US+	290	37.99 (12.43)	91	40.66 (13.57)	NR	NR
		hrHPV+/ASC-US-	410	38.87 (13.33)	103	37.10 (12.58)	1.73 (-1.27 to 4.53)	0.202
		hrHPV+/ASC-US+	204	39.77 (12.5)	69	39.97 (12.35)	-0.25 (-3.79 to 3.03)	0.885
	STAI-TRAIT, mean (SD)	All responders	1877	40.12 (11.40)	596	40.13 (11.49)	-0.10 (-1.27 to 1.13)	0.858
		hrHPV-/ASC-US-	971	38.84 (11.34)	331	39.00 (11.13)	NR	NR
		hrHPV-/ASC-US+	289	39.95 (11.08)	91	41.57 (12.43)	NR	NR
		hrHPV+/ASC-US-	413	40.54 (11.83)	105	39.39 (10.80)	1.07 (-1.30 to 3.41)	0.386
		hrHPV+/ASC-US+	204	41.28 (10.89)	69	40.88 (11.54)	0.36 (-2.80 to 3.53)	0.819

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = atypical cells of undetermined significance; CG = control group; CI = confidence interval; GHQ = General Health Questionnaire; hrHPV = high risk human papillomavirus; IG = intervention group; NR = not reported; SD = standard deviation

Table 19. Psychological Harms Reported in the Included Observational Studies

Author, Year Quality	Outcome	Subgroup	N Analyzed	Results	Between Group Comparisons
McCaffery, 2004[120] Fair	CSQ score, mean (95% CI)	hrHPV-/cytology-	185	8.9 (8.4 to 9.3)	hrHPV+ (cytology- vs. cytology +): p=0.0001 hrHPV- (cytology - vs. cytology +): p<0.0001 Cytology+ (hrHPV+ vs. hrHPV-): p=0.002 Cytology - (hrHPV+ vs. hrHPV-): p<0.0001
		hrHPV-/cytology+	17	14 (12 to 15)	
		hrHPV+/cytology-	13	13 (12 to 14)	
		hrHPV+/cytology+	23	17 (16 to 18)	
	STAI score, mean (95% CI)	hrHPV-/cytology-	185	29.8 (27.9 to 31.7)	hrHPV+ (cytology - vs. cytology +): p=0.55 hrHPV- (cytology - vs. cytology +): p=0.0008 Cytology + (hrHPV+ vs. hrHPV-): p=NSD Cytology - (hrHPV+ vs. hrHPV-): p<0.0001
		hrHPV-/cytology+	17	41.1 (34.9 to 47.5)	
		hrHPV+/cytology-	46	43.5 (39.7 to 47.3)	
		hrHPV+/cytology+	23	46 (40.6 to 51.4)	
	Feelings about current partner, worse than usual	hrHPV-/cytology-	162	2 (99)	Cytology+ (hrHPV+ vs. hrHPV-): NSD Cytology - (hrHPV+ vs. hrHPV-): p=0.04
		hrHPV-/cytology+	16	0 (0)	
		hrHPV+/cytology-	36	3 (8)	
		hrHPV+/cytology+	16	2 (13)	
	Feelings about future partners, worse than usual	hrHPV-/cytology-	176	3 (2)	Cytology + (hrHPV+ vs. hrHPV-): p=0.02 Cytology - (hrHPV+ vs. hrHPV-): p<0.0001
		hrHPV-/cytology+	15	0 (0)	
		hrHPV+/cytology-	44	12 (27)	
		hrHPV+/cytology+	22	7 (32)	
	Feelings about previous partners, worse than usual	hrHPV-/cytology-	23	2 (99)	Cytology + (hrHPV+ vs. hrHPV-): p=0.01 Cytology - (hrHPV+ vs. hrHPV-): p<0.0001
		hrHPV-/cytology+	45	0 (0)	
		hrHPV+/cytology-	15	15 (33)	
		hrHPV+/cytology+	169	8 (35)	

Abbreviations: CSQ = Cervical Screening Questionnaire; hrHPV = high-risk human papillomavirus; STAI = Spielberger's State Trait Anxiety Inventory

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
Benefits								
KQ 1: Effectiveness of hrHPV testing or cotesting vs. cytology alone for reducing cervical cancer incidence and mortality								
hrHPV primary screening	k=3 RCTs, 1 cohort study n=326,580	In 3 RCTs reporting results over 1 to 2 rounds of screening spanning 4 to 7 years, hrHPV testing found more CIN3+ in an initial screening round; cumulative rates of CIN3+ were highter in the intervention group in the single completed study with 2 rounds of screening. In this trial, all women with a positive hrHPV test were referred to colposcopy. Overall, CIN3+ detection ranged from 0.3% to 0.8% across studies. The HPV FOCAL trial has not published complete results. Invasive cancers were only reported in 1 RCT, but numbers were very small (<0.1%), so statistical comparisons were not meaningful. Mortality data were not reported.	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening Imprecise/NA for cervical cancer incidence	Not detected	RCTs: 1 good, 2 fair Cohort: 1 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup tests and protocol; trials underpowered to assess cervical cancer incidence and mortality.	We are moderately confident that the estimate of higher detection of CIN3+ in the initial screening round for primary hrHPV-based screening strategies vs. cytology lies close to the true effect; with considerable heterogeneity in study design, testing protocols, and followup, some uncertainty remains. We have limited confidence that the estimate of the effect of primary hrHPV screening on cumulative CIN3+ detection or ICC incidence lies close to the true effect for this outcome. The body of evidence has numerous deficiencies. Evidence is insufficient to determine the effect of hrHPV testing on cervical cancer incidence and mortality in unscreened and underscreened women.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
hrHPV cotesting with cytology	k=4 RCTs, 2 cohort studies N= 127,717 (RCTs) N=351,613 (cohorts)	In 4 RCTs reporting results over 1 to 2 rounds of screening spanning 4.5 to 9 years, cotesting found similar cumulative rates of CIN3+ between treatment groups. 13-year followup in 1 trial did not detect a difference between arms. A large single cohort study (n=331,818) found 0.7% of women screened with cotesting had CIN3+ over 6 years. Among women who screened negative and were rescreened after 3 years, 0.05% were found to have CIN3+. Another cohort study (n=19,795) found decreasing rates of CIN3+ detected over 2 screening rounds (0.57% in round 1, 0.05% in round 2).	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening Imprecise/NA for cervical cancer incidence	Not detected	RCTs: 2 good, 2 fair Cohorts: 2 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup tests and protocol; trials underpowered to assess cervical cancer incidence and mortality Single cohort study with no comparison group.	We are moderately confident that the estimate of no difference in the initial screening round or cumulative difference in CIN3+ detection for hrHPV cotesting screening strategies vs. cytology lies close to the true effect; with considerable heterogeneity in study design, testing protocols, and followup, some uncertainty remains. Evidence is insufficient to determine the effect of hrHPV testing on cervical cancer incidence and mortality in unscreened and underscreened women.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV primary screening or cotesting with cytology	k=1 (IPD meta-analysis) N=176,464	An IPD meta-analysis combined 5 trials (1 primary screening trial and 4 cotesting trials) with different populations, hrHPV test types, and screening protocols. A total of 107 cases of ICC among 176,464 women were identified in the trials, with a pooled RR of 0.60 (95% CI, 0.40 to 0.89) for hrHPV testing	For the IPD meta-analysis, findings were reasonably statistically consistent and precise for ICC detection over 1 to 2 rounds of screening	Not detected		Pooled outcomes of trials using primary hrHPV testing and cotesting with marked heterogeneity in study design, testing protocols, followup and ICC ascertainment were combined at the individual level	For the IDP meta-analysis, we have limited confidence that the estimate of the effect of primary hrHPV screening on cumulative CIN3+ detection or ICC incidence lies close to the true effect for this outcome. Evidence is insufficient to determine the effect of hrHPV testing on cervical cancer incidence and mortality in unscreened and underscreened women.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
								care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
KQ 1a: Subpopulation differences in screening for reducing cervical cancer incidence and mortality								
hrHPV primary screening in women aged <30-35 years	k=3 RCTs, 1 cohort study n=84,483	3 RCTs report absolute detection of CIN3+; 2 trials reported only 1 round of screening, 1 trial reported on 2 rounds. Women <35 years had higher rates of cumulative CIN3+ detection across studies. Cumulative CIN3+ remained higher in the study with 2 screening rounds (NTCC Phase II) (RR, 4.0 [95% CI, 2.07 to 7.73]). Across trials, CIN3+ rates ranged from 0.2% to 3.0%. Findings from the cohort study, with higher rates of CIN2+ in women aged 25-29 years, were consistent with the trials. Mortality data were not reported.	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening Imprecise/NA for cervical cancer incidence	Not detected	RCTs: 1 good, 2 fair Cohort: 1 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup tests and protocol; trials underpowered to assess cervical cancer incidence and mortality.	We are moderately confident based on strong evidence that CIN3+ rates were highest in women aged <30-35 years but comparative performance of hrHPV primary testing vs. cytology was similar to the overall trial results Evidence is insufficient to determine the effect of hrHPV primary testing on cervical cancer incidence and mortality in unscreened and underscreened women ages <30-35 years.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
hrHPV cotesting with cytology in women aged <30-35 years	k=3 RCTs n=23,243	3 cotesting trials reported on women age <35; 2 reported on 2 rounds of screening. CIN3+ detection rates were higher in women aged <30-35 years, rates were comparable between the IG and CG for both rounds, with no significant differences in cumulative CIN3+; detection rates ranged from 0.1% to 3.3% across trials. Invasive cancers were very rare in this age group and statistical comparisons were not meaningful. Mortality data were not reported.	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening Imprecise/NA for cervical cancer incidence or mortality	Not detected	RCTs: 2 good, 1 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup tests and protocol; trials underpowered to assess cervical cancer incidence and mortality. Single cohort study with no comparison group	We are moderately confident based on strong evidence that CIN3+ rates were highest in women aged <30-35 years but comparative performance of hrHPV cotesting vs. cytology was similar to the overall trial results Evidence is insufficient to determine the effect of hrHPV cotesting on cervical cancer incidence and mortality in unscreened and underscreened women aged <30-35 years.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV primary screening or cotesting with cytology in women aged <30-35 years	k=1 IPD meta-analysis N=176,464 all age groups N not broken down by age group	The IPD meta-analysis reported ICC rate ratios by age. The lowest RR was for 30-34 years (0.36 [95% CI, 0.14 to 0.94]), but this RR did not differ significantly from the RR for women age ≥35 years. Mortality data were not reported.		Not detected		Pooled outcomes of trials using primary hrHPV testing and cotesting with marked heterogeneity in study design, testing protocols, followup and ICC ascertainment were combined at the individual level		All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
								care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV primary screening in women age ≥30-35 years	k=3 RCTs, 1 cohort study n=170,900	3 RCTs report findings from a single screening round (2 to 3.5 yrs) and 1 reported results from 2 rounds of screening. CIN3+ outcomes were similar to the overall group results, with only 1 trial (NTCC Phase II trial) reporting cumulative detection over 2 rounds of screening, with an RR of 1.57 (95% CI, 1.03 to 2.40). CIN3+ detection rates ranged from 0.2% to 0.5%. The cohort study found lower rates of CIN2+ in women aged 30-64 years over 2 rounds of primary hrHPV screening. Mortality data were not reported.	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening Imprecise/NA for cervical cancer incidence or mortality	Not detected	RCTs: 1 good, 2 fair Cohort: 1 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup tests and protocol; trials underpowered to assess cervical cancer incidence and mortality.	We are moderately confident based on strong evidence that for women age ≥35 years, comparative performance of hrHPV primary screening vs. cytology was similar to the overall trial results Evidence is insufficient to determine the effect of hrHPV primary screening testing on cervical cancer incidence and mortality in unscreened and underscreened women age >30-35 years	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV cotesting with cytology in women age ≥30-35 years	k=4 RCTs n=99,073	4 RCTs report findings from a single screening round (2.2 to 4 yrs) and 3 report results from 2 rounds of screening. CIN3+ outcomes were similar to the overall group results, with no significant differences in cumulative	Reasonably consistent and precise for CIN3+ detection over 1 to 2 rounds of screening	Not detected	RCTs: 2 good, 2 fair	Randomization not maintained for more than 1 or 2 rounds of screening; heterogeneity in screening and followup	We are moderately confident based on strong evidence that CIN3+ rates were highest in women aged <30-35 years but comparative performance of hrHPV cotesting vs. cytology was similar to the	All trials were in organized screening programs in European countries with nationalized health systems.

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
		CIN3+ detection in any trial. CIN3+ detection rates ranged from 0.03% to 1.4% Mortality data were not reported.	Imprecise/NA for cervical cancer incidence or mortality			tests and protocol; trials underpowered to assess cervical cancer incidence and mortality. Single cohort study with no comparison group	overall trial results Evidence is insufficient to determine the effect of hrHPV cotesting on cervical cancer incidence and mortality in unscreened and underscreened women aged ≥30-35 years.	Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV primary screening or cotesting with cytology in women ≥ 30-35 years	1 IPD meta-analysis N=176,464	As noted above, the IPD meta-analysis did not find statistical differences in the pooled rate ratio by age groups. Mortality data were not reported		Not detected				All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without access to organized screening programs or access to health care, and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
hrHPV primary screening in unscreened women	k=0	NA	NA	NA	NA	NA	NA	NA
hrHPV cotesting with cytology in unscreened women	k=1 cohort study n=1,832	1 single cohort study of underscreened women suggested 1-time hrHPV cotesting would detect more CIN3 and ICC; of 9 CIN3+ cases, all were hrHPV+ and 6 had positive cytology.	Imprecise Consistency NA	Not detected	1 Fair	Lack of a comparison group, substantial loss to followup	We have low confidence, based on limited evidence from 1 small cohort study, that the CIN3+ detection rate among unscreened women is improved with hrHPV testing	Only 1 study conducted in Spain
KQ 1b and 1c: Relationship of rescreening intervals to future cancer incidence or progression								
HPV primary screening or cotesting compared to cytology	No comparative studies	No completed trials compared screening intervals with use of hrHPV testing. Trials comparing hrHPV testing to cytology used 2- to 5-year intervals, but given variability of screening protocols, comparison between trials was not meaningful. No evidence on subpopulations	NA	NA	NA	NA	Evidence is insufficient for comparison of rescreening intervals with hrHPV testing on cancer-related outcomes. No evidence on subpopulations and rescreening intervals was identified.	NA
Harms								
KQ 2: Adverse effects of hrHPV testing or cotesting vs. cytology								
hrHPV primary screening	Colposcopy, biopsy, false positives, and false negatives k=3 RCTs, 1 cohort study n=326,580	False positive rates were consistently higher in the IG. NTCC Phase II had more referrals to colposcopy among women in the IG vs. CG in round 1 of screening (7.9% vs. 2.8%); the 2 other trials had similar rates of referral to colposcopy at round 1 in both trial arms (3% in HPV FOCAL; 1% in FINNISH). The highest rates of colposcopy referral were	Reasonably consistent Reasonably Precise	Not detected	RCTs: 1 good, 2 fair Cohort: 1 fair	Heterogeneity in screening followup protocols make it difficult to draw conclusions about relative harms of different hrHPV screening strategies compared to	We are moderately confident that the estimates for colposcopy referrals, false positive rates of HPV-based screening strategies vs. cytology lie close to the true effects We have insufficient evidence for estimating differences in the false negative rates, and no evidence on complications	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
		in the NTCC trial, which referred all HPV+ women to colposcopy. Data from an Italian cohort had similar round 1 false positive rates (6.4%) and colposcopy referrals (4.4%), with both approximately halved at the second screening round. Cases of ICC among screen-negative women were not consistently reported, and numbers were too small to draw comparisons. None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN. Cases of ICC among screen-negative women were not consistently reported, and numbers were too small to draw comparisons.				cytology alone. Limited data on harms of screening and diagnostic procedures. Not all trials reported colposcopy and biopsy rates.	of screening.	access to health care and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.
hrHPV cotesting with cytology	Colposcopy, biopsy, false positives, and false negatives k=4 RCTs, 2 cohort studies N=127,717 (RCTs) N=351,613 (cohorts)	False positive rates were consistently higher in the IG. 2 trials reported referrals to colposcopy. NTCC Phase I reported more women in the IG vs. CG arm were referred at round 1 (10.9% vs. 3.3%). Round 2 results, reported only in the ARTISTIC trial, were similar between treatment groups (IG: 2.7% vs. CG: 2.1%). Women age ≥35 years to colposcopy. Cohort data from screened women in Germany	Reasonably consistent Reasonably Precise	Not detected	RCTs: 2 good, 2 fair Cohort: 1 fair	Heterogeneity in screening followup protocols make it difficult to draw conclusions about relative harms of different hrHPV screening strategies compared to cytology alone Limited data on	We are moderately confident that the estimates for colposcopy referrals, false positive rates of HPV-based screening strategies vs. cytology lie close to the true effects We have insufficient evidence for estimating differences in the false negative rates, and no evidence on complications of screening.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
		(WOLPHSCREEN) found colposcopy referral rates of 3.9% after 1 round of screening with cotesting, and an additional 1.0% at the second round. None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN.				harms of screening and diagnostic procedures. Not all trials reported colposcopy and biopsy rates.		access to care in health systems with organized cervical cancer screening programs.
hrHPV primary screening or cotesting with cytology	Colposcopy, biopsy, false positives, and false negatives 1 IPD meta-analysis N=176,464	The IPD meta-analysis did not report colposcopy rates, but reported biopsy rates for the 5 included trials. Pooled biopsy rates had very high heterogeneity explained by the 2-fold difference in biopsy rates for the NTCC trials. Biopsy rates were similar between arms for the other trials. False positive rates for CIN2+ detection were higher in the IG for 5 trials reporting sufficient data for this outcome at round 1. In 2 trials with data on round 2 false positive rates, they were similar in the trial with the most complete followup, and remained higher in the IG for the other (ARTISTIC). None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN.		Not detected		High heterogeneity in pooled estimate of biopsy rates	We have limited confidence that the pooled estimate for biopsy rate lies close to the true effect.	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs.

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
hrHPV primary screening	Psychological harms k=0	NA	NA	NA	NA	NA	NA	NA
hrHPV cotesting with cytology	Psychological harms k=1 RCT, 1 cross-sectional study n=2,508 (RCT) n=428 (cross sectional)	2 studies reported psychological effects of HPV testing; positive hrHPV test results were associated with higher anxiety and distress and lower satisfaction with current and past sexual partnerships, particularly when cytology findings are normal.	Reasonably consistent Reasonably Precise	Undetected	2 Fair	Limited data ava1one trial reporting psychological harms of screening, 1 cross-sectional study	We are moderately confident that the estimates for psychological effects of screening lie close to the true effect.	Psychological harms assessed in women enrolled in organized screening in the UK, findings may not be fully applicable to U.S. women
KQ 2a: Subpopulations (adverse effect differences by age)								
hrHPV primary screening in women aged <30-35 years	Colposcopy, biopsy, false positives, and false negatives k=3 RCTs N=40,836	Colposcopy referral rates were considerably higher in the IG than the CG with 1 round of screening. 1 trial (HPV Focal) also reported colposcopy referrals for the youngest women, ages 25 to 29, and these were the highest observed for any trial group (19.9% [95% CI, 17.9% to 22.1%]). None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN by age. Psychological harms also were not reported by age. None of the trials with more than 1 round of screening data available reported colposcopy rates at round 2 by age. False negatives and psychological harms by age were not reported.	Reasonably consistent Reasonably precise	Undetected	RCTs: 1 good, 2 fair		We are moderately confident that the estimates for colposcopy referrals and false positive rates of HPV-based screening strategies vs. cytology lie close to the true effects for women age <35 years. We identified no evidence on psychological harms by age group or on complications related to biopsies and subsequent treatments	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
hrHPV cotesting with cytology in women aged <30-35 years	Colposcopy, biopsy, false positives, and false negatives k=1 RCT N=11,810	1 trial of cotesting provided false positive rates by age, with the most pronounced group differences seen among younger women: FPR 20% among IG women and FPR 4% among CG women ages 25 to 34 None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN by age. Psychological harms also were not reported by age. None of the trials with more than 1 round of screening data available reported colposcopy rates at round 2 by age. False negatives and psychological harms by age were not reported.	Reasonably consistent Reasonably precise	Undetected	1 good		We are moderately confident that the estimates for colposcopy referrals and false positive rates of HPV-based screening strategies vs. cytology lie close to the true effects for women age <35 years. We identified. no evidence on psychological harms by age group or on complications related to biopsies and subsequent treatments	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs
hrHPV primary screening in women aged ≥30-35 years	Colposcopy, biopsy, false positives, and false negatives k=3 RCTs N=165,797	All 3 trials reported colposcopy referrals for women age >30 or >35 years at round 1. Rates tended to be higher in the IG, similar to the overall findings for KQ 2, but were slightly lower in magnitude. None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN by age. Psychological harms also were not reported by age.	Reasonably consistent Reasonably precise	Undetected	1 good, 2 fair		We are moderately confident that a single round of HPV-based screening in women age >30-35 will result in higher rates of colposcopy compared to cytology-based screening. We have no evidence to estimate the effect of HPV-based screening on other potential harms of screening	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with access to care in health systems with organized

Table 20. Summary of Evidence on hrHPV Testing Alone (Primary Screening) or With Cytology (Cotesting) for Cervical Cancer Screening

Testing method	# of Studies (k), # of Observations (n) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for That KQ	Applicability
								cervical cancer screening programs
hrHPV cotesting with cytology in women aged ≥30-35 years	Colposcopy, biopsy, false positives, and false negatives k=1 RCT, 1 cohort N=33,364 (RCT) N=331,818 (cohort)	Only 1 trial reported colposcopy referrals. NTCC Phase I found higher referral rates in the IG vs. CG group (10.6% vs. 3.0%). This trial also found higher FPRs in the IG vs. CG (10% vs. 3%) among women aged 35 to 60; this was lower magnitude and less discrepant than FPRs among younger women. None of the included studies reported adverse events associated with screening, diagnostic testing, or treatment of CIN by age. Psychological harms also were not reported by age.	Reasonably consistent Reasonably precise	Undetected	1 good		We are moderately confident that a single round of HPV-based screening in women aged >30 or 35 will result in higher rates of colposcopy compared to cytology based screening. We have no evidence to estimate the effect of HPV-based screening on other potential harms of screening	All trials were in organized screening programs in European countries with nationalized health systems. Applicability may be lower for women in the U.S. without regular access to health care and higher for U.S. women with access to care in health systems with organized cervical cancer screening programs
KQ 2b and 2c: Relationship of rescreening intervals to future cancer incidence or progression								
HPV primary screening or cotesting compared to cytology	No comparative studies	No completed trials compared screening intervals with use of hrHPV testing. Trials comparing hrHPV testing to cytology used 2- to 5-year intervals, but given variability of screening protocols, comparison between trials was not meaningful. No evidence on subpopulations.	NA	NA	NA	NA	Evidence is insufficient for comparison of rescreening intervals with hrHPV testing on cancer-related outcomes. No evidence on subpopulations and rescreening intervals was identified.	NA

Synthesized Literature Search Strategies

CDSR

#1 (cervical or cervix):ti,ab,kw near/3 (screen* or detect*):ti,ab,kw
#2 "liquid based cytology":ti,ab,kw
#3 (papillomavirus or "papilloma virus" or hpv):ti,ab,kw near/3 (test* or screen* or detect*):ti,ab,kw
#4 (papillomavirus or "papilloma virus" or hpv):ti,ab,kw near/3 vaccin*:ti,ab,kw
#5 (or #1-#4) Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews and Protocols)

DARE

Line	Search
1	(((cervical or cervix) ADJ3 (screen* or detect*))) IN DARE FROM 2010 TO 2015
2	("liquid based cytology") IN DARE FROM 2010 TO 2015
3	(papillomavirus or "papilloma virus" or hpv) ADJ3 (test* or screen or detect*) IN DARE FROM 2010 TO 2015
4	(papillomavirus or "papilloma virus" or hpv) ADJ3 vaccin*) IN DARE FROM 2010 TO 2015
5	#1 OR #2 OR #3 OR #4

HTA (via CRD)

Line	Search
1	((cervical or cervix) ADJ3 (screen* or detect*)) IN HTA FROM 2010 TO 2015
2	("liquid based cytology") IN HTA FROM 2010 TO 2015
3	((papillomavirus or "papilloma virus" or hpv) ADJ3 (test* or detect*)) IN HTA FROM 2010 TO 2015
4	((papillomavirus or "papilloma virus" or hpv) ADJ3 vaccin*) IN HTA FROM 2010 TO 2015
5	#1 OR #2 OR #3 OR #4

Medline

Database: Ovid MEDLINE(R) <1946 to February Week 2 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 24, 2015>, Ovid MEDLINE(R) Daily Update <February 15, 2017>
Search Strategy:
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1 Cervical Intraepithelial Neoplasia/ ()
2 "Squamous Intraepithelial Lesions of the Cervix"/ ()
3 Uterine Cervical Neoplasms/ ()
4 Uterine Cervical Dysplasia/ ()
5 Papillomaviridae/ ()
6 Papillomavirus Infections/ ()
7 Alphapapillomavirus/ ()

8 Human papillomavirus 16/ ()
9 Human papillomavirus 18/ ()
10 Human papillomavirus 31/ ()
11 or/1-10 ()
12 Mass screening/ ()
13 Vaginal Smears/ ()
14 Papanicolaou Test/ ()
15 DNA Probes, HPV/ ()
16 Human Papillomavirus DNA Tests/ ()
17 screen$.ti,ab. ()
18 vaginal smear$.ti,ab. ()
19 (papanicolau or papanicolaou).ti,ab. ()
20 pap.ti,ab. ()
21 cervical smear$.ti,ab. ()
22 or/12-21 ()
23 11 and 22 ()
24 ((cervical or cervix) adj3 (screen$ or detect$)).ti,ab. ()
25 liquid based cytology.ti,ab. ()
26 ((papillomavirus or papilloma virus) adj3 (test$ or screen$ or detect$)).ti,ab. ()
27 (hpv adj3 (test$ or screen$ or detect$)).ti,ab. ()
28 23 or 24 or 25 or 26 or 27 ()
29 Papillomavirus Vaccines/ ()
30 ((Papillomavirus or papilloma virus) adj3 vaccin$).ti,ab. ()
31 (hpv adj3 vaccin$).ti,ab. ()
32 29 or 30 or 31 ()
33 28 or 32 ()
34 limit 33 to (english language and yr="2010 -Current") ()
35 limit 34 to systematic reviews ()
36 remove duplicates from 35 ()
37 Animals/ not (Humans/ and Animals/) ()
38 36 not 37 ()

PubMed, publisher-supplied

Search	Query
#8	Search #7 AND systematic[sb] AND publisher[sb] AND English[Language] AND ("2010"[Date - Publication] : "3000"[Date - Publication])
#7	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6
#6	Search hpv[tiab] AND vaccin*[tiab]
#5	Search hpv[tiab] AND (test*[tiab] OR screen*[tiab] OR detect*[tiab])
#4	Search (papillomavirus[tiab] or "papilloma virus"[tiab]) AND (vaccin*[tiab])
#3	Search (papillomavirus[tiab] or "papilloma virus"[tiab]) AND (test*[tiab] OR screen*[tiab] OR detect*[tiab])
#2	Search "liquid based cytology"[tiab]
#1	Search (cervical[tiab] OR cervix[tiab]) AND (screen*[tiab] OR detect*[tiab])

Primary Literature Search Strategies

CENTRAL

#1 hpv*:ti,ab,kw near (test* or detect* or screen* or smear* or assay*):ti,ab,kw
#2 papillomavir*:ti,ab,kw near (test* or detect* or screen* or smear* or assay*):ti,ab,kw
#3 (papilloma* next vir*):ti,ab,kw near (test* or detect* or screen* or smear* or assay*):ti,ab,kw
#4 #1 or #2 or #3
#5 "hybrid capture":ti,ab,kw
#6 (HC2 or "HC 2" or HCII or "HC II"):ti,ab,kw
#7 cobas:ti,ab,kw
#8 APTIMA:ti,ab,kw
#9 Cervista:ti,ab,kw
#10 digene:ti,ab,kw
#11 amplicor:ti,ab,kw
#12 pcr:ti,ab,kw
#13 (polymerase next chain next reaction*):ti,ab,kw
#14 "linear array":ti,ab,kw
#15 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 (hpv* or papillomavir* or (papilloma next vir*)):ti,ab,kw
#17 #15 and #16
#18 #4 or #17 Publication Year from 2011 to 2017, in Trials

MEDLINE
Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily Update
Search Strategy:
---

1 Papillomavirus Infections/di [Diagnosis] ()
2 Papillomaviridae/cy, ip [Cytology, Isolation & Purification] ()
3 Alphapapillomavirus/ip [Isolation & Purification] ()
4 Human papillomavirus 16/ip [Isolation & Purification] ()
5 Human papillomavirus 18/ip [Isolation & Purification] ()
6 DNA Probes, HPV/ ()
7 Human Papillomavirus DNA Tests/ ()
8 (hpv$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
9 (papillomavir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
10 (papilloma vir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 ()
12 Papillomavirus Infections/ ()
13 Papillomaviridae/ ()
14 Alphapapillomavirus/ ()
15 Human papillomavirus 16/ ()
16 Human papillomavirus 18/ ()
17 Human papillomavirus 31/ ()
18 12 or 13 or 14 or 15 or 16 or 17 ()
19 Mass screening/ ()
20 Early detection of cancer/ ()
21 Vaginal smears/ ()
22 Papanicolaou Test/ ()
23 "Diagnostic Techniques, Obstetrical and Gynecological"/ ()
24 Cytological Techniques/ ()
25 Histocytological Preparation Techniques/ ()
26 Cytodiagnosis/ ()
27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 ()
28 18 and 27 ()
29 Hybrid Capture.ti,ab. ()
30 HC2.ti,ab. ()
31 hc 2.ti,ab. ()
32 hcII.ti,ab. ()
33 hc II.ti,ab. ()
34 cobas.ti,ab. ()
35 APTIMA.ti,ab. ()
36 Cervista.ti,ab. ()
37 digene.ti,ab. ()
38 amplicor.ti,ab. ()
39 polymerase chain reaction/ ()
40 Reverse Transcriptase Polymerase Chain Reaction/ ()
41 polymerase chain reaction$.ti. ()
42 pcr.ti. ()
43 linear array.ti,ab. ()
44 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 ()
45 papillomavir$.ti,ab,hw. ()

46 papilloma vir$.ti,ab,hw. ()
47 hpv$.ti,ab,hw. ()
48 45 or 46 or 47 ()
49 44 and 48 ()
50 11 or 28 or 49 ()
51 limit 50 to systematic reviews ()
52 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
53 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
54 Random$.ti,ab. ()
55 control groups/ or double-blind method/ or single-blind method/ ()
56 clinical trial$.ti,ab. ()
57 controlled trial$.ti,ab. ()
58 meta analy$.ti,ab. ()
59 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ ()
60 cohort.ti,ab. ()
61 longitudinal.ti,ab. ()
62 (follow up or followup).ti,ab. ()
63 Registries/ ()
64 (registr$ or register$).ti,ab. ()
65 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 ()
66 50 and 65 ()
67 51 or 66 ()
68 Animal/ not (Animal/ and Human/) ()
69 67 not 68 ()
70 Male/ not (Female/ and Male/) ()
71 69 not 70 ()
72 limit 71 to (english language and yr="2011 -Current") ()
73 remove duplicates from 72 ()

PsycInfo (via Ovid)
Database: PsycINFO
Search Strategy:
---

1 human papillomavirus/ ()
2 testing/ ()
3 Cancer Screening/ ()
4 Screening/ ()
5 exp Screening Tests/ ()
6 2 or 3 or 4 or 5 ()
7 1 and 6 ()
8 (hpv$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
9 (papillomavir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
10 (papilloma vir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab. ()
11 7 or 8 or 9 or 10 ()
12 limit 11 to (english language and yr="2011 -Current") ()

PubMed

Search	Query
#8	Search ((#7) AND English[Language]) AND ("2011/01/01"[Date - Publication] : "3000"[Date - Publication])
#7	Search #6 AND publisher[sb]
#6	Search #5 AND (systematic[sb] OR random*[tiab] OR trial*[tiab] OR cohort*[tiab] OR longitudinal[tiab] OR follow up[tiab] OR followup[tiab] OR retrospective[tiab] OR prospective[tiab] OR register*[tiab] OR registr*[tiab])
#5	Search #3 AND #4
#4	Search HPV [tiab] OR papillomavir* [tiab] OR papilloma vir*[tiab] OR “hybrid capture*” [tiab] OR HC2 [tiab] OR HCII [tiab] OR “HC 2” [tiab] OR “HC II” [tiab] OR cobas[tiab] OR aptima[tiab] OR cervista[tiab] OR digene[tiab] OR amplicor[tiab] OR PCR[tiab] OR polymerase chain reaction*[tiab] OR “linear array”[tiab] OR ((viral [tiab] OR virolog* [tiab]) AND (DNA [tiab]))
#3	Search #1 AND #2
#2	Search (cancer* [tiab] OR carcinoma OR adenocarcinoma OR neoplas* [tiab] OR dysplas* [tiab] OR lesion*[tiab] OR dyskaryos* [tiab] OR squamous [tiab] OR CIN [tiab] OR CINII* [tiab] OR CIN2* [tiab] OR CINIII* [tiab] OR CIN3* [tiab] OR SIL [tiab] OR HSIL [tiab] OR H-SIL [tiab] OR LSIL [tiab] OR L-SIL [tiab] OR ASCUS [tiab] OR AS-CUS [tiab])
#1	Search (cervix [tiab] OR cervical [tiab] OR cervico* [tiab])

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Aim	**KQs 1, 2:** Studies targeting cervical cancer screening or development of cervical cancer over time	**KQs 1, 2:** Use of HPV or cytology testing for posttreatment surveillance or other purposes
Population	**KQs 1, 2:** Women age ≥21 years who have a cervix	**KQs 1, 2:** • High-risk populations (e.g., women who are HIV-positive) • Women without a cervix • Women who have had a hysterectomy with the removal of the cervix • Pregnant women
Interventions	**KQs 1, 2:** • Primary HPV screening strategies*†: o Alone o In combination with cytology (cotesting) o In combination with cytology triage of positive HPV (reflex cytology) • Self- or clinician-collected HPV specimens, collected at home or in a clinic	**KQs 1, 2:** Nonprimary HPV screening strategies (e.g., primary cytology-based screening, cytology with HPV triage [reflex HPV])
Comparators	**KQs 1, 2:** Comparative effectiveness (i.e., cytology-based [conventional or liquid-based] or other primary HPV screening strategies [cotesting, reflex cytology, or reflex HPV])	**KQs 1, 2:** Comparative effectiveness of cytology-based screening strategies (liquid-based cytology vs. conventional cytology alone); cytology with HPV triage vs. cytology-based screening strategies
Outcomes	**KQ 1:** • Early detection of disease (CIN3+) • Invasive cancer • Mortality (all-cause or cervical cancer) • Improved quality of life The following hierarchy[112] of outcomes for new cervical cancer screening methods will be used: Rank 1: Cervical cancer mortality (quality-adjusted life-years gained) Rank 2: Cervical cancer morbidity/stage IB+ incidence Rank 3: Cervical cancer incidence (including microinvasive) Rank 4: Reduced CIN3+ incidence or p16 immunohistochemistry-associated high-grade squamous intraepithelial lesion incidence[113] Rank 5: Increased detection of CIN3+ (or CIN2+) • More CIN3+ detection overall (cumulative CIN3+) • More CIN2+ detection followed by less CIN3+ detection at subsequent screening (note: CIN2+ detection may include overdiagnosis) Rank 6: Increased test positivity with increased, similar, or minimally reduced positive predictive value **KQ 2:** • Rates of false-positive and false-negative screening test results • Rates of colposcopy and/or biopsy • Labeling • Stigma (e.g., sexually transmitted infection) • Partner discord • Psychological distress (e.g., anxiety) • Reduced quality of life	

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Study Designs	**KQs 1, 2:** • Individual patient data meta-analyses and systematic reviews • Randomized, controlled trials; controlled clinical trials • Cohort studies, including patient registries	**KQs 1, 2:** • Case-control studies • Case reports • Case series • Narrative reviews • Editorials
Setting	**KQs 1, 2:** Primary care (e.g., internal medicine, family medicine, obstetrics/gynecology) or other settings generalizable to primary care (e.g., university-based health clinics, mobile clinics, sexually transmitted infection clinics, family planning clinics)	**KQs 1, 2:** • Community/university research laboratories or other nonmedical centers • Correctional facilities • Worksites • Inpatient/residential facilities
Country	**KQs 1, 2:** Countries with cervical cancer screening programs comparable to those of the United States and categorized as "Very High" or equivalent on the 2014 Human Development Index (as defined by the United Nations Development Programme)	**KQs 1, 2:** Countries not categorized as "Very High" on the Human Development Index or not applicable to U.S. clinical settings or populations
Language	**KQs 1, 2:** English only	**KQs 1, 2:** Non-English publications
Quality	**KQs 1, 2:** Fair- or good-quality, according to USPSTF design-specific criteria	**KQs 1, 2:** Poor-quality, according to USPSTF design-specific criteria

*Primary screening strategies refer to the use of a certain type of test in the first step of a screening approach.
†HPV tests approved by the U.S. Food and Drug Administration include: the Hybrid Capture 2 High-Risk HPV DNA Test (Digene Corp., Gaithersburg, MD), cobas HPV Test (Roche Molecular Systems, Inc., Pleasanton, CA), APTIMA® HPV Assay (E6/E7 mRNA) (Gen-Probe Inc., San Diego, CA), Cervista™ HPV 16/18 (Hologic, Inc., Madison, WI), and Cervista™ HR HPV.

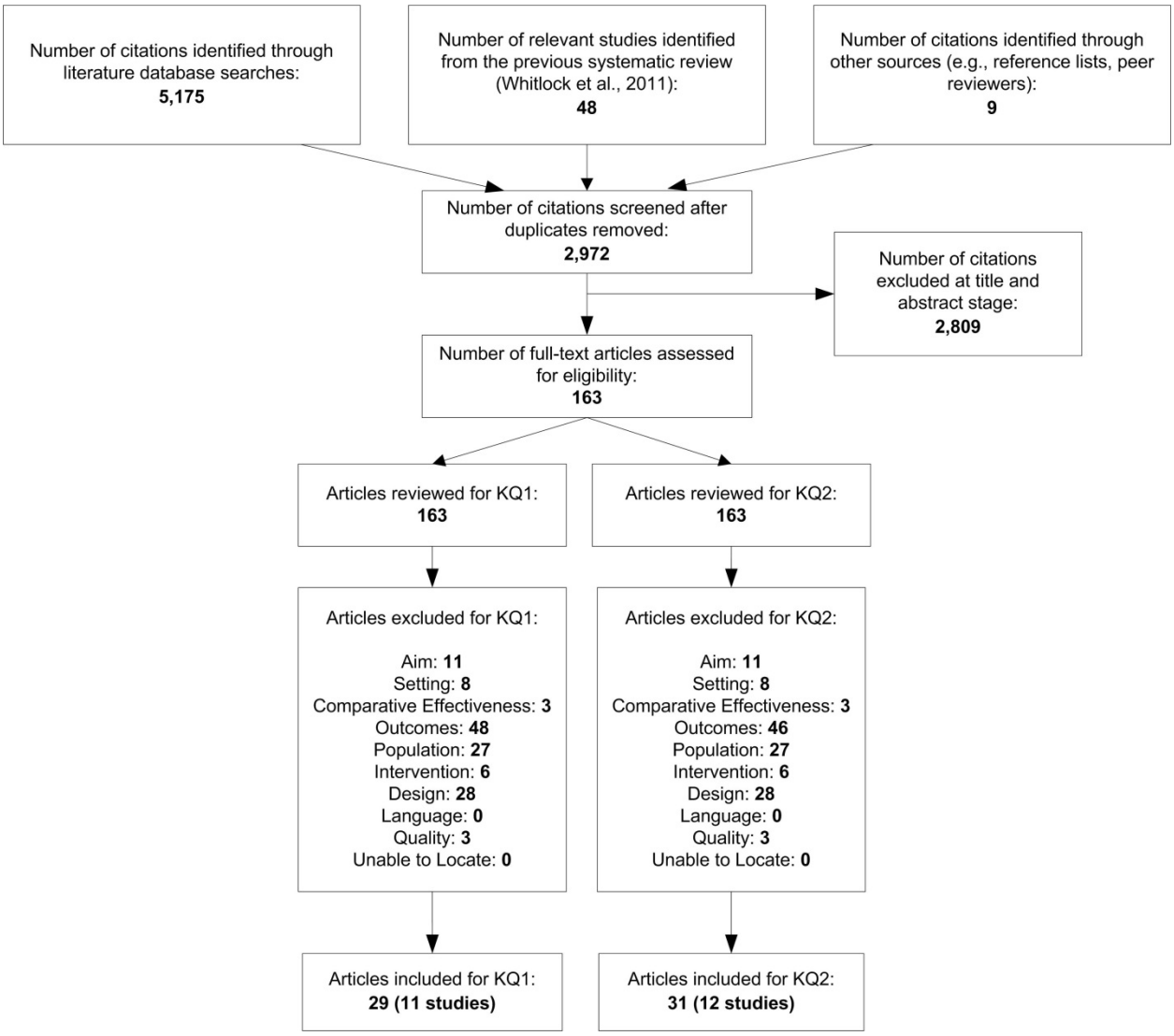
Abbreviations: CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; KQ = Key Question; USPSTF = U.S. Preventive Services Task Force

Appendix A Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[114]	• Was there adequate participation in the study by eligible/invited persons? • Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Was there a difference in attrition between groups after randomization? • Was the reading (interpretation) of the pathology results adequate? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there risk of contamination? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable followup? • Was there evidence of selective reporting of outcomes?
Cohort studies, adapted from the Newcastle-Ottawa Scale[115]	• Was there representativeness of the exposed cohort? • Was the non-exposed systematic selected? • Was the ascertainment of exposure reported? • Were eligibility criteria specified? • Were groups similar at baseline? • Was the reading (interpretation) of the pathology results adequate? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was followup long enough for outcomes to occur? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there adjustment for confounders? • Was there acceptable followup?

Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

Appendix A Figure 1. Literature Flow Diagram



Abbreviations: KQ = Key Question

Appendix B. Cervical Cancer Screening Recommendations of Other Organizations Published Since the 2012 USPSTF Recommendation

Organization	Year	Recommendation Statement
American Society of Clinical Oncology (ASCO)[184]	2016	• HPV testing is recommended in all resource settings. Co-testing is an option in maximal settings (which would include the US), however the added value on the basis of increased costs is limited. • Self-collection of samples may be used for HPV testing. • In maximal settings, women aged 25-65 years should be screened every 5 years (≥ 9 screens in a lifetime). • Women with abnormal triage results should receive colposcopy, followed by LEEP or cryotherapy/cold coagulation. 12-month post-treatment followup is recommended.
American College of Physicians (ACP)[185]	2015	Best practice advice: • Clinicians should not screen average-risk women younger than 21 years for cervical cancer. • Clinicians should start screening average-risk women for cervical cancer at age 21 years once every 3 years with cytology (cytologic tests without human papillomavirus [HPV] tests). • Clinicians should not screen average-risk women for cervical cancer with cytology more often than once every 3 years. • Clinicians may use a combination of cytology and HPV testing once every 5 years in average-risk women aged 30 years or older who prefer screening less often than every 3 years. • Clinicians should not perform HPV testing in average-risk women younger than 30 years. • Clinicians should stop screening average-risk women older than 65 years for cervical cancer if they have had 3 consecutive negative cytology results or 2 consecutive negative cytology plus HPV test results within 10 years, with the most recent test performed within 5 years. • Clinicians should not screen average-risk women of any age for cervical cancer if they have had a hysterectomy with removal of the cervix.
Society for Gynecologic Oncology (SGO), the American Society for Colposcopy and Cervical Pathology (ASCCP), the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), the American Society of Cytopathology (ASC), the College of American Pathologists (CAP) and the American Society for Clinical Pathology (ASCP)[69]	2015	Interim guidance: A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result. Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to current U.S. cytology-based cervical cancer screening methods. Cytology alone and co-testing remain the screening options specifically recommended in major guidelines. Based on limited data, triage of hrHPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women. Re-screening after a negative primary hrHPV screen should occur no sooner than every 3 years. Primary hrHPV screening should not be initiated before 25 years of age.
National Comprehensive Cancer Network (NCCN)[186, 187]	2014	The NCCN endorses the 2012 ACS, ASCCP, and ASCP recommendations (see below).
Canadian Preventive Services Task Force (CPSTF)[188]	2013	For women younger than 20 years of age, the CPSTF recommends not routinely screening for cervical cancer (strong recommendation; high-quality evidence). For women aged 20–24 years, the CPSTF recommends not routinely screening for cervical cancer (weak recommendation; moderate-quality evidence). For women aged 25–29 years, the CPSTF recommends routine screening for cervical cancer every 3 years (weak recommendation; moderate-quality evidence). For women aged 30–69 years, the CPSTF recommends routine screening for cervical cancer every 3 years (strong recommendation; high-quality evidence). For women aged 70 years and older who have undergone adequate screening (i.e., 3 successive negative Pap test results in the previous 10 years), the CPSTF recommends that routine screening may end. For women aged 70 years and older who have not undergone adequate screening, the CPSTF recommends continued screening

Appendix B. Cervical Cancer Screening Recommendations of Other Organizations Published Since the 2012 USPSTF Recommendation

Organization	Year	Recommendation Statement
		until 3 negative test results have been obtained (weak recommendation; low-quality evidence).
Institute for Clinical Systems Improvement (ICSI)[189]	2013	**Endorses the 2012 USPSTF recommendations (see Section II).**
World Health Organization (WHO)[190]	2013	Where resources permit, HPV screening should be done on women aged 30 years and older, followed by treating with cryotherapy (or LEEP when not available), over screening with visual inspection with acetic acid or screening with cytology followed by colposcopy. This strategy is favored over screening with HPV testing followed by colposcopy.
American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP)[67]	2012	**Age to Begin Screening:** Cervical cancer screening should begin at age 21 years. Women aged younger than 21 years should not be screened regardless of the age of sexual initiation or other risk factors. **Screening Periodicity:** Women at any age should NOT be screened annually by any screening method; rather, recommended screening intervals for women are based on age and clinical history. **Women Aged 21 to 29 Years:** For women aged 21 to 29 years, screening with cytology alone every 3 years is recommended. For women aged 21 to 29 years with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e., more than 3 years). HPV testing should not be used to screen women in this age group, either as a stand-alone test or as a co-test with cytology. **Women Aged 30 to 65 Years:** Women aged 30 to 65 years should be screened with cytology and HPV testing ("co-testing") every 5 years (preferred) or cytology alone every 3 years (acceptable). There is insufficient evidence to change screening intervals in this age group following a history of negative screens. **Management of Women With HPV-Positive, Cytology-Negative Co-tests:** Women co-testing HPV positive, cytology negative should be followed with either (as noted in the interim ASCCP guidelines): Option 1) repeat co-testing in 12 months or Option 2) immediate HPV genotype-specific testing for HPV16 alone or for HPV16/18. If co-testing is repeated at 12 months, women testing positive on either test (HPV positive or LSIL or more severe cytology) should be referred to colposcopy; women testing negative on both tests (HPV-negative and ASC-US or negative cytology) should return to routine screening. If immediate HPV genotype-specific testing is used, women testing positive for HPV16 or HPV16/18 should be referred directly to colposcopy; women testing negative for HPV16 or HPV16/18 should be co-tested in 12 months, with management of results as described in option 1. Women co-testing HPV positive, cytology negative should not be referred directly to colposcopy. Furthermore, they should not be tested for individual HPV genotypes other than HPV16 and HPV18. The use of HPV genotype-specific testing for HPV16 or HPV16/18 is recommended only for the management of HPV-positive, cytology-negative women. Currently, there is insufficient evidence to support the use of non-HPV biomarkers. **Management of Women With HPV-Negative, ASC-US Cytology Results:** Women with ASC-US cytology and a negative HPV test result should continue with routine screening as per age-specific guidelines. **Screening With HPV Testing Alone:** In most clinical settings, women aged 30 years to 65 years should not be screened with HPV testing alone as an alternative to co-testing at 5-year intervals or cytology alone at 3-year intervals. **Women Aged Older Than 65 Years:** Women aged older than 65 years with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened for cervical cancer with any modality (adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative co-tests within the 10 years before ceasing

Appendix B. Cervical Cancer Screening Recommendations of Other Organizations Published Since the 2012 USPSTF Recommendation

Organization	Year	Recommendation Statement
		screening, with the most recent test occurring within the past 5 years). Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner. **Women Aged Older Than 65 Years With a History of CIN2, CIN3, or Adenocarcinoma In Situ:** Following spontaneous regression or appropriate management of CIN2, CIN3, or adenocarcinoma in situ, routine screening should continue for at least 20 years (even if this extends screening past age 65 years). **Women Who Have Undergone Hysterectomy and Have No History of CIN2+:** Women at any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. Once screening is discontinued, it should not resume for any reason, including a woman's report of having a new sexual partner. **Screening Following Vaccination: Looking to the Future:** Recommended screening practices should not change on the basis of HPV vaccination status.
American Academy of Family Physicians (AAFP)[191]	2012	Endorses the 2012 USPSTF recommendation (see Section II).
American College of Obstetrics and Gynecologists (ACOG)[192]	2012	The following recommendations are based on good and consistent scientific evidence (Level A): • Cervical cancer screening should begin at age 21 years. Women younger than age 21 years should not be screened regardless of the age of sexual initiation or the presence of other behavior-related risk factors. • Women aged 21–29 years should be tested with cervical cytology alone, and screening should be performed every 3 years. Co-testing should not be performed in women younger than 30 years. • For women aged 30–65 years, co-testing with cytology and HPV testing every 5 years is preferred. • In women aged 30–65 years, screening with cytology alone every 3 years is acceptable. Annual screening should not be performed. • Women who have a history of cervical cancer, have HIV infection, are immunocompromised, or were exposed to diethylstilbestrol in utero should not follow routine screening guidelines. • Both liquid-based and conventional methods of cervical cytology collection are acceptable for screening. • In women who have had a hysterectomy with removal of the cervix (total hysterectomy) and have never had CIN 2 or higher, routine cytology screening and HPV testing should be discontinued and not restarted for any reason. • Screening by any modality should be discontinued after age 65 years in women with evidence of adequate negative prior screening results and no history of CIN 2 or higher. Adequate negative prior screening results are defined as three consecutive negative cytology results or two consecutive negative co-test results within the previous 10 years, with the most recent test performed within the past 5 years. The following recommendations are based on limited and inconsistent scientific evidence (Level B): • Women with ASC-US cytology and negative HPV co-testing results have a very low risk of CIN 3 and should continue with routine screening as indicated for their age. • Women with a history of CIN 2, CIN 3, or adenocarcinoma in situ should continue to undergo routine age-based screening for 20 years after the initial posttreatment surveillance period, even if it requires that screening continue past age 65 years. • Women should continue to be screened if they have had a total hysterectomy and have a history of CIN 2 or higher in the past 20 years or cervical cancer

Appendix B. Cervical Cancer Screening Recommendations of Other Organizations Published Since the 2012 USPSTF Recommendation

Organization	Year	Recommendation Statement
		ever. Continued screening for 20 years is recommended in women who still have a cervix and a history of CIN 2 or higher. Therefore, screening with cytology alone every 3 years for 20 years after the initial post treatment surveillance period seems reasonable for women with a hysterectomy. • Women with negative cytology and positive HPV co-testing results who are aged 30 years and older should be managed in one of two ways: 1. Repeat co-testing in 12 months. If the repeat cervical cytology test result is LSIL or higher or the HPV test result is still positive; the patient should be referred for colposcopy. Otherwise, the patient should return to routine screening (see Figure 1 in the original guideline document). 2. Immediate HPV genotype-specific testing for HPV-16 alone or HPV-16/18 should be performed. Women with positive results from tests for HPV-16 alone or HPV-16/18 should be referred directly for colposcopy. Women with negative results from tests for HPV-16 or HPV-16/18 should be co-tested in 12 months, with management of results as described (see Figure 2 in the original guideline document). The following recommendations are based primarily on consensus and expert opinion (Level C): • Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated.

Abbreviations: ASC-US = atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelis neoplasia; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion

Appendix C. Excluded Studies

Reasons for exclusion
E1. Wrong aim or irrelevant
E2. Wrong setting a. Non-HDI country
E3. Wrong comparator a. Comparative effectiveness (e.g., liquid-based cytology vs. conventional cytology alone) b. No comparator
E4. No relevant outcomes a. Observational study reporting outcomes represented in RCTs
E5. Wrong population a. Ages 18-21 years b. Studies conducted in women with abnormal screening results (e.g., cytology with HPV triage, HPV positive women only) c. Cohort defined by testing results (e.g., lab-based study)
E6. Wrong intervention (not an HPV primary screening strategy)
E7. Wrong study design a. Observational study, n<10,000 participants b. Single group cohort study with one round of screening; exceptions to the rule include addressing a subpopulation of interest
E8. Non-English
E9. Poor quality a. High or differential attrition b. Other quality issues
E10. Unable to locate

Abbreviations: HDI = Human Development Index; HPV = human papillomavirus; RCT = randomized controlled trial

1. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. J Natl Cancer Inst. 2000;92(5):397-402. PMID: 10700419. http://dx.doi.org/10.1093/jnci/92.5.397 **KQ1E5b, KQ2E5b.**
2. Long-term follow-up of ARTISTIC cervical screening trial cohort. http://www.nets.nihr.ac.uk/projects/hta/9804501. Accessed PMID: None. **KQ1E4, KQ2E4.**
3. Agorastos T, Chatzistamatiou K, Katsamagkas T, et al. Primary screening for cervical cancer based on high-risk human papillomavirus (HPV) detection and HPV 16 and HPV 18 genotyping, in comparison to cytology. PLoS One. 2015;10(3). PMID: 25793281. http://dx.doi.org/10.1371/journal.pone.0119755 **KQ1E7a, KQ2E7a.**
4. Amarosa EJ, Winer RL, Hong KJ, et al. Impact of Possibly Oncogenic High-Risk Human Papillomavirus (HPV) Types in Triage for ASC-US Cervical Cytology Results. J Low Genit Tract Dis. 2015;19(4):307-10. PMID: 26125096. http://dx.doi.org/10.1097/LGT.0000000000000132 **KQ1E5, KQ2E5.**
5. Andersson S, Dillner L, Elfgren K, et al. A comparison of the human papillomavirus test and Papanicolaou smear as a second screening method for women with minor cytological abnormalities. Acta Obstet Gynecol Scand. 2005;84(10):996-1000. PMID: 16167918. http://dx.doi.org/10.1111/j.0001-6349.2005.00702.x **KQ1E5b, KQ2E5b.**
6. Anonymous. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. BMJ. 2016;353:i2823. PMID: 27193898. http://dx.doi.org/10.1136/bmj.i2823 **KQ1E1, KQ2E1.**

7. Anonymous. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. BMJ. 2016;355:i5782. PMID: 27789534. https://dx.doi.org/10.1136/bmj.i5782 **KQ1E4, KQ2E4.**
8. Anttila A, Hakama M, Kotaniemi-Talonen L, et al. Alternative technologies in cervical cancer screening: a randomised evaluation trial. BMC Public Health. 2006;6:252. PMID: 17042938. http://dx.doi.org/10.1186/1471-2458-6-252 **KQ1E4, KQ2E4.**
9. Anttila A, Kotaniemi-Talonen L, Leinonen M, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. BMJ. 2010;340:c1804. PMID: 20423964. http://dx.doi.org/10.1136/bmj.c1804 **KQ1E4, KQ2E4.**
10. Ascus-Lsil Traige Study Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol. 2003;188(6):1383-92. PMID: 12824967. http://dx.doi.org/10.1067/mob.2003.457 **KQ1E5b, KQ2E5b.**
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89. McKenna M, McMenamin MM. Human papillomavirus testing in young women: clinical outcomes of human papillomavirus triage in a UK cervical screening program. Cancer Cytopathol. 2014;122(9):702-10. PMID: 24888573. http://dx.doi.org/10.1002/cncy.21444 **KQ1E6, KQ2E6.**
90. Monsonego J, Hudgens MG, Zerat L, et al. Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study. Int J Cancer. 2011;129(3):691-701. PMID: 20941740. http://dx.doi.org/10.1002/ijc.25726 **KQ1E4a, KQ2E4a.**
91. Monsonego J, Hudgens MG, Zerat L, et al. Risk assessment and clinical impact of liquid-based cytology, oncogenic human papillomavirus (HPV) DNA and mRNA testing in primary cervical cancer screening (the FASE study). Gynecol Oncol. 2012;125(1):175-80. PMID: 22233689. http://dx.doi.org/10.1016/j.ygyno.2012.01.002 **KQ1E4a, KQ2E4a.**
92. Moy LM, Zhao FH, Li LY, et al. Human papillomavirus testing and cervical cytology in primary screening for cervical cancer among women in rural China: comparison of sensitivity, specificity, and frequency of referral. Int J Cancer. 2010;127(3):646-56. PMID: 19960441. http://dx.doi.org/10.1002/ijc.25071 **KQ1E2a, KQ2E2a.**
93. Naucler P, Ryd W, Tornberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst. 2009;101(2):88-99. PMID: 19141778. http://dx.doi.org/10.1093/jnci/djn444 **KQ1E4, KQ2E4.**
94. Niekerk D, Ogilvie G, Krajden M, et al. hrHPV DNA testing in cervical cancer screening. First round results From the HPV for CervicAL screening (HPV FOCAL) trial. Histopathology. 2012 61: Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/086/CN-01004086/frame.html. **KQ1E4, KQ2E4.**
95. Ogilvie G, Krajden M, Ehlen T, et al. Age specific round 1 results of a cervical cancer screening trial: HPV FOCAL. Sex Transm Infect. 2013. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/410/CN-01060410/frame.html. **KQ1E4, KQ2E4.**
96. Ogilvie G, Smith L, Cook D, et al. HPV focal trial: HPV infection rates at 48 month exit for women HPV negative at baseline. International Journal of Gynecology and Obstetrics (varpagings). 2015;131:E269. PMID: None. **KQ1E4, KQ2E4.**
97. Ogilvie GS, Krajden M, van Niekerk DJ, et al. Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial -- the HPV FOCAL Study. Br J Cancer. 2012;107(12):1917-24. PMID: 23169286. http://dx.doi.org/10.1038/bjc.2012.489 **KQ1E4, KQ2E4.**

98. Ogilvie GS, Smith LW, van Niekerk DJ, et al. Women's intentions to receive cervical cancer screening with primary human papillomavirus testing. Int J Cancer. 2013;133(12):2934-43. PMID: 23754203. http://dx.doi.org/10.1002/ijc.28324 **KQ1E1, KQ2E1.**
99. Pan Q, Belinson JL, Li L, et al. A thin-layer, liquid-based pap test for mass screening in an area of China with a high incidence of cervical carcinoma. A cross-sectional, comparative study. Acta Cytol. 2003;47(1):45-50. PMID: 12585030. **KQ1E2a, KQ2E2a.**
100. Passamonti B, Gustinucci D, Giorgi Rossi P, et al. Cervical human papilloma virus (HPV) DNA primary screening test: Results of a population-based screening programme in central Italy. J Med Screen. 2016. PMID: 27614992. https://dx.doi.org/10.1177/0969141316663580 **KQ1E4, KQ2E4.**
101. Petry KU, Menton S, Menton M, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. Br J Cancer. 2003;88(10):1570-7. PMID: 12771924. http://dx.doi.org/10.1038/sj.bjc.6600918 **KQ1E7, KQ2E7.**
102. Petry KU, Rinnau F, Bohmer G, et al. Annual Papanicolaou screening for 5 years among human papillomavirus-negative women. BMC Cancer. 2013;13:379. PMID: 23937771. http://dx.doi.org/10.1186/1471-2407-13-379 **KQ1E7, KQ2E7.**
103. Phillips S, Cornall AM, Machalek DA, et al. Comparison of the Roche Cobas 4800 HPV assay to Roche Amplicor for detection of high-risk human papillomavirus. Eur J Clin Microbiol Infect Dis. 2016;35(8):1305-7. PMID: 27177752. http://dx.doi.org/10.1007/s10096-016-2665-1 **KQ1E7, KQ2E7.**
104. Poljak M, Ostrbenk A, Seme K, et al. Three-year longitudinal data on the clinical performance of the Abbott RealTime High Risk HPV test in a cervical cancer screening setting. J Clin Virol. 2016;76 Suppl 1:S29-39. PMID: 26643051. http://dx.doi.org/10.1016/j.jcv.2015.11.021 **KQ1E7a, KQ2E7a.**
105. Porras C, Wentzensen N, Rodriguez AC, et al. Switch from cytology-based to human papillomavirus test-based cervical screening: implications for colposcopy. Int J Cancer. 2012;130(8):1879-87. PMID: 21607948. http://dx.doi.org/10.1002/ijc.26194 **KQ1E2a, KQ2E2a.**
106. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol. 2008;9(10):929-36. PMID: 18805733. http://dx.doi.org/10.1016/S1470-2045(08)70210-9 **KQ1E2a, KQ2E2a.**
107. Reid JL, Wright TC, Jr., Stoler MH, et al. Human papillomavirus oncogenic mRNA testing for cervical cancer screening: baseline and longitudinal results from the CLEAR study. Am J Clin Pathol. 2015;144(3):473-83. PMID: 26276778. http://dx.doi.org/10.1309/AJCPHVD7MIP3FYVV **KQ1E5, KQ2E5.**
108. Rijkaart DC, Berkhof J, van Kemenade FJ, et al. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int J Cancer. 2012;130(3):602-10. PMID: 21400507. http://dx.doi.org/10.1002/ijc.26056 **KQ1E7b, KQ2E7b.**
109. Rijkaart DC, Berkhof J, van Kemenade FJ, et al. HPV DNA testing in population-based cervical screening (VUSA-Screen study): results and implications. Br J Cancer. 2012;106(5):975-81. PMID: 22251922. http://dx.doi.org/10.1038/bjc.2011.581 **KQ1E7b, KQ2E7b.**

110. Ronco G, Brezzi S, Carozzi F, et al. The New Technologies for Cervical Cancer Screening randomised controlled trial. An overview of results during the first phase of recruitment. Gynecol Oncol. 2007;107(1 Suppl 1):S230-2. PMID: 17822751. http://dx.doi.org/10.1016/j.ygyno.2007.07.021 **KQ1E4, KQ2E4.**
111. Ronco G, Cuzick J, Segnan N, et al. HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. Eur J Cancer. 2007;43(3):476-80. PMID: 17223540. http://dx.doi.org/10.1016/j.ejca.2006.11.013 **KQ1E5b, KQ2E5b.**
112. Ronco G, Giorgi Rossi P, Giubilato P, et al. A first survey of HPV-based screening in routine cervical cancer screening in Italy. Epidemiol Prev. 2015;39(3 Suppl 1):77-83. PMID: 26405779. **KQ1E7, KQ2E7.**
113. Royer HR, Falk EC. Young women's beliefs regarding human papillomavirus. Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns. 2012;41(1):92-102. PMID: 22150824. http://dx.doi.org/10.1111/j.1552-6909.2011.01309.x **KQ1E1, KQ2E1.**
114. Sankaranarayanan R, Chatterji R, Shastri SS, et al. Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: results from a multicenter study in India. Int J Cancer. 2004;112(2):341-7. PMID: 15352050. http://dx.doi.org/10.1002/ijc.20396 **KQ1E2a, KQ2E2a.**
115. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360(14):1385-94. PMID: 19339719. http://dx.doi.org/http://dx.doi.org/10.1056/NEJMoa0808516 **KQ1E2a, KQ2E2a.**
116. Sasaki Y, Iwanari O, Arakawa I, et al. Cervical Cancer Screening With Human Papillomavirus DNA and Cytology in Japan. Int J Gynecol Cancer. 2016. PMID: 27997455. https://dx.doi.org/10.1097/igc.0000000000000898 **KQ1E4, KQ2E4.**
117. Schiffman M, Glass AG, Wentzensen N, et al. A long-term prospective study of type-specific human papillomavirus infection and risk of cervical neoplasia among 20,000 women in the Portland Kaiser Cohort Study.[Erratum appears in Cancer Epidemiol Biomarkers Prev. 2012 Aug;21(8):1390-1]. Cancer Epidemiol Biomarkers Prev. 2011;20(7):1398-409. PMID: 21602310. http://dx.doi.org/10.1158/1055-9965.EPI-11-0206 **KQ1E7, KQ2E7.**
118. Schiffman M, Hyun N, Raine-Bennett TR, et al. A cohort study of cervical screening using partial HPV typing and cytology triage. Int J Cancer. 2016;139(11):2606-15. PMID: 27509172. https://dx.doi.org/10.1002/ijc.30375 **KQ1E4, KQ2E4.**
119. Shastri SS, Dinshaw K, Amin G, et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. Bull World Health Organ. 2005;83(3):186-94. PMID: 15798842. http://dx.doi.org/S0042-96862005000300011 **KQ1E2a, KQ2E2a.**
120. Smelov V, Elfstrom KM, Johansson ALV, et al. Long-term HPV type-specific risks of high-grade cervical intraepithelial lesions: A 14-year follow-up of a randomized primary HPV screening trial. Int J Cancer. 2015 Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/151/CN-01072151/frame.html. **KQ1E4, KQ2E4.**
121. Smelov V, Elfstrom M. HPV type-specific risks for high-grade lesions: Long-term follow-up of the swedescreen study. Sex Transm Infect. 2013. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/716/CN-01010716/frame.html. **KQ1E4, KQ2E4.**

122. Sorbye SW, Fismen S, Gutteberg TJ, et al. Primary cervical cancer screening with an HPV mRNA test: a prospective cohort study. BMJ Open. 2016;6(8):e011981. PMID: 27515759. https://dx.doi.org/10.1136/bmjopen-2016-011981 **KQ1E4, KQ2E4.**
123. Thomsen LT, Frederiksen K, Munk C, et al. High-risk and low-risk human papillomavirus and the absolute risk of cervical intraepithelial neoplasia or cancer. Obstet Gynecol. 2014;123(1):57-64. PMID: 24463664. http://dx.doi.org/10.1097/AOG.0000000000000056 **KQ1E3c, KQ2E3c.**
124. Uijterwaal MH, Polman NJ, Van Kemenade FJ, et al. Five-Year Cervical (Pre)Cancer Risk of Women Screened by HPV and Cytology Testing. Cancer Prevention Research. 2015;8(6):502-8. PMID: 25776933. http://dx.doi.org/10.1158/1940-6207.CAPR-14-0409 **KQ1E7b, KQ2E7b.**
125. Veijalainen O, Kares S, Kujala P, et al. Human papillomavirus test with cytology triage in organized screening for cervical cancer. Acta Obstet Gynecol Scand. 2016;95(11):1220-7. PMID: 27591407. https://dx.doi.org/10.1111/aogs.13013 **KQ1E4, KQ2E4.**
126. Veldhuijzen NJ, Berkhof J, Gillio-Tos A, et al. The age distribution of type-specific high-risk human papillomavirus incidence in two population-based screening trials. Cancer Epidemiol Biomarkers Prev. 2015;24(1):111-8. PMID: 25300476. http://dx.doi.org/10.1158/1055-9965.EPI-14-0628 **KQ1E4, KQ2E4.**
127. Wheeler CM, Hunt WC, Cuzick J, et al. The influence of type-specific human papillomavirus infections on the detection of cervical precancer and cancer: A population-based study of opportunistic cervical screening in the United States. Int J Cancer. 2014;135(3):624-34. PMID: 24226935. http://dx.doi.org/10.1002/ijc.28605 **KQ1E5c, KQ2E5c.**
128. Wright TC, Jr., Stoler MH, Behrens CM, et al. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol. 2012;206(1):46.e1-.e11. PMID: 21944226. http://dx.doi.org/10.1016/j.ajog.2011.07.024 **KQ1E9b, KQ2E9b.**
129. Wright TC, Jr., Stoler MH, Behrens CM, et al. Interlaboratory variation in the performance of liquid-based cytology: insights from the ATHENA trial. Int J Cancer. 2014;134(8):1835-43. PMID: 24122508. http://dx.doi.org/10.1002/ijc.28514 **KQ1E1, KQ2E1.**
130. Wright TC, Stoler MH, Behrens CM, et al. Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015;136(2):189-97. PMID: 25579108. http://dx.doi.org/http://dx.doi.org/10.1016/j.ygyno.2014.11.076 **KQ1E9b, KQ2E9b.**
131. Wright TC, Jr., Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol. 2011;136(4):578-86. PMID: 21917680. http://dx.doi.org/10.1309/AJCPTUS5EXAS6DKZ **KQ1E1, KQ2E1.**
132. Zhao C, Weng B, Li Z, et al. Follow-up outcomes of a large cohort of low-risk women with negative imaged liquid-based cytology and negative HPV test results. Am J Clin Pathol. 2013;139(1):32-8. PMID: 23270896. http://dx.doi.org/10.1309/AJCP4DF7ACLBFFGY **KQ1E5c, KQ2E5c.**
133. Zhou H, Mody RR, Luna E, et al. Clinical performance of the Food and Drug Administration-Approved high-risk HPV test for the detection of high-grade cervicovaginal lesions. Cancer Cytopathol. 2016;124(5):317-23. PMID: 26774025. http://dx.doi.org/10.1002/cncy.21687 **KQ1E5c, KQ2E5c.**

Appendix D. Included Studies

Below is a list of included studies and their ancillary publications (indented below main results publication):

1. Ibanez R, Autonell J, Sarda M, et al. Protecting the underscreened women in developed countries: the value of HPV test. BMC Cancer. 2014;14:574. PMID: 25102758. http://dx.doi.org/10.1186/1471-2407-14-574.
2. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011;12(7):663-72. PMID: 21684207. http://dx.doi.org/10.1016/S1470-2045(11)70145-0.
    a. Gage JC, Hunt WC, Schiffman M, et al. Similar risk patters after cervical screening in two large U.S. populations. 2016;128(6):1248-57.
    b. Gage JC, Schiffman M, Katki HA, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. J Natl Cancer Inst. 2014;106(8). PMID: 25038467. http://dx.doi.org/10.1093/jnci/dju153
    c. Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women who test Pap-negative but are HPV-positive. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S56-63. PMID: 23519306. http://dx.doi.org/10.1097/LGT.0b013e318285437b
3. Kitchener HC, Almonte M, Thomson C, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol. 2009;10(7):672-82. PMID: 19540162. http://dx.doi.org/10.1016/S1470-2045(09)70156-1.
    a. Kitchener HC, Almonte M, Gilham C, et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess. 2009;13(51):1-150, iii-iv. PMID: 19891902. http://dx.doi.org/10.3310/hta13510
    b. Kitchener HC, Fletcher I, Roberts C, et al. The psychosocial impact of human papillomavirus testing in primary cervical screening-a study within a randomized trial. Int J Gynecol Cancer. 2008;18(4):743-8. PMID: 17944916. http://dx.doi.org/10.1111/j.1525-1438.2007.01113.x
    c. Kitchener HC, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess. 2014;18(22):1-196. PMID: 24762804.
    d. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524-32. PMID: 24192252.
4. Leinonen MK, Nieminen P, Lonnberg S, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. BMJ. 2012;345:e7789. PMID: 23197596. http://dx.doi.org/10.1136/bmj.e7789.
5. Luyten A, Buttmann-Schweiger N, Luyten K, et al. Early detection of CIN3 and cervical cancer during long-term follow-up using HPV/Pap smear co-testing and risk-adapted follow-up in a locally organised screening programme. Int J Cancer. 2014;135(6):1408-16. PMID: 24519782. http://dx.doi.org/10.1002/ijc.28783
    a. Petry KU, Luyten A, Scherbring S. Accuracy of colposcopy management to detect CIN3 and invasive cancer in women with abnormal screening tests: results from a primary HPV

screening project from 2006 to 2011 in Wolfsburg, Germany. Gynecol Oncol. 2013;128(2):282-7. PMID: 23088926. http://dx.doi.org/10.1016/j.ygyno.2012.10.017

6. McCaffery K, Waller J, Forrest S, et al. Testing positive for human papillomavirus in routine cervical screening: examination of psychosocial impact. BJOG. 2004;111(12):1437-43. PMID: 15663132. http://dx.doi.org/10.1111/j.1471-0528.2004.00279.x.
7. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007;357(16):1589-97. PMID: 17942872. http://dx.doi.org/10.1056/NEJMoa073204.
   a. Elfstrom KM, Smelov V, Johansson AL, et al. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. BMJ. 2014;348:g130. PMID: 24435414. http://dx.doi.org/10.1136/bmj.g130
   b. Naucler P, Ryd W, Tornberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst. 2009;101(2):88-99. PMID: 19141778. http://dx.doi.org/10.1093/jnci/djn444
   c. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524-32. PMID: 24192252.
8. Ogilvie G, Krajden M, van Niekerk D, et al. HPV for cervical cancer screening (HPV FOCAL): complete Round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. Int J Cancer. 2016. PMID: None.
   a. Ogilvie GS, van Niekerk DJ, Krajden M, et al. A randomized controlled trial of Human Papillomavirus (HPV) testing for cervical cancer screening: trial design and preliminary results (HPV FOCAL Trial). BMC Cancer. 2010;10:111. PMID: 20334685. http://dx.doi.org/10.1186/1471-2407-10-111
   b. Cook DA, Mei W, Smith LW, et al. Comparison of the Roche cobas 4800 and Digene Hybrid Capture 2 HPV tests for primary cervical cancer screening in the HPV FOCAL trial. BMC Cancer. 2015;15:968. PMID: 26674353. http://dx.doi.org/10.1186/s12885-015-1959-5
   c. Coldman A. Preliminary 48 month exit results from HPV FOCAL cervical cancer screening trial: outcomes in subjects negative at baseline. 2016. PMID. None.
   d. Coldman AJ, Gondara L, Smith LW, et al. Disease detection and resource use in the safety and control arms of the HPV FOCAL cervical cancer screening trial. Br J Cancer. 2016;115(12):1487-94. PMID: 27855441. http://dx.doi.org/https://dx.doi.org/10.1038/bjc.2016.368
9. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010;11(3):249-57. PMID: 20089449. http://dx.doi.org/10.1016/S1470-2045(09)70360-2 (NTCC Phase I).
   a. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol. 2006;7(7):547-55. PMID: 16814206. http://dx.doi.org/10.1016/S1470-2045(06)70731-8
   b. Ronco G, Segnan N, Giorgi-Rossi P, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst. 2006;98(11):765-74. PMID: 16757701. http://dx.doi.org/10.1093/jnci/djj209

   c. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524-32. PMID: 24192252.

10. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010;11(3):249-57. PMID: 20089449. http://dx.doi.org/10.1016/S1470-2045(09)70360-2 (NTCC Phase II).
   a. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst. 2008;100(7):492-501. PMID: 18364502. http://dx.doi.org/10.1093/jnci/djn065
   b. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524-32. PMID: 24192252.
11. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 2012;13(1):78-88. PMID: 22177579. http://dx.doi.org/10.1016/S1470-2045(11)70296-0.
   a. Bulkmans NW, Rozendaal L, Snijders PJ, et al. POBASCAM, a population-based randomized controlled trial for implementation of high-risk HPV testing in cervical screening: design, methods and baseline data of 44,102 women. Int J Cancer. 2004;110(1):94-101. PMID: 15054873. http://dx.doi.org/10.1002/ijc.20076
   b. Dijkstra MG, van Zummeren M, Rozendaal L, et al. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. BMJ. 2016;355:i4924. PMID: 27702796. http://dx.doi.org/10.1136/bmj.i4924
   c. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383(9916):524-32. PMID: 24192252.
12. Zorzi M, Frayle H, Rizzi M, et al. A 3-year interval is too short for re-screening HPV negative women: a population-based cohort study. BJOG. 2017. PMID: 28120382. http://dx.doi.org/https://dx.doi.org/10.1111/1471-0528.14575
   a. Zorzi M, Del Mistro A, Farruggio A, et al. Use of a high-risk human papillomavirus DNA test as the primary test in a cervical cancer screening programme: a population-based cohort study. BJOG. 2013;120(10):1260-7; discussion 7-8. PMID: 23786222. http://dx.doi.org/10.1111/1471-0528.12272

Appendix E. Ongoing Studies

Table 1.

Study	Country	Population	Interventions	Relevant Outcomes	Anticipated Completion
Cervical cancer screening					
Aoki, 2015[193] (CITRUS Study)	Japan	Women aged 30-64 years (n=30,000)	LBC + HPV vs. LBC	CIN Colposcopy Invasive cancer	March 2020
Canfell & Saville, 2015[194] (COMPASS)	Australia	Women aged 25-69 years (n=121,000)	HPV vs. LBC	CIN Invasive cancer	December 2022
Murphy, 2008[195]*	Canada	Women aged 18 years or older (n=1,712)	HPV vs. Pap test	Colposcopy	January 2011 (no publications)
Ngan, 2011[196]*	Hong Kong	Women aged 30-60 years (n=12,000)	HPV + Pap test vs. Pap test	CIN	June 2017
Self-collection methods for cervical cancer screening					
Haguenoer, 2011 (APACHE-1)[197, 198]	France	Women age 20-65 years (n=734)	Self-collection vs. clinical-collected	Diagnostic accuracy	Completed
Haguenoer, 2014[199] (APACHE-2)	France	Women age 30-65 years (n=5,998)	Self-collection vs. clinician-collected	Diagnostic accuracy	Completed December 2012
Haguenoer & Sengchanh, 2015[200] (APACHE-3)	France	Women age 30-65 years (n=3,612)	At-home self-sample vs. usual care	HPV	September 2016
Kiviat, 2014[201]	United States	Women age ≥ 21 years (n=2,000)	Home-based HPV screening vs. usual care	Diagnostic accuracy for CIN1+	August 2016
Lytwyn, 2011[202]	Canada	Women age 35-69 years overdue for a Pap test (n=1,440)	Self-collection vs. reminder letter for Pap test	CIN3	Completed January 2013; no publications
Svanholm, 2008[203]	Denmark	Women age ≥ 23 years (n=100)	Tampon self-test vs. routine Pap test	Diagnostic accuracy	Completed March 2008, no publications
Szarewski, 2011[204] (Westminister Self-Sampling Study)	United Kingdom	Women age ≥ 25 years (n=3,000)	Self-collection vs. invitation letter	Positive test	Completed
Virtanen, 2011[205]	Finland	Women age 30-65 who did not take part in a screening exam (n=8,699)	Self-collection vs. reminder letter	HPV	Completed
Winer, 2014[206]	United States	Women age 30-64 years (n=17,600)	Mailed in-home HPV testing kit vs. usual care	CIN2+	February 2018
Zehbe, 2013[207, 208] (Anishinaabek Cervical Cancer Screening Study [ACCSS])	Canada	Women age 25-69 years (n=1,200)	At-home HPV test kits vs. routine Pap test	HPV	Completed 2014
Gage, 2015	United States	Women age 26-65 years (n=1000)	Self-collection vs. clinical-collected	CIN 2+ Diagnostic accuracy	June 2015

*Identified as ongoing in the previous review

Abbreviations: CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; LBC = liquid-based cytology; vs = versus

Appendix F Table 1. Baseline Population Characteristics of Included Trials, Ordered by Screening Approach

Author, Year & Quality	Mean Age (range)	Race/ Ethnicity	Smoking Status	% Vaccinated	SES	Prior History
Ronco, 2010[1, 2] NTCC Phase II Good	42 (25-60) Younger women (25-34 years): 27.9% Older women (35-60 years): 72.1%	NR	NR	NR	NR	Screening test registered w/in 4 years: 52.1%
Ogilivie, 2017[127, 133-135] HPV FOCAL Fair	46 (25-65) Younger women (25-34 years): 19.2% Older women (35-65 years): 80.9%	NR	Ever smoked (regularly): 36%	NR	HS or less: 17% Some university: 54% Trade school or college: 29% University graduate or higher: 47.2%	NR
Leinonen, 2012[126] FINNISH Fair	NR (25-65) Younger women (25-34 years): 16.8% Older women (35-65 years): 83.2%	NR	NR	NR	NR	NR
Ronco, 2010[1, 131, 132] NTCC Phase I Good	41.1 (25-60) Younger women (<35 years): 26.1% Older women (≥35 years): 73.9%	NR	NR	NR	NR	Previous round of cervical cancer screening in prior 4 years: 48.8%
Naucler, 2007[121, 136] SWEDESCREEN Fair	35.1 (32-38)	NR	NR	NR	NR	NR
Kitchener, 2009[119, 137-139] ARTISTIC Fair	NR (NR) Younger women (Age 20-29 years): 21.1% Older women (Age 30-64 years): 78.9%	NR	NR	NR	NR	NR
Rijkaart, 2012[122, 140, 141] POBASCAM Good	40 (29-61) Younger women (29-33 years): 14.2% Older women (34-56 years): 76.7%	NR	NR	NR	NR	Time since last cytological result for women with CIN2+, median (IQR): 5.0 (4.5-5.5)

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CIN = cervical intraepithelial neoplasia; HS = high school; IQR = interquartile range; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; SES = socioeconomic status; w/in = within

Appendix F Table 2. Screening, Treatment, and Subsequent Testing Protocols in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Group	Rescreening Interval of Screened Negatives	Criteria for Immediate Colposcopy	Treatment Threshold and Strategy	Definition of a Screened Positive	Next Protocol Step for Screened Positives	Detailed Subsequent Testing	Protocol Changes Between Rounds
Ronco, 2010[1, 2] NTCC Phase II Good	HPV alone	3 years	HPV+	CIN2+; CIN1 followed up via colposcopy NR	HPV+	Colposcopy	Women w/CIN1 followed up w/colposcopy; if no CIN detected, HPV+ women were actively recalled for repeat testing with HPV + LBC while HPV remained positive; referred to colposcopy if LBC was ASC-US+	Screened with CC in Round 2
	CC	3 years	LSIL+ or ASC-US+ (7 centers)	CIN2+; CIN1 followed up via colposcopy NR	LSIL+ ASC-US	Colposcopy Colposcopy (7 centers) or repeat and refer to colposcopy if LSIL+ (2 centers)	2 centers recommended repeat cytological examination and referred LSIL+ from repeat test to colposcopy	NA
Ogilivie, 2017[127, 133-135] HPV FOCAL Fair	HPV LBC triage	2 years (if originally randomized to safety arm) or 4 years (if randomized to intervention arm)	HPV+/ASC-US+	CIN2+ (assumed); treatment based on colposcopy results, directed biopsy as well as endocervical curettage when appropriate Excisional treatment for CIN2+, most commonly LEEP and occasionally cone biopsy	HPV+	Triaged with LBC [HPV+/ASC-US+ referred to immediate colposcopy]	HPV+ triaged with LBC: HPV+/ ASC-US+ referred to immediate colposcopy; if HPV+/ASC-US-, recalled at 12 months (previously 6 months) for HPV and LBC testing with referral to colposcopy if positive on either. Exit screen at 4 years w/LBC: ASC-US cases triaged w/HPV testing (no further details).	NA
	LBC HPV triage	2 years	ASC-H or LSIL+	CIN2+ (assumed); treatment based on colposcopy results, directed biopsy as well as endocervical curettage when appropriate Excisional treatment for CIN2+, most commonly LEEP and occasionally cone biopsy	ASC-H or LSIL+ ASC-US	Colposcopy Triaged with HPV [HPV+/ASC-US referred to immediate colposcopy]	ASC-US triaged w/HPV testing: HPV+ referred to colposcopy; HPV- repeat cytology at 12 months. Repeat cytology of HPV-/ASC-US at 12 months: ASC-US+ referred to colposcopy; ASC-US- rescreened at 2 years.	Threshold for HPV triage ASC-US+ at Round 2

Appendix F Table 2. Screening, Treatment, and Subsequent Testing Protocols in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Group	Rescreening Interval of Screened Negatives	Criteria for Immediate Colposcopy	Treatment Threshold and Strategy	Definition of a Screened Positive	Next Protocol Step for Screened Positives	Detailed Subsequent Testing	Protocol Changes Between Rounds
Leinonen, 2012[126] FINNISH Fair	HPV CC triage	5 years	HPV+ and mild, moderate and severe dyskaryosis, carcinoma cells; ASC-H, LSIL, HSIL and glandular atypia; after 2006, HPV+ and LSIL+	Histologically-confirmed precancerous lesions; all CIN1+ cervical lesions until December 31, 2006, after which CIN2+ treated and women age <30 years w/CIN1 were managed w/surveillance only until lesions regressed or were treated if progression occurred LEEP	HPV+	Triaged with CC [HPV+ and mild, moderate and severe dyskaryosis, carcinoma cells referred to colposcopy; ASC-H, LSIL, HSIL and glandular atypia referred to colposcopy; after 2006, HPV+/LSIL+ referred to immediate colposcopy]	HPV+ triaged to cytology: mild, moderate, and severe dyskaryosis, carcinoma cells; ASC-H, LSIL, HSIL and glandular atypia referred to colposcopy; cytological normal to benign changes recalled w/intensified screening after 12 months from initial visit. After 2006, HPV+ triaged to cytology: women w/LSIL+ referred to colposcopy Recalled women, if persistant HPV+, underwent intensified followup and eventually referred to colposcopy	NA
	CC	5 years	Mild, moderate and severe dyskaryosis, carcinoma cells; ASC-H, LSIL, HSIL and glandular atypia; after 2006, LSIL+	Histologically-confirmed precancerous lesions; all CIN1+ cervical lesions until December 31, 2006, after which CIN2+ treated and women age <30 years w/CIN1 were managed w/surveillance only until lesions regressed or were treated if progression occurred LEEP	Mild, moderate and severe dyskaryosis, carcinoma cells or ASC-H, LSIL, HSIL and glandular atypia or LSIL+ (after 2006)	Colposcopy	Borderline changes or reactive and ASC-US recalled at 6-12 months; invited to more intensified screening after 12 months Women w/negative histological confirmation invited to intensified screening after 12 months	NA

Appendix F Table 2. Screening, Treatment, and Subsequent Testing Protocols in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Group	Rescreening Interval of Screened Negatives	Criteria for Immediate Colposcopy	Treatment Threshold and Strategy	Definition of a Screened Positive	Next Protocol Step for Screened Positives	Detailed Subsequent Testing	Protocol Changes Between Rounds
Ronco, 2010[1, 131, 132] NTCC Phase I Good	HPV cotesting	3 years	ASC-US+ and/or HPV+ among women age ≥35 years	CIN2+; CIN1 followed up via colposcopy NR	HPV+ (women age ≥35 years only) and/or ASC-US+	Colposcopy	Repeat colposcopy when lack of histology-confirmed CIN in the prescence of clearly abnormal cytology Women age <35 years who had normal cytology but HPV+ were advised to repeat both tests after 1 year; referred to colposcopy if repeat testing was HPV+ or ASC-US+	Screened with CC in Round 2
	CC	3 years	LSIL+ or ASC-US+ (7 centers)	CIN2+; CIN1 followed up via colposcopy NR	LSIL+ ASC-US	Colposcopy Colposcopy (7 centers) or repeat and refer to colposcopy if LSIL+ (2 centers)	2 centers recommended repeat cytological examination and referred LSIL+ from repeat test to colposcopy Repeat colposcopy when lack of histology-confirmed CIN in the prescence of clearly abnormal cytology	NA
Naucler, 2007[121, 136] SWEDE-SCREEN Fair	HPV cotesting	3 years	ASC-US+ (varied by site)	CIN2+. Endocervical biopsies taken from all lesions that turned white with acetic acid and lesions that were not stained by Lugol's iodine solution; if not, 2 specimens obtained at 12:00 and 6:00 on ectocervix close to the squamocolumnar-cell junction; an endocervical-cell sample taken from all women Conization, loop excision	HPV+/ASC-US+ HPV+/ASC-US- or HPV-/ASC-US+	Colposcopy Repeat testing at 12 months [HPV+ referred to colposcopy]	HPV+ and no record of referral due to an abnormal Pap test offered a second round of cotesting at 12 months; if HPV+, referred to colposcopy. Annual cotesting with colposcopy if HPV+ in addition to following routine clinical practice for abnormal Pap, colposcopy, or histopathological findings.	Unblinding of HPV test 3 years after enrollment and 4 months after completion of Round 1 Screened with CC in Round 2
	CC	3 years	ASC-US+ (varied by site)	CIN2+. Endocervical biopsies taken from all lesions that turned white with acetic acid and	ASC-US+	Colposcopy	NR; in Round 1, women randomly selected for a second test 12 months later and offered colposcopy (unclear protocol)	NA

Appendix F Table 2. Screening, Treatment, and Subsequent Testing Protocols in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Group	Rescreening Interval of Screened Negatives	Criteria for Immediate Colposcopy	Treatment Threshold and Strategy	Definition of a Screened Positive	Next Protocol Step for Screened Positives	Detailed Subsequent Testing	Protocol Changes Between Rounds
				lesions that were not stained by Lugol's iodine solution; if not, 2 specimens obtained at 12:00 and 6:00 on ectocervix close to the squamocolumnar-cell junction; an endocervical-cell sample taken from all women Conization, loop excision				
Kitchener, 2009[119, 137-139] ARTISTIC Fair	HPV cotesting	3 years	HSIL+	CIN2+ Loop excision (fron CIN2+, CIN3+), punch biopsy without further excision (CIN1 or less)	HSIL+ regardless of HPV test result ASC-US or LSIL regardless of HPV test results Normal cytology and HPV+	Colposcopy Repeat cotest at 6 months Repeat HPV test at 12 months	ASC-US or LSIL, repeat LBC test at 6 months, if LSIL+, referred to colposcopy; if cyto- or ASC-US, recalled for 3rd test at 12 months. If ASC-US+ at 12 months, referred to colposcopy; if cyto-, recalled for 4th test at 24 months (a 4th test is not shown in the clinical management figures). HPV+/cyto-, repeat HPV test at 12 months; if HPV+, choice was to undergo colposcopy, or repeat test at 24 months and if still HPV+ would be offered colposcopy.	NA
	LBC	3 years	HSIL+	CIN2+ Loop excision (fron CIN2+, CIN3+), punch biopsy without further excision (CIN1 or less)	HSIL+ ASC-US or LSIL	Colposcopy Repeat cotest at 6 months	ASC-US or LSIL, repeat LBC test at 6 months, if LSIL+, referred to colposcopy; if cyto- or ASC-US, recalled for 3rd test at 12 months. If ASC-US+ at 12 months, referred to colposcopy; if cyto-, recalled for 4th test at 24 months (a 4th test is not shown in the clinical management figures)	NA

Appendix F Table 2. Screening, Treatment, and Subsequent Testing Protocols in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Group	Rescreening Interval of Screened Negatives	Criteria for Immediate Colposcopy	Treatment Threshold and Strategy	Definition of a Screened Positive	Next Protocol Step for Screened Positives	Detailed Subsequent Testing	Protocol Changes Between Rounds
Rijkaart, 2012[122, 140, 141] POBASCAM Good	HPV cotesting	5 years	BMD+	Histological biopsies taken when cervical abnormalities seen (regardless of HPV status) Treated according to standard protocols	BMD+ regardless of HPV result Normal cytology and HPV+	Colposcopy Repeat cotesting at 6 and 18 months	HPV+/cyto- advised to repeat at 6 and 18 months: if HPV+/cyto- or HPV+/BMD at 18 months, referred to colposcopy; if HPV-/cyto- or HPV-/BMD at 18 months, recalled at next screening round Women HPV+/BMD at 6 months, or HPV+/BMD or HPV+/cyto- at 18 months, referred to colposcopy; if HPV-/BMD or HPV-/cyto- at 18 months, women recalled at next screening round.	Cytology threshold for colposcopy referral HSIL+ in Round 2
	CC	5 years	BMD+	Histological biopsies taken when cervical abnormalities seen (regardless of HPV status) Treated according to standard protocols	BMD+	Colposcopy	BMD advised to repeat at 6 and 18 months: if BMD+ after either 6 or 18 months, referred to colposcopy; if cyto- at 18 months, recalled at next screening round.	Screened with HPV cotesting in Round 2

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-H = atypical cells of high-grade; ASC-US = atypical cells of undetermined significance; BMD = borderline or mild dyskaryotic; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; cyto = cytology; HPV = human papillomavirus; HSIL = high grade squamous intraepithelial lesion; LBC = liquid based cytology; LEEP = loop electrosurgical excision procedure; LSIL = low grade squamous intraepithelial lesion; NA = not applicable; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; w/ = with

Appendix F Table 3. Intervention and Control Group Descriptions in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Arm	Test Name and Manufacturer	Sample Collection Method	Sample Collected By	Sample Processed By	Sample Interpreted By
Ronco, 2010[1, 2] NTCC Phase II Good	HPV alone	Hybrid Capture 2 (Digene)	Sample of cervical cells taken by a broom-like device (Digene Cervical Sampler) and put in standard transport medium (Digene) used only for HPV testing	NR	NR	NR
	CC	NR	Sample taken with a plastic Ayre's spatula and cytobrush	NR	Cytoscreeners	Cytoscreeners, cytopathologists or local supervisor
Ogilivie, 2017[127, 133-135] HPV FOCAL Fair	HPV LBC triage	Digene Hybrid Capture 2 (Qiagen)	Two samples collected w/ ThinPrep broom-like collection device during the initial screening appointment and placed in ThinPrep PreservCyt vial (Hologic); LBC collected first (see CG for details) and the second sample is collected and frozen for future use; aliquot from first specimen used for HPV testing processed w/ Qiagen sample conversion kit	NR	Cytotechnologist	Pathologist
	LBC HPV triage	ThinPrep PreservCyt (Hologic Inc)	Two samples collected w/ ThinPrep broom-like collection device during the initial screening appointment and placed in ThinPrep PreservCyt vial (Hologic); LBC collected first and the second sample is collected and frozen for future use; all samples processed according to manufacturer's recommendations	NR	Cytotechnologist	Pathologist
Leinonen, 2012[126] FINNISH Fair	HPV CC triage	Digene Hybrid Capture 2 (Qiagen)	Two spatular subsamples of the vaginal, cervical, and endocervical smear collected with wooden or plastic Ayre's spatula (cytology); endocervical subsample by placing the tip of the sample cone-shaped cervical sample brush) of the kit to the transport medium after cytological smear	Nurse or midwife	Cytotechnicians	Cytotechnicians or pathologist
	CC	NR	Cytology smear taken w/ Ayre spatula and a cytobrush; sample prepared on a glass slide according to standard procedures; glass slide subject to routine staining	Nurse or midwife	Cytotechnicians	Cytotechnicians or pathologist

Appendix F Table 3. Intervention and Control Group Descriptions in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Arm	Test Name and Manufacturer	Sample Collection Method	Sample Collected By	Sample Processed By	Sample Interpreted By
Ronco, 2010[1, 131, 132] NTCC Phase I Good	HPV cotesting	Hybrid Capture 2; ThinPrep (Digene Corporation; Cytyc Corporation)	Cervical cell samples collected using a plastic Ayre's spatula and cytobrush; placed in PreservCyt solution (ThinPrep); one sample used for both LBC preparation and HPV testing. One cytology slide per woman prepared according to manufacturer's instructions; 4 mL of remaining sample processed w/ Digene Sample Conversion Kit followd by HC2 assay	NR	Cytologist	Cytologist; local supervisor or panel of cytologists
	CC	NR	Cervical cell samples collected using a plastic Ayre's spatula and cytobrush; one slide per woman prepared according to manufacturer's instructions.	NR	Cytologist	Cytologist; local supervisor or panel of cytologists
Naucler, 2007[121, 136] SWEDESCREEN Fair	HPV cotesting	PCR/GP5+/6+ (NR)	Endocervical and ectocervical samples were taken with a cytologic brush (assume endocervical or Cervex brush from CG description); after a conventional smear had been prepared, the brush was swirled in 1 ml of sterile 0.9% sodium chloride to release the remaining cells for analysis of HPV DNA	Clinical personnel	Laboratory technician	NR
	CC	NR	Endocervical brush (Stockholm, Gothenburg, Uppsala, and Malmo) or Cervex brush (Umea); conventional smear prepared first	Clinical personnel	NR	NR
Kitchener, 2009[119, 137-139] ARTISTIC Fair	HPV cotesting	Hybrid Capture 2 (Qiagen)	Cervical samples were collected using the Rovers Cervex-brush cervical sampler (Rovers Medical Devices) [part of the ThinPrep Cytyc kit] and rinsed into a vial containing PreservCyt transport medium; HPV test performed on liquid residue cells of the LBC sampple and read and calculated on the Digene Microplate Luminometer 2000	NR	NR	Cytoscreener; checked by biomedical scientist or cytopathologist (LBC)
	LBC	ThinPrep T3000 (Hologic)	Cervical samples were collected using the Rovers Cervex-brush cervical sampler (Rovers Medical Devices) [part of the ThinPrep Cytyc kit] and rinsed into a vial containing PreservCyt transport medium	NR	NR	Cytoscreener; checked by biomedical scientist or cytopathologist (LBC)

Appendix F Table 3. Intervention and Control Group Descriptions in Included Trials, Ordered by Screening Approach

Author, Year & Quality	Arm	Test Name and Manufacturer	Sample Collection Method	Sample Collected By	Sample Processed By	Sample Interpreted By
Rijkaart, 2012[122, 140, 141] POBASCAM Good	HPV cotesting	PCR/GP5+/6+ (NR)	Taken by GP or assistant using the Cervex-Brush or a cytobrush; after making a conventional smear, cytobrush placed in a vial containing collection medium (5 ml phosphate buffered saline and 0.5% thiomersal) for HPV testing	GP or assistant	NR	NR
	CC	Cervex-Brush (Rovers)	Taken by GP or assistant using the Cervex-Brush or a cytobrush	GP or assistant	NR	Cytotechnologist and cytopathologist (abnormal only)

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CC = conventional cytology; CG = control group; DNA = deoxyribonucleic acid; GP = general practitioner; HC2 = Hybrid Capture 2; HPV = human papillomavirus; hr = high-risk; LBC = liquid-based cytology; mL = milliliter(s); NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; PCR/GP = polymerase chain reaction general primer; POBASCAM = Population Based Screening Study Amsterdam Program ; w/ = with

Appendix F Table 4. Cumulative Incidence of CIN and Invasive Cervical Cancer in Screened Negative Women From the Long-Term Followup of Two Randomized Controlled Trials

Outcome	Study	Followup (years)	Cumulative Incidence (%) in IG Participants Screened hrHPV- (95% CI)	Cumulative Incidence (%) in IG Participants Screened hrHPV- and ASC-US- (95% CI)	Cumulative Incidence (%) in CG Participants Screened ASC-US- (95% CI)	Between Group Difference
CIN2+	SWEDESCREEN	13	1.74 (1.24 to 2.45), n=5,866	1.63 (1.11 to 2.32), n=6,028	2.73 (2.17 to 3.44), n=6,034	NR
CIN3+	POBASCAM[141]	9	0.31 (0.24 to 0.41), n=215,308	0.27 (0.20 to 0.36) , n=211,544	0.69 (0.58 to 0.82) , n=219,449	NR
		14	0.56 (0.45 to 0.70), n=215,308	0.52 (0.41 to 0.66) , n=211,544	1.20 (1.01 to 1.37) , n=219,449	IG HPV- in Round 3 vs. CG ASC-US- in Round 2: RR 0.82 (0.62 to 1.09), p=0.17* IG HPV-/ASC-US- in Round 3 vs. CG ASC-US- in Round 2: RR 0.76 (0.57 to 1.03), p=0.07
	SWEDESCREEN	13	0.89 (0.53 to 1.51) , n=5,866	0.84 (0.48 to 1.47) , n=6,028	1.54 (1.10 to 2.15) , n=6,034	NR
Invasive cervical cancer	POBASCAM[141]	9	0.03 (0.01 to 0.06), n=215,308	0.01 (0.0 to 0.05), n=211,544	0.09 (0.05 to 0.14), n=219,449	NR
		14	0.09 (0.04 to 0.18), n=215,308	0.07 (0.03 to 0.17), n=211,544	0.19 (0.12 to 0.28), n=219,449	IG hrHPV- in Round 3 vs. CG ASC-US- in Round 2: RR 0.97 (0.41 to 2.31), p=0.95 IG hrHPV-/ASC-US- in Round 3 vs. CG ASC-US- in Round 2: RR 0.83 (0.32 to 2.15), p=0.69

Abbreviations: ASC-US = atypical squamous cells of undetermined significance; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papillomavirus; IG = intervention group; RR = risk ratio

Appendix F Table 5. Baseline Population Characteristics of Included Observational Studies

Author, Year & Quality	Mean Age (range)	Race/Ethnicity	Smoking Status	% Vaccinated	SES	Prior History
Katki, 2011[124, 143, 144, 181-183] KPNC Fair	NR (≥30)	NR	NR	NR	NR	NR
Ibanez, 2014[123] Fair	54.1 (40-88)	NR	NR	NR	NR	Not screened in past 5 years: 100%
Luyten, 2014[125, 129] WOLPHSCREEN Fair	48.2 (≥ 35) Older women (> 70 years): 5.5%	NR	NR	NR	NR	NR
McCaffery, 2004[120] Fair	32 (20-61) Younger women (< 35 years): 73.1% Older women (≥ 35 years): 26.9%	NR	Current Smoker: 30.3%	NR	Age ≤ 16 when left full-time education: 7.4% Age 17-18 when left full-time education: 13.6% Age ≥ 19 when left full-time education: 73.1%	NR
Zorzi, 2017[128] Fair	25-64	NR	NR	NR	NR	NR

Abbreviations: KPNC = Kaiser Permanente Northern California; NR = not reported; SES = socioeconomic status

Appendix F Table 6. Intervention and Control Group Descriptions in Included Observational Studies

Author, Year & Quality	Intervention	Test Name and Manufacturer	Sample Collection Method	Sample Collected By	Sample Process By	Sample Interpreted By
Katki, 2011[124, 143, 144, 181-183] KPNC Fair	HPV cotesting	Hybrid Capture 2 (Qiagen); BD FocalPoint Slide Profiles or BD SurePath	NR	NR	NR	NR
Ibanez, 2014[123] Fair	HPV cotesting	Hybrid Capture 2 (Qiagen)	Cytologies performed w/ conventional Pap smear; a few centers used LBC	NR	NR	NR
Luyten, 2014[125, 129] WOLPHSCREEN Fair	HPV cotesting	Hybrid Capture 2 (NR)	Routine pelvic examination w/ Pap smear followed by a separate cervical sample taken w/ a Medscan brush for hrHPV testing	NR	NR	NR
McCaffery, 2004[120] Fair	HPV cotesting	Digene Hybrid Capture 2 (NR)	NR	Clinician or clinic nurse	NR	NR
Zorzi, 2017[128, 209] Fair	HPV Primary with cytology triage	Hybrid Capture 2 (Qiagen)	Cytologies performed w/ conventional Pap smear	Midwives	Cytologist	Cytologist

Abbreviations: HPV = human papillomavirus; hr = high-risk; KPNC = Kaiser Permanente Northern California; LBC = liquid-based cytology; NR = not reported; w/ = with

Appendix F Table 7. CIN and Invasive Cervical Cancer Among Screened Positive Women in Included Trials, All Participants

Parameter	Rnd	NTCC Phase II[1,2]	HPV FOCAL[127,133-135]	FINNISH[126]	NTCC Phase I[1,131,132]	SWEDESCREEN[121,136]	ARTISTIC[119,137-139]	POBASCAM[122,140,141]
Ages recruited	--	25-60 years	25-65 years	25-65 years	25-60 years	32-38 years	20-64 years	29-61 years
Definition of screened positive	1	IG: hrHPV+ CG: ASC-US+	IG: hrHPV+/ASC-US+ CG: ASC-US+	IG: hrHPV+/ASC-US+ CG: ASC-US+	IG: hrHPV+ or ASC-US+ CG: ASC-US+	IG: hrHPV+ or ASC-US+ CG: ASC-US+	IG: hrHPV+ or ASC-US+ CG: ASC-US+	IG: hrHPV+ or BMD+ CG: BMD+
	2	IG: ASC-US+ CG: ASC-US+	--	--	IG: ASC-US+ CG: ASC-US+	IG: ASC-US+ CG: ASC-US+	IG: hrHPV+ or ASC-US+ CG: ASC-US+	IG: hrHPV+ or BMD+ CG: hrHPV+ or BMD+
Followup (years)	1	3.5 years (maximum)	2-4 years (maximum)	5 years (maximum)	3.5 years (maximum)	3 years (maximum)	2.2 years (maximum)	4 years (maximum)
	2	3.5 years (maximum)	2 years (maximum)	--	3.5 years (maximum)	NR	2.3 years (maximum)	5 years (maximum)
Number of screened positive women with CIN2+ (PPV)	1	IG: 137/1,936 (7.1%) CG: 55/825 (6.7%)	NR	IG: 509/4,971 (10.2%)* CG: 267/4,506 (5.9%)*	IG: 120/2,822 (4.3%) CG: 84/855 (9.8%)	IG: NR CG: 78/150 (52.0%)	IG: 453/4,019 (11.3%) CG: 133/786 (16.9%)	IG: 257/1,406 (18.3%) CG: 193/706 (27.3%)
	2	NR	--	--	NR	NR	IG: 80/1,258 (6.4%)* CG: 34/210 (16.2%)*	IG: 132/742 (17.8%) CG: 162/774 (20.9%)
Number of CIN2+ in screened positive women	1	IG: 137/137 (100%) CG: 55/55 (100%)	NR	IG: 509/540 (94.3%) CG: 267/319 (83.7%)	IG: 120/120 (100%) CG: 84/84 (100%)	IG: NR CG: 78/119 (65.5%)	IG: 453/453 (100%) CG: 133/133 (100%)	IG: 257/267 (96.3%) CG: 193/215 (89.8%)
	2	NR	--	--	NR	NR	IG: 80/85 (94.1%)* CG: 34/35 (97.1%)*	IG: 132/160 (82.5%) CG: 162/184 (88.0%)
False positive rate for CIN2+	1	IG: 1,799/24,428 (7.4%) CG: 770/24,038 (3.2%)	NR	IG: 4,462/61,597 (7.2%) CG: 4,239/65,480 (6.5%)	IG: 2,702/22,042 (12.3%) CG: 771/21,972 (3.5%)	IG: NR CG: 72/6,192 (1.2%)	IG: 3,566/17,933 (19.9%) CG: 653/5,991 (10.9%)	IG: 1,149/19,742 (5.8%) CG: 513/19,913 (2.6%)
	2	NR	--	--	NR	NR	IG: 1,178/10,512 (11.2%)* CG: 176/3,832 (4.6%)*	IG: 610/9,572 (6.4%) CG: 612/9,450 (6.5%)

Appendix F Table 7. CIN and Invasive Cervical Cancer Among Screened Positive Women in Included Trials, All Participants

Parameter	Rnd	NTCC Phase II[1,2]	HPV FOCAL[127,133-135]	FINNISH[126]	NTCC Phase I[1,131,132]	SWEDESCREEN[121,136]	ARTISTIC[119,137-139]	POBASCAM[122,140,141]
Number of screened positive women with CIN3+ (PPV)	1	IG: 59/1,936 (3.0%) CG: 26/825 (3.2%)	NR	IG: 184/4,971 (3.7%) CG: 97/4,506 (2.2%)	IG: 53/2,822 (1.9%) CG: 53/855 (6.2%)	IG: NR CG: 56/150 (37.3%)	IG: 233/4,019 (5.8%) CG: 80/786 (10.2%)	IG: 168/1,406 (11.9%) CG: 138/706 (19.5%)
	2	NR	--	--	NR	NR	IG: 34/1,258 (2.7%)* CG: 18/210 (8.6%)*	IG: 80/742 (10.8%) CG: 110/774 (14.2%)
Number of CIN3+ in screened positive women	1	IG: 59/59 (100%) CG: 26/26 (100%)	NR	IG: 184/195 (94.4%) CG: 97/118 (82.2%)	IG: 53/53 (100%) CG: 53/53 (100%)	IG: NR CG: 56/85 (65.9%)	IG: 233/233 (100%) CG: 80/80 (100%)	IG: 168/171 (98.2%) CG: 138/150 (92.0%)
	2	NR	--	--	NR	NR	IG: 34/35 (97.1%)* CG: 18/19 (94.7%)*	IG: 80/88 (90.9%) CG: 110/130 (84.6%)
False positive rate for CIN3+	1	IG: 1,877/24,506 (7.7%) CG: 799/24,067 (3.3%)	NR	IG: 4,787/61,922 (7.7%) CG: 4,409/65,650 (6.7%)	IG: 2,769/22,109 (12.5%) CG: 802/22,003 (3.6%)	IG: NR CG: 94/6,214 (1.5%)	IG: 3,786/18,153 (20.9%) CG: 706/6,044 (11.7%)	IG: 1,235/19,831 (6.2%) CG: 568/19,968 (2.8%)
	2	NR	--	--	NR	NR	IG: 1,224/10,558 (11.6%)* CG: 192/3,848 (5.0%)*	IG: 662/9,624 (6.9%) CG: 664/9,502 (7.0%)
Number of screened positive women with ICC	1	NR	NR	NR	NR	NR	IG: 5/4,019 (0.1%) CG: 4/786 (0.5%)	IG: 12/1,406 (0.8%) CG: 5/706 (0.7%)
	2	NR	--	--	NR	NR	IG: 3/1,258 (0.2%)* CG: 0/210 (0%)*	IG: 3/742 (0.4%) CG: 10/774 (1.3%)
Number of women diagnosed with ICC that had screened positive	1	NR	NR	NR	NR	NR	IG: 5/5 (100%) CG: 4/4 (100%)	IG: 12/12 (100%) CG: 5/6 (83.3%)
	2	NR	--	--	NR	NR	IG: 3/3 (100%)* CG: 0/0 (0%)*	IG: 3/4 (75%) CG: 9/14 (64.3%)

Test positivity was based on referral to colposcopy or more intensive screening
*From author inquiry
†Preliminary or incomplete results

Abbreviations: ASC-US = atypical cells of undetermined significance; BMD = borderline or mild dyskaryotic; CG = control group; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; ICC = invasive cervical cancer; IG = intervention group; NR = not reported; Rnd = round.

Appendix F Table 8. Colposcopies and Biopsies of Included Randomized Controlled Trials

Parameter	Round	NTCC Phase II[1]	HPV FOCAL[210]	FINNISH[126]	NTCC Phase I[1]	SWEDESCREEN[121]	ARTISTIC[119]	POBASCAM[122]
Number of women referred to colposcopy	1	IG: 1,936/24,661 (7.9%)† CG: 679/25,435 (2.8%)†	IG: 5.9% (95% CI, 5.5 to 6.3)* CG: 3.1% (95% CI, 2.8 to 3.5)*	IG: 796/66,410 (1.2%) CG: 755/65,784 (1.1%)	IG: 2,470/22,708 (10.9%)† CG: 738/22,466 (3.3%)†	NR	IG: 1,247/18,386 (6.8%) CG: 320/6,124 (5.2%)	NR
	2	NR	--	--	NR	NR	IG: 284/10,716 (2.7%)‡ CG: 74/3,514 (2.1%)‡	NR
Number of women undergoing colposcopy	1	IG: 1,813/1,936 (93.6%)† CG: 615/679 (90.6%)†	IG: 340/361 (94.1%)† CG: 185/196 (94.1%)†	NR	IG: 2,319/2,470 (93.9%)† CG: 674/738 (91.3%)†	NR	NR	NR
	2	NR	--	--	NR	NR	NR	NR
Number of women undergoing a biopsy	1	IG: 788/1,813 (43.5%) CG: 323/617 (52.4%)	NR	NR	NR	NR	NR	NR
	2	NR	--	--	NR	NR	NR	NR

*Converted from rate per 1,000 women
†Estimated data from figure
‡Preliminary or incomplete results

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CG = control group; HPV = human papillomavirus; IG = intervention group; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program

Appendix F Table 9. CIN and Invasive Cervical Cancer Among Screened Negative Women In Included Trials, All Participants

Parameter	Rnd	NTCC Phase II[1,2]	HPV FOCAL[127,133-135‡]	FINNISH[126]	NTCC Phase I[1,131,132]	SWEDESCREEN[121,136]	ARTISTIC[119,137-139]	POBASCAM[122,140,141]
Ages recruited	--	25-60 years	25-65 years	25-65 years	25-60 years	32-38 years	20-64 years	29-61 years
Definition of screened negative	1	IG: hrHPV- CG: ASC-US-	IG: hrHPV- CG: ASC-US-	IG: hrHPV- CG: ASC-US-	IG: hrHPV-/ASC-US- CG: ASC-US-	IG: hrHPV-/ASC-US- CG: ASC-US-	IG: hrHPV-/ASC-US- CG: ASC-US-	IG: hrHPV-/BMD- CG: BMD-
	2	IG: ASC-US- CG: ASC-US-	--	--	IG: ASC-US- CG: ASC-US-	IG: ASC-US- CG: ASC-US-	IG: hrHPV-/ASC-US- CG: ASC-US-	IG: hrHPV-/BMD- CG: hrHPV-/BMD-
Followup (years)	1	3.5 years (maximum)	2-4 years (maximum)§	5 years (maximum)	3.5 years (maximum)	3 years (maximum)	2.2 years (maximum)	4 years (maximum)
	2	3.5 years (maximum)	2 years (maximum)	--	3.5 years (maximum)	NR	2.3 years (maximum)	5 years (maximum)
Number of screened negative women with ICC	1	NR	NR	IG: 5/57,135 (0.01%) CG: 2/61,241 (0.003%)	NR	NR	IG: 0/14,367 (0%) CG: 0/5,338 (0%)	IG: 0/18,593 (0%) CG: 1/19,400 (0.005%)
	2	NR	--	--	NR	NR	IG: 0/9,334 (0%)* CG: 0/3,656 (0.0%)*	IG: 0/8,962 (0%) CG: 0/8,838 (0%)
Number of women diagnosed with ICC that had been screened negative	1	NR	NR	IG: 5/17 (29.4%) CG: 2/9 (22.2%)	NR	NR	IG: 0/5 (0%) CG: 0/4 (0%)	IG: 0/12 (0%) CG: 1/6 (16.7%)
	2	NR	--	--	NR	NR	IG: 0/3 (0%)* CG: 0/0 (0%)*	IG: 0/4 (0%) CG: 0/14 (0%)

*Preliminary or incomplete results
†In the control group, this is the second round of screening 4 years after enrollment; the first round of screening occurred 2 years after enrollment identified 17/6,447 [0.3%] women with CIN3+
‡From author inquiry
§HPV FOCAL had two randomized hrHPV arms: safety arm (screening every 2 years) and intervention arm (screening every 4 years); control arm screened every 2 years

Abbreviations: ASC-US = atypical cells of undetermined significance; BMD = borderline or mild dyskaryotic; CG = control group; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; ICC = invasive cervical cancer; IG = intervention group; NR = not reported