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A Systematic Review of Tests for Postcolposcopy and Posttreatment Surveillance

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Objective: For the 2019 ASCCP Risk-Based Management Consensus Guidelines, we conducted a systematic review of diagnostic assays for postcolposcopy and posttreatment management.

Materials and Methods: A literature search was conducted to identify articles reporting on tests/assays for cervical cancer screening, triage, postcolposcopy surveillance, and posttreatment surveillance published between 2012 and 2019 in PubMed and Embase. Titles and abstracts were evaluated by co-authors for inclusion. Included articles underwent full-text review, data abstraction, and quality assessment. Pooled absolute pretest and posttest risk estimates were calculated for studies evaluating management of patients after treatment.

Results: A total of 2,862 articles were identified through the search. Of 50 articles on postcolposcopy, 5 were included for data abstraction. Of 66 articles on posttreatment, 23 were included for data abstraction and were summarized in the meta-analysis. The pooled posttreatment risk of cervical intraepithelial neoplasia (CIN) 2+ in all studies was 4.8% (95% CI = 3.4%–6.8%), ranging from 0.4%–19.5% ($\tau^2 = 0.57$) in individual studies. Among individuals testing negative for human papillomavirus (HPV) posttreatment, the risk of CIN 2+ was 0.69% (95% CI = 0.3%–1.5%); among individuals testing positive for HPV posttreatment, the risk of CIN 2+ was 18.3% (95% CI = 12.1%–26.6%) in all studies. All risk estimates were substantially higher for liquid-based cytology. The HPV–cytology co-testing provided slightly better reassurance compared with HPV alone at the cost of much higher positivity.

Conclusions: Despite a large number of published studies on postcolposcopy and posttreatment surveillance, only few met criteria for abstraction and were included in the meta-analysis. More high-quality studies are needed to evaluate assays and approaches that can improve management of patients with abnormal screening.

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The 2019 ASCCP Consensus Guidelines address clinical management of patients with abnormal screening results, patients who are under surveillance after colposcopy, and patients who are undergoing surveillance after treatment. The new guidelines separate the process of setting clinical action thresholds (risk thresholds) from the actual risk assessment that is based on a patient's cervical test results and other factors such as screening history.

The uniform biology and well-understood natural history of cervical cancer has led to development of a variety of new assays, including both human papillomavirus (HPV)-based and non-HPV tests, that are very effective for screening, triage, and management of cervical precancers.[1–4] Current cervical cancer screening and management relies on HPV testing and cytology from cervical samples. In the United States, any test that is used for clinical management requires regulatory approval by the Food and Drug Administration. Several tests have been approved for primary screening, including liquid-based cytology (LBC), HPV testing alone, and HPV testing in combination with cytology (co-testing). The large effort and costs associated with conducting regulatory trials, balanced against the relatively small target populations, makes it unlikely that these trials will address management questions.[5] Therefore, tests for management are typically used "off-label," because they have not been approved for the specific management indications, only recommended because of other studies and expert opinion.

It is in the purview of clinical practice guidelines to evaluate posttest risk estimates in relation to clinical action thresholds for management indications and make recommendations for clinical use. Two major data sources were used to develop the 2019 guidelines. Clinical databases, most importantly from Kaiser Permanente Northern California, were used to calculate risk estimates integrating HPV testing, cytology, and screening history. Because these databases do not include all currently available assays and strategies, other data sources are needed to supplement risk estimates of clinically relevant outcomes. Therefore, to inform the ASCCP consensus guidelines on management, we conducted a comprehensive systematic review and meta-analysis of published studies with thorough quality assessment (Clarke et al., in this issue) to evaluate tests for postcolposcopy and posttreatment surveillance.

METHODS

Search Strategy

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; see Figure 1) guidelines. The literature search focused on identifying articles reporting on tests/assays for cervical cancer screening, triage, postcolposcopy surveillance and posttreatment surveillance. We searched English-language, peer-reviewed studies published since 2012, when the guidelines were last updated, in the MEDLINE database via PubMed and Embase

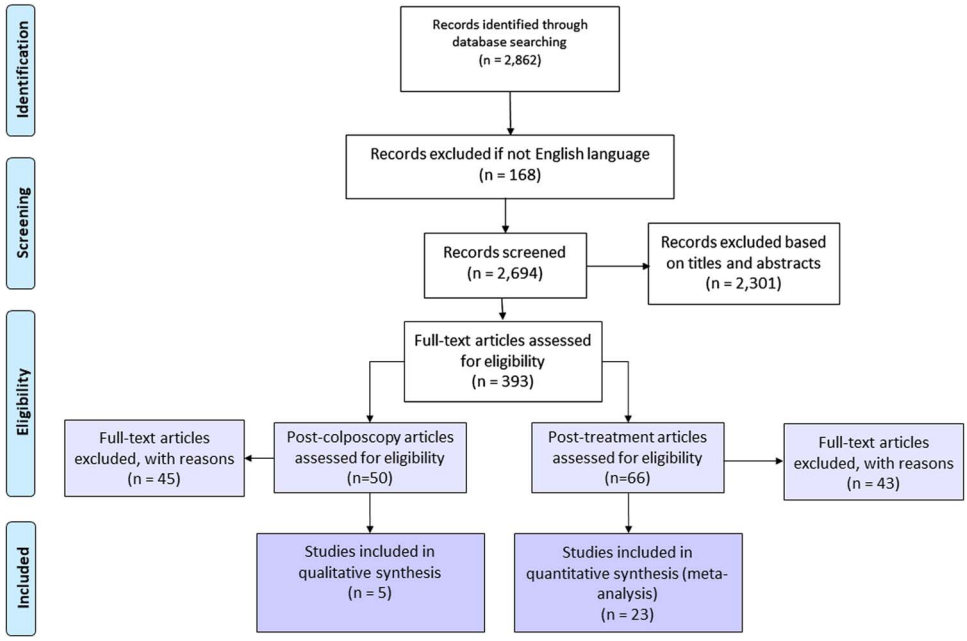

FIGURE 1. The PRISMA flow diagram illustrates the different phases of this systematic review. It includes the number of records identified and those that were included and excluded for postcolposcopy and posttreatment surveillance studies.

using search terms defined in the Supplemental Methods, http://links.lww.com/LGT/A153. We also reviewed reference lists of articles identified in the primary search for additional relevant studies. For the main literature search, results were limited to articles in English language published between January 1, 2012, and January 28, 2019. One specific question related to the ASCCP consensus guidelines was to evaluate HPV alone versus HPV-cytology co-testing posttreatment. During the period of the systematic review, only 2 studies directly compared HPV-cytology co-testing to HPV alone for posttreatment management. In 2012, a systematic review was published that included 8 additional studies published between 2004 and 2011,[6] we included these articles to address the HPV versus co-testing question.

Titles and abstracts of identified articles were equally divided among working group members to be screened for inclusion. Articles not relevant to tests/assays for cervical cancer screening, triage, postcolposcopy surveillance, and posttreatment surveillance were excluded. Full-text versions of eligible articles were reviewed to determine eligibility; for these articles, the indication and assay type were recorded. Data abstraction was conducted in 2 phases for posttreatment surveillance and postcolposcopy surveillance to address the aims of the ASCCP consensus guidelines. We abstracted data on study location, study design, treatment modality (if applicable), assay/test, study inclusion criteria, follow-up algorithms, testing intervals, and the number of cases and noncases by various test results.

For this meta-analysis, articles were included if they evaluated the clinical performance of assays/tests for postcolposcopy surveillance and/or posttreatment surveillance. For studies of postcolposcopy surveillance, tests had to be conducted among individuals who underwent colposcopy and biopsy, without an indication for treatment. Studies that predominantly evaluated risk in women who had an indication for treatment, but were not treated for various reasons, were not considered since they do not reflect the typical postcolposcopy population. For studies of posttreatment surveillance, tests had to be conducted after individuals were treated predominantly for histologically confirmed CIN 2+ or CIN 3+. If a study evaluated more than one assay on the same patients, we prioritized assays that were used more commonly to allow pooling of data. If a study evaluated more than one assay on different subsets of patients, we included both sets of results in the analysis.

Quality Assessment

The quality of selected studies was independently evaluated by N.W. and M.A.C. using adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 revised tool criteria for quality assessment of included articles (Clarke et al., in this issue). Briefly, each article was evaluated in 4 areas (population, index test, reference test, flow and timing) using standardized signaling questions adapted to studies of cervical cancer screening and management. For each question, the risk of bias was evaluated, in categories of yes/no/unclear.

Statistical Analysis

We used data abstracted on cases (CIN 2+ and CIN 3+) and noncases (<CIN 2) to estimate pooled absolute risks and 95% CI using multilevel logistic-normal random effects models. Between-study variation was quantified using the τ^2 statistic. A lower τ^2 value is an indicator of lower between-study variance and hence less heterogeneity. We visualized variation in study-specific estimates using forest plots. We evaluated pooled risk estimates for the following assay classes/types: HPV (all assays), cytology, and co-testing. For HPV assays, we further evaluated pooled risks for Hybrid Capture 2 (HC2), the most widely used test in the articles reviewed. For each assay/test, we calculated pooled risks of CIN 2+ or CIN 3+ among the full study population (i.e., baseline risk), the pooled risk in the test positives (corresponding to the positive predictive value), and the pooled risk in the test negatives (corresponding to the complement of the negative predictive value). All analyses were performed in Stata, Version 15.1 (StataCorp, College Station, TX).

Role of the Funding Source

The guidelines effort received support from the National Cancer Institute and ASCCP. Participating organizations supported travel for their participating representatives. All participating consensus organizations, including the primary funders, had equal and

balanced roles in the consensus process including data analysis and interpretation, writing of manuscript, and decision to submit for publication. No industry funds were used in the development of these guidelines. The corresponding authors had final responsibility for the submission decision.

RESULTS

Systematic Review

The PRISMA diagram summarizes the systematic review process (see Figure 1). A total of 2,862 articles were identified through the search, of which 168 non-English articles were excluded. Title and abstract review removed 2,301 articles, leaving 393 articles for all indications, including 50 articles for postcolposcopy and 66 articles for posttreatment indications, respectively. For the postcolposcopy surveillance indication, 50 articles underwent full-text review and 5[7–11] were included for data abstraction. Given that too few studies were available to conduct a meta-analysis per assay/test, we performed a qualitative synthesis of posttest risks, but all studies were included in a meta-analysis of baseline risk, which is independent of the assay used. For the posttreatment surveillance indication, 66 articles underwent full-text review and 23[12–34] of these studies were included in the meta-analysis.

Summary of Assays

Among 28 articles included in the evaluation of postcolposcopy and posttreatment surveillance, data on 14 different assays were reported (see Table 1). These included LBC, dual stain cytology, p16 histology, 9 HPV DNA assays, and 2 HPV mRNA assays. The HC2 was the most widely used HPV DNA assay. With few exceptions, most assays used in the studies are available as commercial kits, and several of the HPV assays have regulatory approval for screening either alone or in co-testing.

Postcolposcopy Surveillance

Only 5 articles included data that could be abstracted to evaluate test performance for postcolposcopy surveillance. The baseline postcolposcopy risk of CIN 2+ in all included studies was 11% (95% CI = 8%–15%) ranging from 7%–17% ($\tau^2 = 0.13$) in individual studies (Supplemental Figure 1, http://links.lww.com/LGT/A148). There were not enough studies available to conduct a meta-analysis for each assay type. Two studies evaluated HPV testing, one using PCR (GP5+6+),[8] and the other evaluating both HC2 and an HPV DNA Chip.[10] In these studies, the risk of CIN 2+ after a negative HPV test ranged from 1.3% to 8.0%. Among those with a positive HPV test, the risk of CIN 2+ ranged from 11.1% to 16.3%. In the 2 studies that evaluated HPV 16/18 genotyping, one with GP5+6+[8] and the other with HPV GenoArray,[9] the risks among individuals testing negative were 7.0% and 13.0%, respectively, and the risks among individuals testing positive were 26.8% and 34.0%, respectively. In the one study that evaluated risk of CIN 2+ after p16 histology testing,[7] the risk among individuals testing negative was 5.5% and 17.6% among individuals testing positive (see Figure 2).

Posttreatment Surveillance

In total, 23 studies were included in the meta-analysis. The HC2 was evaluated in 13 studies, whereas the remaining 10 studies evaluated other HPV tests, with 3 of these studies comparing HC2 with another HPV test in the same population (see Table 1). Most studies were conducted in Europe (57%), followed by Korea (17%), China (13%), North America (9%), and Thailand (4%). A majority evaluated testing at 6 months after treatment; outcomes were ascertained for a range of follow-up periods between 6 and 121 months, with most studies ranging from 24 to 36 months.

The posttreatment risk of CIN 2+ in all studies was 4.8% (95% CI = 3.4%–6.8%), ranging from 0.4%–19.5% ($\tau^2 = 0.57$) in individual studies (Supplemental Figure 2, http://links.lww.com/LGT/A149). The risk was similar in studies that evaluated HC2 (5.0%, 95% CI = 2.8%–8.7%) and other HPV tests (4.2%, 95% CI = 2.5%–6.8%; p-Het = 0.6).

Among individuals testing negative for HPV posttreatment, the risk of CIN 2+ was 0.69% (95% CI = 0.3%–1.5%) in all studies, ranging from 0.0% to 8.6% ($\tau^2 = 2.11$) in individual studies. In studies evaluating HC2, the risk was 0.82% (95% CI = 0.3%–2.2%) and in studies evaluating other HPV tests the risk was 0.41% (0.1%–1.6%; p-het = 0.417). Among individuals testing positive for HPV posttreatment, the risk of CIN 2+ was 18.3% (95% CI = 12.1%–26.6%) in all studies, ranging from 2.0% to 59.5% ($\tau^2 = 1.05$) in individual studies. In studies evaluating HC2, the risk was 22.2% (95% CI = 12.6%–36.2%) and in studies evaluating other HPV tests the risk was 13.9% (95% CI = 7.6%–24.2%; p-het = 0.257; see Figure 3).

A total of 10 studies evaluated LBC testing after treatment. Most studies defined a positive cytology result as atypical squamous cell of undetermined significance or worse, with the exception of one study that used an low-grade squamous intraepithelial lesion cutoff.[26] The posttreatment risk of CIN 2+ in all studies was 6.8% (95% CI = 4.7%–9.7%; Supplemental Figure 3, http://links.lww.com/LGT/A150). Among individuals with negative cytology, the posttreatment risk of CIN 2+ was 1.7% (95% CI = 1.0%–3.1%) and among individuals with positive cytology, the posttreatment risk of CIN 2+ was 36.6% (95% CI = 28.4%–45.7%; see Figure 4).

Human Papilloma Virus Alone Versus Co-testing in Management

A specific question related to the ASCCP consensus guidelines was to evaluate the posttest risk associated with a positive and negative test result for HPV alone versus HPV-cytology co-testing after treatment. During the period of the systematic review, only 2 studies directly compared HPV-cytology co-testing to HPV alone for posttreatment management.[25,30] In 2012, a systematic review was published that included 8 additional studies published between 2004 and 2011.[6] We conducted a meta-analysis pooling all 10 studies evaluating co-testing versus HPV and cytology testing for posttreatment. Overall, the risk of CIN 2+ in these studies was 9.5% (95% CI = 6.4%–14.0%; Supplemental Figure 4, http://links.lww.com/LGT/A151). Among individuals with negative co-test results, the risk of CIN 2+ was 0.68% (95% CI = 0.2%–2.0%) and the risks among individuals with negative HPV and cytology results were 1.4% (95% CI = 0.9%–2.1%) and 2.5% (95% CI = 1.4%–4.5%), respectively (p value for heterogeneity = .069). Among individuals with positive co-test results, the risk of CIN 2+ was 24.9% (95% CI = 19.8%–30.8%) and the risks among individuals with positive HPV and cytology results were 31.7% (95% CI = 24.1%–40.4%) and 32.2% (95% CI = 24.7%–40.7%), respectively (p value for heterogeneity = .228; see Figure 5).

DISCUSSION

We conducted a systematic review and meta-analysis of diagnostic assays addressing management of individuals in surveillance after colposcopy and after treatment. We identified several assays that were used for these indications, but we were only able to conduct a formal meta-analysis for posttreatment surveillance. For the posttreatment indication, there were enough data to pool HPV DNA tests; however, other assays, such as HPV mRNA testing, dual stain, or methylation, had limited data and could not be pooled. We had enough data to separately pool risk estimates for HC2 and combined other HPV tests. To provide evidence for

TABLE 1. Summary of Included Studies

First author	Year	Test	Country	Design	Treatment type	No. tested	Time of testing, mo	Follow-up, mo
Postcolposcopy studies								
Cortecchia S[7]	2013	CINtec p16INK4a Histology Kit	Italy	Prospective		610	At diagnosis	36
Gurumurthy M[8]	2014	GP5+/6+	United Kingdom	RCT		155	Within 3 years of diagnosis	36
Ye J[9]	2017	HPV GenoArray	China	Prospective		273	At diagnosis	24
Kang WD[10]	2018	HC2 and HPV DNA Chip	Korea	Retrospective		2880	At diagnosis	4–60 mo (18 mo average)
Tverelv LR[11]	2018	LBC	Norway	Retrospective		374	At diagnosis	78
Posttreatment studies								
Bruhn LV[12]	2018	LBC, Cobas	Denmark	Retrospective	Cone	128	Unclear	Unclear
Byun JM[13]	2018	MyHPV Chip	Korea	Prospective	Cone, LEEP	172	6	36
Ceballos KM[14]	2017	HC2	Canada	Prospective	LEEP	2340	18	36
Cubie HA[15]	2014	HC2, Abbot, Cervista, Cobas, Aptima	United Kingdom	Prospective	Not specified	1020	6	24
Du R[16]	2013	PCR Chip – 21 HPV types	China		LEEP	141	6	12
Fan A[17]	2018	HPV genotyping YN-H16	China	Prospective	Cone, LEEP	172	6	24
Friebe K[18]	2017	HC2, Abbot	Germany	Retrospective	Cone	103	6	6
Gosvig CF[19]	2015	HC2, LBC	Denmark	Retrospective	Cone, LEEP	477	6	121
Hansen J[20]	2017	HC2, LBC	Germany	Retrospective	LEEP	153	Unclear	25
Herfs M[21]	2015	Amplicor	Belgium	Retrospective	LEEP	131	Unclear	20
Innamaa A[22]	2015	HC2, Cobas	United Kingdom	Retrospective	LEEP	1405	6	8
Kalampokas E[23]	2018	Abbot	United Kingdom	Retrospective	LLETZ	213	Unclear	12
Kang WD[24]	2016	HC2, LBC	Korea	Retrospective	LEEP	206	Unclear	24
Khunamornpong S[25]	2015	HC2, LBC	Thailand	Prospective	LEEP	82	6	24
Kong TW[26]	2014	HC2, LBC	Korea	Retrospective	Cone	684	Unclear	25
Lubrano A[27]	2012	HC2	Spain	Retrospective	LEEP	439	6	6
Molloy M[28]	2016	Cobas	Ireland	Retrospective	LLETZ	251	6	12
Persson M[29]	2012	Linear Array, Aptima, LBC	Sweden	Retrospective	LEEP, Cryo, CKC, Laser, Cone	143	12	36
Polman NJ[30]	2017	hrHPV, LBC	The Netherlands	Prospective	LEEP	299	6	12
Ryu A[31]	2012	HC2, MyHPV Chip, LBC	Korea	Retrospective	LEEP	180	3	24
Torne A[32]	2013	HC2, LBC	Spain	Prospective	LEEP	132	6	24
Wu J[33]	2016	LBC	China	Retrospective	LEEP	541	3	20
Zhao C[34]	2014	HC2	United States	Retrospective	Not specified	514	Unclear	36

CKC indicates cold knife cone; Cryo, cryotherapy; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; RCT, randomized controlled trial.

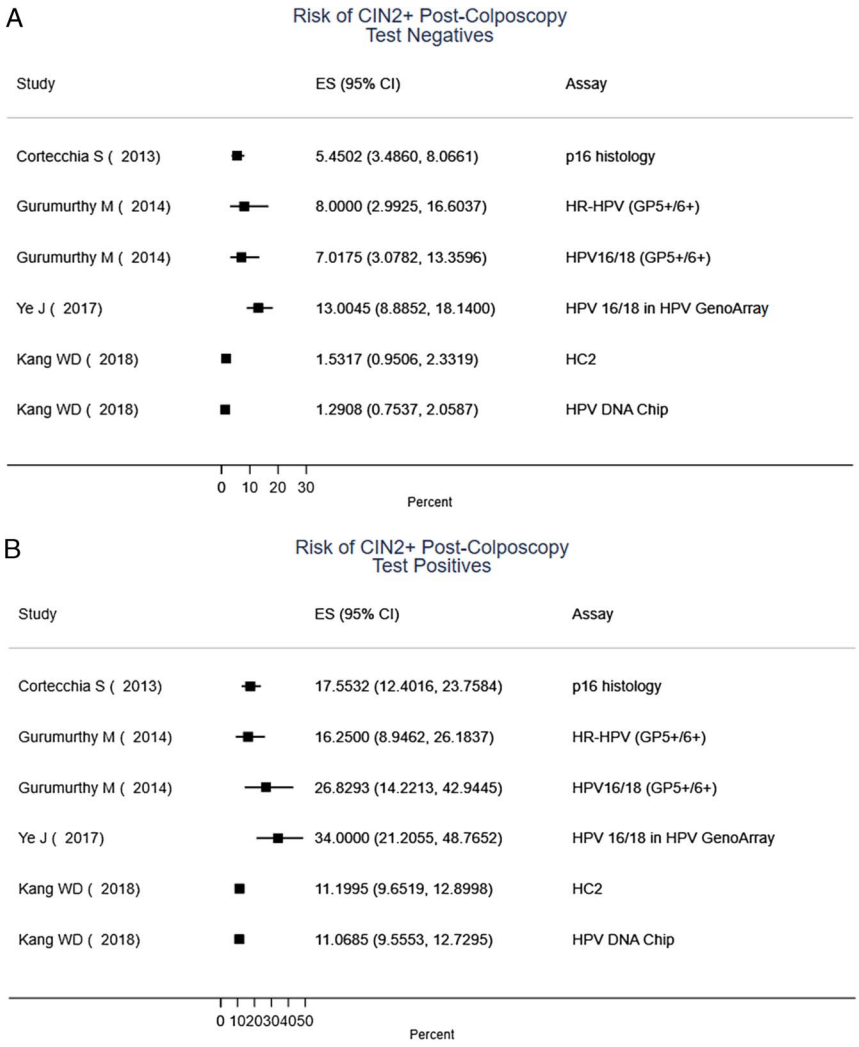

FIGURE 2. Posttest risks of CIN 2+ in postcolposcopy surveillance studies. The risks and 95% CIs of CIN 2+ for patients testing negative (A) and positive (B) are summarized on the forest plot according to which assay was used. ES indicates estimate.

the risk-based approach underlying the consensus guidelines effort, we pooled estimates of baseline risk, of risk in test negatives, and of risk in test positives. To inform recommendations for the consensus guidelines, absolute risk estimates from the systematic review were evaluated in the context of clinical management thresholds. Two factors are important to make recommendations for clinical management: (*a*) the risk estimate in relation to a clinical threshold and (*b*) the precision of the risk estimate, i.e., how wide the CIs for that estimate are.

For patients with negative HPV DNA testing after treatment, the risk was 0.69% for all HPV tests, and 0.82% and 0.41% for HC2 and other HPV tests, respectively. All of these risk estimates were clearly below the colposcopy referral threshold but had either point estimates above the 1-year return threshold, or wide CIs crossing the 1-year threshold, suggesting that a 1-year return is adequate for individuals evaluated with HC2 or with other HPV assays.

We conducted a thorough assessment of quality using adapted QUADAS-2 criteria (Clarke et al., in this issue). We identified risk of bias in many of the studies, related to all domains of the criteria. Almost all studies had a risk of bias in the patient selection domain, reflecting the wide variation in clinical practice and the lack of standards for conducting posttreatment studies. Several studies showed risk of bias in multiple domains (Supplemental Table 1, http://links.lww.com/LGT/A152). Because most studies used CIN 2+ and not CIN 3 as a primary outcome, we were only able assess risk of CIN 2 +.

Despite these limitations, several clear messages come from this effort: Our data confirm that HPV testing provides superior reassurance compared with cytology in management of individuals after treatment. We also demonstrate that HPV-cytology cotesting only provides a small risk reduction compared with HPV alone, at the cost of higher test positivity.

Pooling absolute risk estimates is a novel approach to summarize studies of diagnostic accuracy in a systematic review and meta-analysis. Most commonly, summary estimates are generated for assay accuracy measures (sensitivity and specificity). Some studies compare new tests to established standards and report relative accuracy measures. Assay performance measures such as sensitivity and specificity and absolute risks are directly connected by the disease prevalence (or pretest risk) in a specific population.[35] For a given assay's performance, absolute risks will be higher in a population with higher disease prevalence. Therefore, absolute risk estimates from studies with possible bias in the patient selection domain may be more variable. We demonstrated that disease prevalence varies substantially across studies. We also

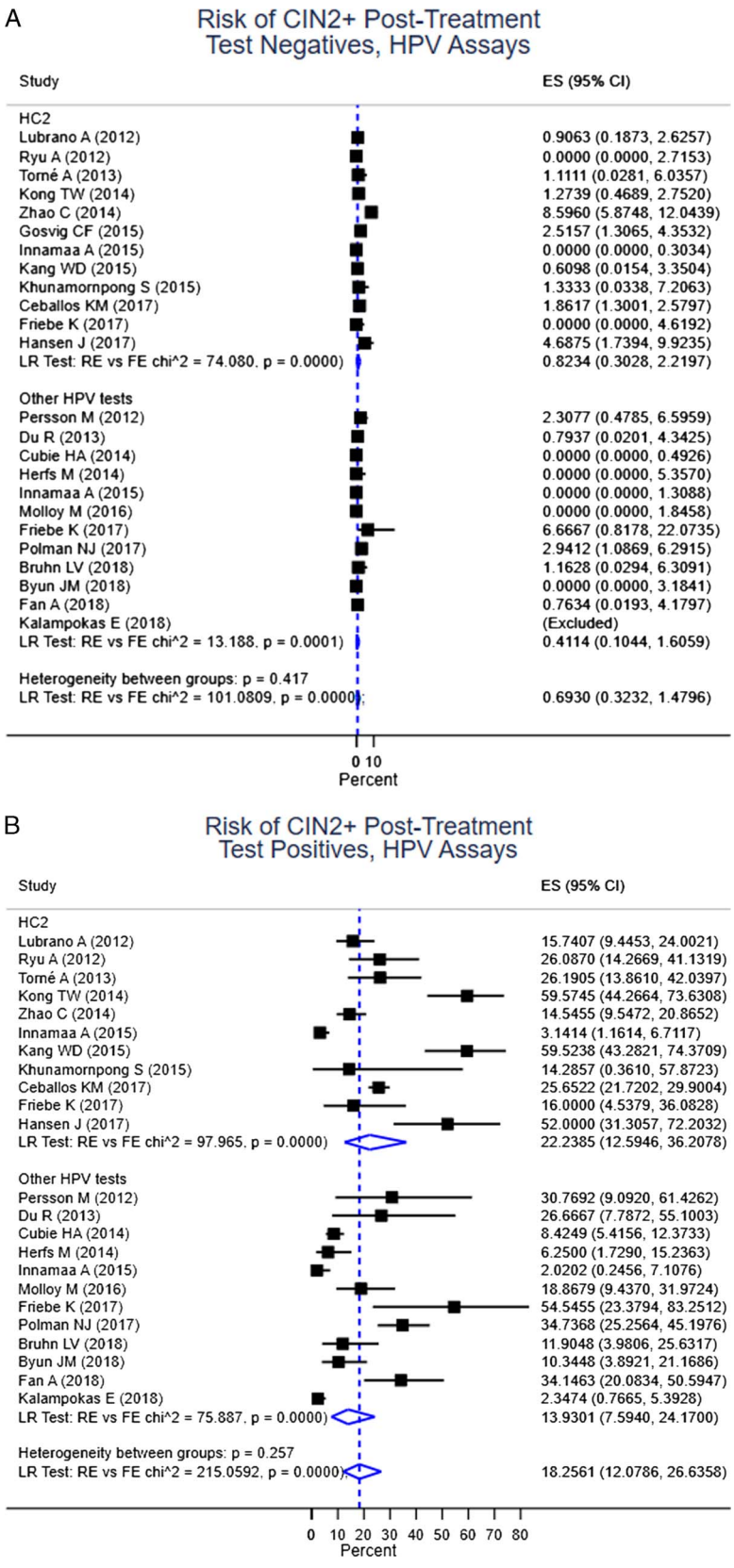

FIGURE 3. Posttest risks of CIN 2+ in posttreatment surveillance studies evaluating HPV assays. The risks and 95% CIs of CIN 2+ for patients testing negative (A) and positive (B) are summarized on the forest plot. Results are stratified by studies that used HC2 and those that used other HPV assays. ES indicates estimate; FE, fixed effects; LR, likelihood ratio; RE, random effects.

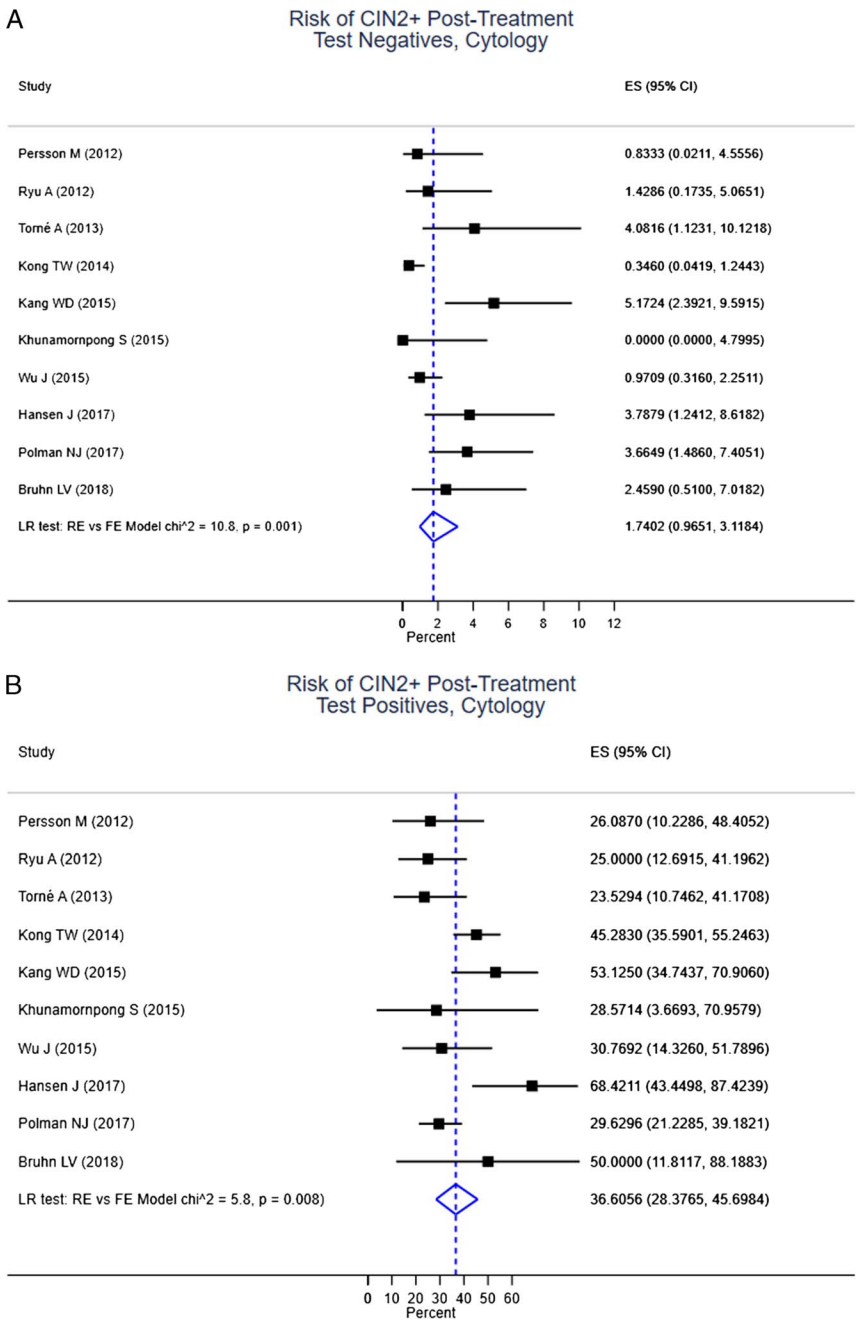

FIGURE 4. Posttest risks of CIN 2+ in posttreatment surveillance studies evaluating cytology. The risks and 95% CIs of CIN 2+ for patients testing negative (A) and positive (B) are summarized on the forest plot. ES indicates estimate; FE, fixed effects; LR, likelihood ratio; RE, random effects.

observed substantial variation of absolute risk in test positives, as a consequence of variation in pretest risk. In contrast, the heterogeneity of risk in HPV-negative patients after treatment was low, with most studies confirming a low risk among HPV-negative individuals.

Despite the variation in risk observed, the risk of HPV-positive patients after treatment is clearly high enough for colposcopy referral but does not cross the threshold for immediate treatment. Conversely, the risk in HPV-negative individuals is consistent with recommendations for follow-up testing in 1 year.

We observed a scarcity of high-quality studies that address the important areas of management of individuals after colposcopy and treatment. The working group felt that it is very important to adhere to quality criteria when designing, conducting, reporting, and evaluating diagnostic studies. As part of this systematic review, QUADAS-2 criteria were adapted to questions related to cervical cancer screening and management. We have demonstrated that meta-analyses of studies with less risk of bias have less heterogeneity, emphasizing the importance of adhering to quality standards.

In summary, we conducted a systematic review and meta-analysis of diagnostic studies for postcolposcopy and posttreatment management. Despite many publications in these areas, only a limited number of studies had data that could be abstracted for a systematic review, limiting the meta-analysis to the posttreatment indication. Even among those studies that we included in the

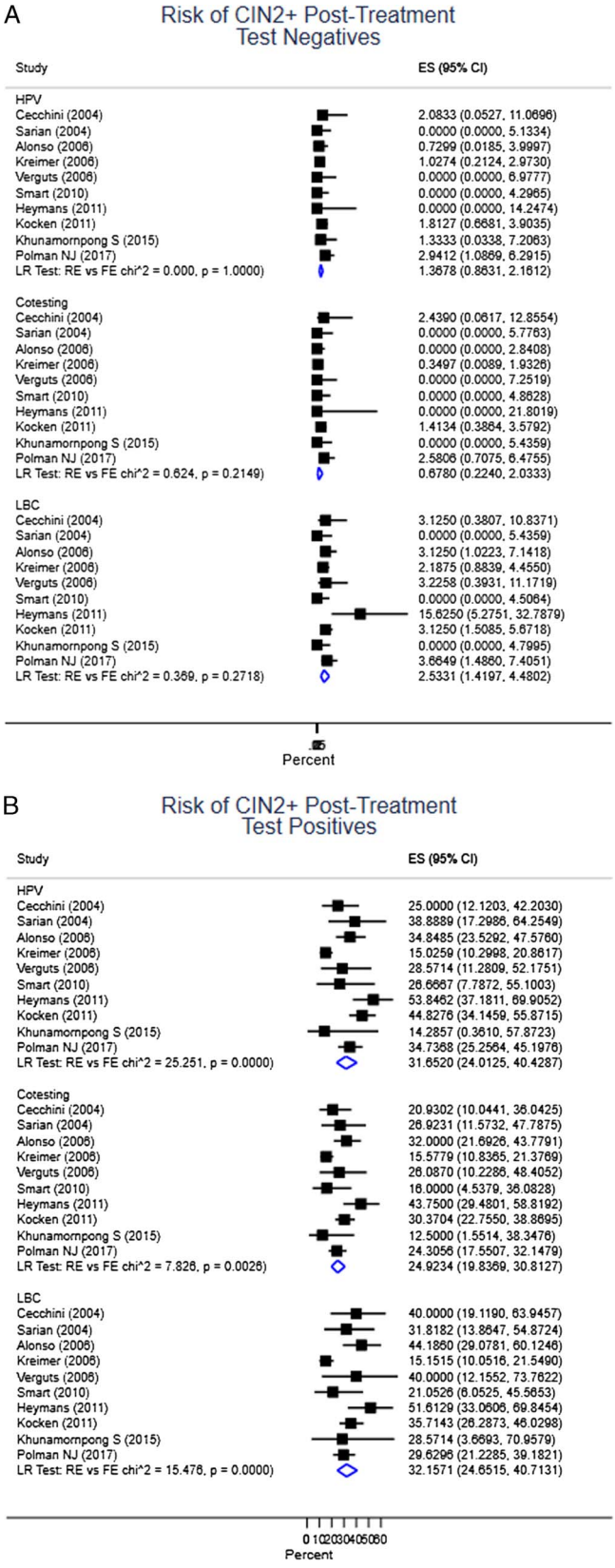

FIGURE 5. Posttest risks of CIN 2+ in posttreatment surveillance studies evaluating HPV and cytology co-testing, HPV alone, and cytology. The risks and 95% CIs of CIN 2+ for patients testing negative (A) and positive (B) are summarized on the forest plot. ES indicates estimate; FE, fixed effects; LBC, liquid-based cytology; LR, likelihood ratio; RE, random effects.

meta-analysis, a majority had a high risk of bias related to various factors, particularly in the domain of the patient selection. There are several new assays that have shown promise for improved detection of precancers but that have not been sufficiently evaluated for management settings. More high-quality studies are needed to properly evaluate these new assays and approaches.

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