J Gynecol Oncol. 2016 Jan;27(1):e3
http://dx.doi.org/10.3802/jgo.2016.27.e3
pISSN 2005-0380 · eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Posttreatment human papillomavirus testing for residual or recurrent high-grade cervical intraepithelial neoplasia: a pooled analysis

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OPEN ACCESS

Received: Mar 23, 2015
Revised: Jul 29, 2015
Accepted: Aug 19, 2015

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ABSTRACT

Objective: We conducted a pooled analysis of published studies to compare the performance of human papillomavirus (HPV) testing and cytology in detecting residual or recurrent diseases after treatment for cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3).
Methods: Source articles presenting data on posttreatment HPV testing were identified from the National Library of Medicine (PubMed) database. We included 5,319 cases from 33 articles published between 1996 and 2013.
Results: The pooled sensitivity of high-risk HPV testing (0.92; 95% confidence interval [CI], 0.90 to 0.94) for detecting posttreatment CIN 2 or worse (CIN 2+) was much higher than that of cytology (0.76; 95% CI, 0.71 to 0.80). Co-testing of HPV testing and cytology maximized the sensitivity (0.93; 95% CI, 0.87 to 0.96), while HPV genotyping (detection of the same genotype between pre- and posttreatments) did not improve the sensitivity (0.89; 95% CI, 0.82 to 0.94) compared with high-risk HPV testing alone. The specificity of high-risk HPV testing (0.83; 95% CI, 0.82 to 0.84) was similar to that of cytology (0.85; 95% CI, 0.84 to 0.87) and HPV genotyping (0.83; 95% CI, 0.81 to 0.85), while co-testing had reduced specificity (0.76; 95% CI, 0.75 to 0.78). For women with positive surgical margins, high-risk HPV testing provided remarkable risk discrimination between test-positives and test-negatives (absolute risk of residual CIN 2+ 74.4% [95% CI, 64.0 to 82.6] vs. 0.8% [95% CI, 0.15 to 4.6]; p<0.001).
Conclusion: Our findings recommend the addition of high-risk HPV testing, either alone or in conjunction with cytology, to posttreatment surveillance strategies. HPV testing can identify populations at greatest risk of posttreatment CIN 2+ lesions, especially among women with positive section margins.

Keywords: Cell Biology; Cervical Intraepithelial Neoplasia; Human Papillomavirus; Posttreatment Surveillance

JOURNAL OF GYNECOLOGIC ONCOLOGY

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Funding

This work was supported by grants from the Ministry of Education, Science, Sports and Culture of Japan (grant # 25462585 and 24791682).

Conflict of Interest

The supporting organizations played no role in the design and implementation of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

KM has received lecture fees from Sekisui Medical Co. Ltd., Hologic Japan, Inc., Japan Vaccine Co. Ltd., GlaxoSmithKline K.K. and MSD K.K., and advisory fees from Hologic Japan, Inc. HY has received lecture and advisory fees from Japan Vaccine Co. Ltd., GlaxoSmithKline K.K. and MSD K.K.

INTRODUCTION

Cytology-based cervical cancer screening programs have greatly reduced the large burden of invasive cervical cancer worldwide by detecting many premalignant lesions (cervical intraepithelial neoplasia grade 2 [CIN 2] or grade 3 [CIN 3]) before these lesions progressed to invasive diseases. Many women diagnosed with premalignant diseases are treated by local therapy including laser ablation, the loop electrosurgical excision procedure (LEEP) and cone biopsies, and 5% to 15% of these women are diagnosed with CIN 2 or CIN 3 or cervical cancer (CIN 2+) again after treatment [1-3]. Women who have been treated for CIN 2 or CIN 3 have 2.8 times higher risk of invasive cervical cancer for the subsequent 20 years compared with women who have not been treated [4]. Therefore, it is of great importance to efficiently identify women at increased or decreased risk of developing residual or recurrent CIN 2+ after treatment.

Japan and most European countries perform cytology-based follow-up after treatment of high-grade CIN [5-7]. By contrast, in the United States, co-testing of human papillomavirus (HPV) testing and cytology has been incorporated into the posttreatment surveillance strategy as well as the primary screening program [8]. The current guideline of American Society for Colposcopy and Cervical Pathology (ASCCP) recommends co-testing of HPV testing and cytology at 12 and 24 months after treatment [8]. However, this recommendation is not based on evidence from randomized controlled trials (RCTs). Although recent large-scale RCTs have demonstrated that high-risk HPV testing, alone or in combination with cytology, can detect CIN 2+ more sensitively than cytology alone in the setting of primary screening [9], no RCT has been conducted for HPV testing during posttreatment follow-up.

In the present study, we conducted a systematic review of 33 published studies that presented data on HPV-based testing methods for the detection of posttreatment residual or recurrent CIN 2+ [10-42]. This pooled analysis included a large number of women (n=5,322) and compared the test performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of various HPV-based test methods (hybrid capture 2 [HC2] test [Qiagen, Hilden, Germany], polymerase chain reaction [PCR]-based oncogenic HPV assays, oncogenic HPV persistence [defined as detection of the same oncogenic HPV type(s) between pre- and posttreatments]) with that of cytology in detecting posttreatment CIN 2+. We also addressed the influence of surgical margin status on the performance of HPV testing for predicting residual disease.

MATERIALS AND METHODS

To assess the performance of HPV-based testing methods for detecting residual or recurrent CIN 2+ in women treated for CIN 2 or CIN 3, we conducted a pooled analysis of published data. Identification of relevant studies was conducted independently by two reviewers (MO and KM) using a multi-step process. Relevant articles presenting the performance of posttreatment HPV testing were identified from National Library of Medicine (PubMed) database. We used the following search terms: CIN, treatment, HPV, posttreatment, conization or LEEP or laser, and recurrence, persistence or residual. Reference lists of systematic reviews and meta-analyses identified from this computer-aided search were used to search for additional relevant articles that might have been missed in the initial search.

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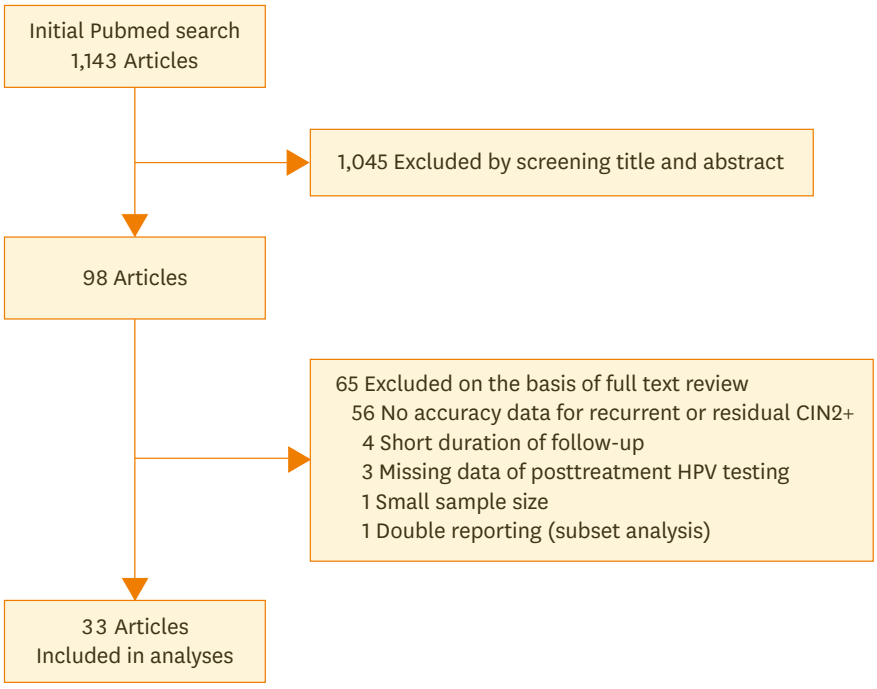

Fig. 1. Literature search. Initial search through PubMed identified 1,143 articles for our systematic review. After reviews of titles, abstracts and full texts, 33 eligible articles were included in our analysis [10-42]. CIN 2, cervical intraepithelial neoplasia grade 2; HPV, human papillomavirus.

The literature search identified 1,143 citations, of which 1,002 were excluded by their titles (**Fig. 1**). After reviewing the abstracts of the remaining 141 citations, a further 43 citations were considered not relevant and 98 citations underwent full text review by two reviewers. Studies were included if the following criteria were fulfilled: (1) women were treated for CIN 2+ using surgical procedures, laser ablation or cryotherapy, (2) the women were subsequently tested for HPV-DNA within 12 months after treatment, and (3) the final eventual outcome (the presence or absence of biopsy-proven residual or recurrent CIN 2+) was documented. Studies in which the presented data were insufficient to calculate sensitivity and specificity of HPV testing in detecting posttreatment CIN 2+ were excluded. We chose CIN 2+ as a clinically important outcome rather than CIN 3+ because: (1) the histological distinction between CIN 2 and CIN 3 is poorly reproducible and (2) CIN 2 is used as a threshold for treatment in current guidelines [6-8]. In studies in which cytologic testing were also performed, we used a threshold of atypical squamous cells of undetermined significance (ASC-US) to define a positive result because ASC-US is a threshold for further examination in current guidelines [5-8]. Studies with small sample size (<20 women) or high rates of loss to follow-up (>30%), and studies reporting follow-up data of pregnant or HIV-positive women were excluded. Studies concerning women immunized with prophylactic HPV vaccines were also excluded. Overall, the review was limited to a total of 33 studies that reported the performance of posttreatment HPV testing between 1996 and 2013, using HPV-based testing methods to identify at least 13 oncogenic strains of HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 [10-42]. When data or data subsets from an identical study had been published in more than one article, only the publication with the largest sample size was included. However, data from different studies conducted by the same study group were included.

http://dx.doi.org/10.3802/jgo.2016.27.e3

JOURNAL OF GYNECOLOGIC ONCOLOGY

For statistical analyses, two reviewers (MO and KM) extracted the following data from full texts of eligible studies: study characteristics (authors, year of publication, and country, study design), patient characteristics (sample size, mean or median age and range, initial treatment and surgical margin status), findings from HPV testing, cytology and cervical biopsies, type of HPV test (HC2, PCR-based assays and genotyping), timing of HPV assay and cytologic testing after treatment and mean or median length of follow-up and range. Data of test results were extracted into 2×2 tables of residual or recurrent CIN 2+ versus test results of HPV assay alone, cytology alone, and co-testing, which was used to calculate pooled sensitivity, specificity, and PPV and NPV. Also, studies were categorized according to type of HPV assays and surgical cut margin status. We reviewed characteristics of individual studies and assessed heterogeneity to determine whether pooling was appropriate. When appropriate, pooled sensitivity and specificity were calculated by a bivariate normal model. In 2×2 table analyses, statistical tests were two-sided and the p-values obtained in all tests were considered significant at <0.05. We used the JMP ver. 10.0J (SAS Institute, Cary, NC, USA) for statistical analysis.

RESULTS

1. Test performance of cytology and HPV testing for detecting posttreatment CIN 2+

In the pooled analysis, a total of 5,319 women from 33 prospective and retrospective studies were evaluated for the performance of HPV testing for the detection of residual or recurrent CIN 2+, and 446 women (8.4%) were histologically diagnosed with CIN 2+ again during follow-up (**Appendix 1**) [10-42]. Of the 5,319 women included in this pooled analysis, 1,667 women from 12 studies were genotyped twice (pre-treatment and posttreatment) [10-21], which allowed us to assess the ability of detection of oncogenic HPV persistence to predict residual or recurrent CIN 2+. Also, information on surgical margin status was obtained from 2,153 women reported in 14 studies [14,15,22-33]. The pooled sensitivity and specificity of cytology and the combination of HPV DNA test and cytology (co-testing) for detecting posttreatment CIN 2+ was evaluated in 4,232 women from 22 studies [13,15,16,18-22,25-29,34-42] and in 2,409 women from 11 studies [13,16,19,25,26,35-40], respectively.

The pooled sensitivity of HPV testing for detecting posttreatment CIN 2+ was much higher than that of ASC-US+ threshold cytology ([0.92; 95% CI, 0.90 to 0.94] vs. [0.76; 95% CI, 0.71 to 0.80]). The sensitivity did not vary between HPV detection methods: 0.94 (95% CI, 0.91 to 0.96) for HC2 testing, 0.92 (95% CI, 0.87 to 0.95) for PCR-based assays and 0.89 (95% CI, 0.82 to 0.94) for oncogenic HPV persistence (HPV genotyping). The high sensitivity of HPV testing yielded the highest NPV (0.99; 95% CI, 0.99 to 1.00). The pooled sensitivity of co-testing (0.93; 95% CI, 0.87 to 0.96) was slightly higher than that of HPV testing alone.

The pooled specificity of HPV testing for the detection of residual or recurrent CIN 2+ was similar to that of ASC-US+ threshold cytology ([0.83; 95% CI, 0.82 to 0.84] vs. [0.85; 95% CI, 0.84 to 0.87]). The specificity did not differ according to HPV detection method: 0.84 (95% CI, 0.83 to 0.85) for the HC2 test, 0.81 (95% CI, 0.79 to 0.83) for PCR-based methods, and 0.83 (95% CI, 0.81 to 0.85) for oncogenic HPV persistence. The pooled specificity of co-testing (0.76; 95% CI, 0.75 to 0.78) was the lowest of all test methods. The percentage of referral to colposcopy was the highest in co-testing (28.0%), followed by cytology (19.1%) and HPV testing (15.9%) (**Table 1**).

http://dx.doi.org/10.3802/jgo.2016.27.e3

JOURNAL OF GYNECOLOGIC ONCOLOGY

Table 1. Test performance of HPV testing and cytology for detection of posttreatment CIN 2 or worse

Testing methods	No. of women included in analysis	No. of test-positive women (colposcopy referral rate, %)	Detection of recurrent or residual CIN 2 or worse			
			Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
High-risk HPV test*	5,322	1,119 (21.0)	0.91 (0.88–0.94)	0.83 (0.82–0.84)	0.28 (0.26–0.31)	0.99 (0.99–1.00)
HPV genotyping†	1,667	399 (23.9)	0.89 (0.82–0.94)	0.83 (0.81–0.85)	0.28 (0.24–0.33)	0.99 (0.98–0.99)
Cytology‡	3,656	813 (22.2)	0.74 (0.68–0.79)	0.85 (0.83–0.86)	0.25 (0.22–0.28)	0.98 (0.97–0.98)
Co-testing§	2,287	645 (28.2)	0.92 (0.87–0.96)	0.76 (0.74–0.78)	0.20 (0.17–0.23)	0.99 (0.99–1.00)

CIN 2, cervical intraepithelial neoplasia grade 2; HPV, human papillomavirus; NPV, negative predictive value; PPV, positive predictive value.
*High-risk HPV tests, all HPV DNA detection assays detecting at least 13 carcinogenic HPV genotypes. †HPV genotyping, detection of HPV persistence between pre- and posttreatments. ‡Cytology, atypical squamous cells of undetermined significance threshold. §Co-testing, combination test of both high-risk HPV test and cytology.

Surgical cut margin status did not affect the test performance (sensitivity and specificity) of carcinogenic HPV testing. In women with positive surgical margins, the sensitivity and specificity of HPV testing for predicting residual CIN 2+ were very high (sensitivity: 0.98, 95% CI, 0.91 to 0.99; specificity: 0.85, 95% CI, 0.78 to 0.90). Similarly, the sensitivity and specificity were considerably high even in women with negative margins (sensitivity: 0.91, 95% CI, 0.79 to 0.97; specificity: 0.80, 95% CI, 0.76 to 0.83).

2. Risk stratification provided by carcinogenic HPV testing, cytology, and surgical margin positivity

We investigated to what extent carcinogenic HPV testing, cytology and surgical margin histology could discriminate the risk of posttreatment CIN 2+ among women treated for cervical precancerous lesions (**Fig. 2**). The absolute risk of residual or recurrent CIN 2+ lesions was 32.7% (95% CI, 30.2 to 35.4) among HPV-positive women, but only 0.9% (95%

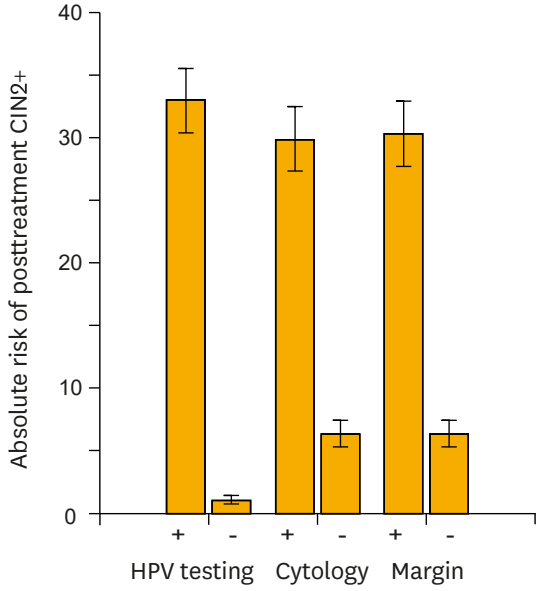

Fig. 2. Risk stratification of posttreatment cervical intraepithelial neoplasia grade 2+ (CIN 2+) provided by carcinogenic human papillomavirus (HPV) testing, cytology, and surgical margin histology. In each test method of high-risk HPV testing, cytology (atypical squamous cells of undetermined significance+) or surgical margin histology, the absolute risks of having recurrent or residual CIN 2+ lesions (■) and 95% confidence intervals (error bars) were calculated for women testing positive or negative for each test. HPV testing provided the greatest risk stratification between test-positive and -negative women.

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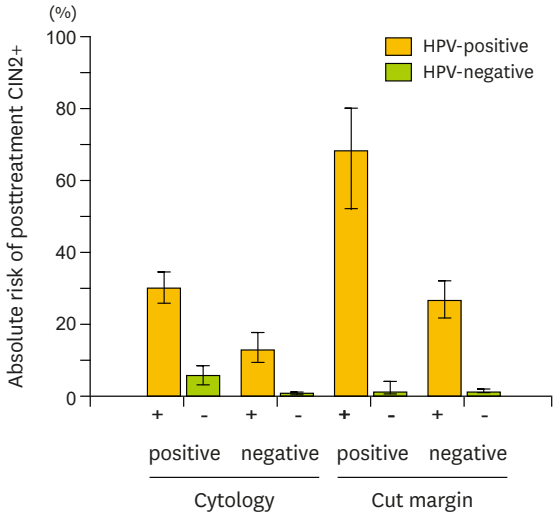

Fig. 3. Further risk stratification of posttreatment cervical intraepithelial neoplasia grade 2+ (CIN 2+) provided by the addition of carcinogenic human papillomavirus (HPV) testing to cytology and surgical margin histology. Carcinogenic HPV testing provided additional risk stratification for posttreatment CIN 2+ lesions according to cytology results (atypical squamous cells of undetermined significance+) or surgical margin status. The absolute risks of having recurrent or residual CIN 2+ lesions and 95% confidence intervals (error bars) were calculated for HPV-positive (■) and -negative women (■) in each category group.

CI, 0.6 to 1.2) among HPV-negative women (odds ratio [OR], 56.0; 95% CI, 44.9 to 70.0; p<0.001). Also, this risk was 29.6% (95% CI, 26.5 to 32.8) among women with ASC-US+ cytology, but decreased to 2.2% (95% CI, 1.8 to 2.8) among those with normal cytology (OR, 18.3; 95% CI, 14.7 to 22.6; p<0.001). In addition, we confirmed that a pooled recurrence rate was significantly higher in women with positive margins (29.7%; 95% CI, 25.4 to 34.4) than in those with negative margins (6.1%; 95% CI, 5.1 to 7.3) (OR, 6.45; 95% CI, 5.0 to 8.4; p<0.001). Although each of HPV testing, cytology and surgical margin histology was useful for posttreatment risk assessment, HPV testing provided the greatest risk discrimination between test-positive and -negative women (**Fig. 2**). This finding supports the clinical utility of incorporating HPV testing into posttreatment surveillance strategies.

The addition of carcinogenic HPV testing to cytology provided additional, more precise risk stratification among women treated for CIN 2+ (**Fig. 3**). The absolute risk of recurrent or residual CIN 2+ lesions was highest among both-positive women (29.9%; 95% CI, 25.3 to 35.0), followed by HPV-positive and cytology-negative women (13.3%; 95% CI, 9.4 to 18.5). This risk of posttreatment CIN 2+ was still high among HPV-negative but cytology-positive women (5.8%; 95% CI, 3.0 to 11.1), suggesting that this population would still need colposcopy referral. For women with both-negative results, the absolute risk of posttreatment CIN 2+ was found to be extremely low (0.9%; 95% CI, 0.4 to 2.0).

Interestingly, HPV testing for women with positive margins provided remarkable risk discrimination for having residual CIN 2+ (**Fig. 3**): women with positive HPV results had a residual CIN 2+ risk of 67.5% (95% CI, 52.3 to 80.2), while HPV-negative women had a risk of only 1.3% (95% CI, 0.4 to 12.5) (OR, 289.1; 95% CI, 63.0 to 1,325.1; p<0.001). This residual CIN 2+ risk in margin-positive but HPV-negative women was similar to that in women with both-negative results (0.9%; 95% CI, 0.4 to 2.2).

http://dx.doi.org/10.3802/jgo.2016.27.e3

JOURNAL OF GYNECOLOGIC ONCOLOGY

DISCUSSION

In this pooled analysis, high-risk HPV testing had a higher sensitivity than cytology for predicting posttreatment CIN2+, as well as comparable specificity; this was in keeping with previously conducted meta-analyses [1-3]. The increased sensitivity of HPV testing over cytology suggests that HPV testing should be incorporated into posttreatment surveillance strategies. The diagnostic accuracy of HPV testing for detecting CIN 2+ in posttreatment settings has been shown to be similar to that in primary screening settings [9]. The greatest sensitivity for detecting posttreatment disease was reached by co-testing with the HPV test and cytology. The sensitivity of co-testing for detecting residual or recurrent CIN 2+ was higher than that of separate individual tests. Because the risk for CIN 2+ is much higher in women treated for CIN 2 or CIN 3 than in screening populations, maximizing sensitivity may be more important than emphasizing specificity in posttreatment surveillance of potentially lethal diseases. These observations support the current ASCCP guideline recommending co-testing of HPV testing and cytology at 12 and 24 months after treatment of women with CIN 2 or CIN 3 [8]. However, the difference in sensitivity between HPV testing alone and co-testing was very small, suggesting that testing for carcinogenic HPV without adjunctive cytology may be sufficiently sensitive for monitoring of women treated for CIN 2 or CIN 3. In the present study, HPV testing alone resulted in fewer referrals for colposcopy than did co-testing (referral rate, 15.9% vs. 28.0%). Taking into consideration a cost of excessive referral to colposcopy, HPV testing without adjunctive cytology may achieve the maximum benefit.

In the present study, the test performance for predicting residual or recurrent disease did not differ according to type of HPV-based test method. However, detection of oncogenic HPV persistence (defined as detection of the same HPV type between pre- and posttreatment) had a slightly reduced sensitivity compared with the HC2 test and PCR-based oncogenic HPV testing. Although all CIN 2+ lesions detected after treatment are a priori considered to be residual or recurrent lesions, this reduced sensitivity may have reflected a proportion of incident lesions arising from acquisition of a new HPV after successful treatment. Testing for carcinogenic HPVs, rather than detection of HPV persistence by expensive HPV genotyping, is recommended for posttreatment surveillance to identify not only women with residual disease, but also women with high-risk HPV infections who are at increased risk for developing incidental lesions.

Although surgical cut margin positivity was significantly associated with elevated risk of residual disease, performance of HPV testing was unaffected by surgical margin status. However, for women with positive section margins, HPV testing may be useful for identifying populations at increased or decreased risk of residual disease: HPV-positive women had a residual CIN 2+ risk of 67.5%, while HPV-negative women had a risk of only 1.3%. Even in women having positive cut margins, negative HPV results conferred as low a risk as that in women with both-negative results. Thus, HPV testing may likely provide greater reassurance for HPV-negative women, thereby permitting safe extension of follow-up intervals.

The present study had several limitations. Our findings from this pooled analysis were limited by the quality of available published studies, publication bias, selection bias, and differences between included studies (for instance, differences in treatment methods, time from treatment to first HPV test, types of HPV detection assays, follow-up periods, number of repeated cytology examinations, types of cytology [conventional vs. liquid-based cytology],

http://dx.doi.org/10.3802/jgo.2016.27.e3

histological assessment of section margin, diagnostic accuracy of treatment failure, etc.). In addition, the heterogeneity of the included studies may be greater than that of previous pooled analyses because of the relatively wide inclusion criteria of this present review. Therefore, our pooled analysis was still insufficient to establish detailed follow-up algorithms for women treated for CIN 2/3. However, despite these limitations, we attempted a pooled analysis because of the lack of RCTs and the relatively small size of previous meta-analyses evaluating the posttreatment performance of HPV testing. A recent meta-analysis of eight well-designed studies indicated that high-risk HPV testing has a higher sensitivity compared with cytology in detecting posttreatment CIN 2+, and a similar specificity [3]. However, the number of women included in this meta-analysis was relatively small (n=1,512), and >50% of the data was obtained from only two studies. Another meta-analysis demonstrated similar results, but focused only on the posttreatment performance of the HC2 test, a commercialized HPV test used commonly worldwide to detect one or more of the representative 13 oncogenic HPV genotypes [2]. In addition, the sample size of that meta-analysis was also relatively small (n=1,032 from five studies). Based on the largest pooled data analysis (n=5,322) to date from 33 published studies [10-42], the present study confirmed the usefulness of HPV testing in detecting residual or recurrent diseases after treatment for CIN 2/3.

Our search found few studies with long-term follow-up data on women treated for CIN 2 or CIN 3. Therefore, our pooled analysis could not evaluate the subsequent risk of cervical cancer and precancerous lesions after 2-year posttreatment surveillance. However, a longitudinal cohort study of Dutch women treated for CIN 2 or CIN 3 demonstrated that the absolute 5- and 10-year risk of CIN 2+ in women with negative co-testing results at 6 and 24 months after treatment is very low (1.0% and 3.6%, respectively) [43], this is similar to that of women with normal cytology in primary cervical cancer screening [9].

Cost-utility analysis would be needed for incorporation of high-risk HPV assays into posttreatment follow-up of women treated for CIN 2 or CIN 3. Japan and most European countries perform cytology-based follow-up after treatment of CIN 2 or CIN 3 [5-7]. In the Netherlands and UK, the current guideline recommends repeated cytology at 6, 12, and 24 months after treatment; following three consecutive negative smears, women return to population-based routine screening [6,7]. In Japan, cytology (3,900 Japanese Yen [JPY]) is more expensive than high-risk HPV testing (3,600 JPY). Therefore, employing HPV testing alone (3,600 JPY) or co-testing with cytology (7,500 JPY) as a single test to decide whether Japanese women treated for CIN 2 or CIN 3 can return to routine screening would substantially reduce the cost of posttreatment surveillance in comparison with repeated cytology (11,700 JPY).

In conclusion, the present study, based on the largest pooled data analysis to date from 33 published studies [10-42], revealed that HPV testing was more sensitive than cytology in detecting posttreatment CIN 2+, and had an equal specificity compared with cytology. Additionally, HPV genotyping to detect persistent infection by the same HPV type did not improve sensitivity and specificity compared with HC2 tests and other PCR-based assays. Women with positive surgical margins may benefit mostly from high-risk HPV testing because of very high PPV and NPV. The present pooled analysis confirmed and expanded the results from previous studies and meta-analyses [1-3]. On the basis of our findings and the data from other published meta-analyses, the addition of HPV testing to posttreatment surveillance strategies is recommended for better protection against cervical cancer and precancerous

JOURNAL OF GYNECOLOGIC ONCOLOGY

lesions. However, large-scale RCTs are warranted to establish detailed evidence-based follow-up algorithms for women treated for CIN 2 or CIN 3.

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Appendix 1. Studies included in the pooled analysis of the performance of posttreatment human papillomavirus testing*

Author (Reference No.)	Journal	Publication Year	Country	HPV test	Time from treatment to first HPV test (mo)	N	Follow-up (mo) (mean or median [range])	Treatment	Cytology
Elfgren K et al. [13]	Am J Obstet Gynecol	1996	Sweden	PCR (GP5+6+)	6	22	16-27	Cone	LBC
Chua KL et al. [22]	Gynecol Oncol	1997	Sweden	PCR (GP5+6+)	<12	48	1-98	Cone	conventional
Distefano AL et al. [14]	Infect Dis Obstet Gynecol	1998	Argentina	PCR (GP5+6+)	6-12	36	6-12	LEEP	NA
Bollen LJ et al. [10]	Gynecol Oncol	1999	Netherlands	PCR (CPI/IIG)	<24	43	13-206	Cone/LEEP/ Cryo/laser	LBC
Nagai Y et al. [25]	Gynecol Oncol	2000	Japan	PCR (L1C1/ L1C2)	6-12	58	31.8 (12-73)	LEEP	NA
Jain S et al. [23]	Gynecol Oncol	2001	Taiwan	HC2	6 wk	79	6-8 wk	LEEP	LBC
Nobbenhuis MA et al. [35]	Br J Cancer	2001	Netherlands	PCR (GP5+6+)	6	184	24 (3-76)	LEEP	conventional
Bodner K et al. [24]	Anticancer Res	2002	Austria	HC2	3	37	24	Cone	LBC
Bekkers RL et al. [15]	Int J Cancer	2002	Netherlands	PCR (SPF10)	6	90	24-47	LEEP	LBC+conventional
Bar-Am A et al. [41]	Gynecol Oncol	2003	Israel	HC2	6	67	63 (50-72)	LEEP	NA
Almog B et al. [12]	Gynecol Oncol	2003	Israel	HC1	6	96	47 (36-60)	Cone	NA
Zielinski GD et al. [36]	Gynecol Oncol	2003	Netherlands	HC2	3	108	29 (2-65)	Cone/LEEP	NA
Cecchini S et al. [37]	Tumori	2004	Italy	PCR (pU1/U2)	6	84	22.8 (11-40)	LEEP	NA
Sarian LO et al. [38]	Gynecol Oncol	2004	Brazil	HC2	6	88	17	LEEP	conventional
Nagai N et al. [25]	Int J Mol Med	2004	Japan	PCR (L1C1/ L1C2)	<12	161	78 (48-118)	LEEP	LBC
Hernádii Z et al. [11]	Eur J Obstet Gynecol Reprod Biol	2005	Hungary	HC2	5	61	25 (3-62)	LEEP	NA
Verguts J et al. [26]	BJOG	2006	Belgium	HC2	3-6	72	24	LEEP	LBC
Alonso I et al. [42]	Gynecol Oncol	2006	Spain	HC2	6	203	20±13	LEEP	conventional
Kreimer AR et al. [16]	Cancer Epidemiol Biomarkers Prev	2006	USA	HC2	6	610	24	LEEP	LBC
Fallani MG et al. [33]	Eur J Gynaecol Oncol	2007	Italy	PCR (Nanogen)	3-6	66	24	Cone	NA
Bae JH et al. [27]	Int J Gynecol Cancer	2007	Korea	HC2	6-12	114	30.7±13.5	LEEP	NA
Kitchener HC et al. [39]	BJOG	2008	UK	HC2	6	917	24	NA	LBC
Brismar S et al. [17]	Am J Obstet Gynecol	2009	Sweden	PCR (Linear Array)	12	84	34 (4-115)	LEEP	conventional
Ribaldone R et al. [30]	Arch Gynecol Obstet	2010	Italy	PCR (INNO-LiPA)	4	78	35.7	Cone	NA
Smart OC et al. [40]	Aust N Z J Obstet Gynaecol	2010	New Zealand	HC2	<18	100	9 (3-18)	Cone/LEEP/ laser	LBC
Gallwas J et al. [28]	Eur J Gynaecol Oncol	2010	Germany	HC2	<12	107	21.4 (2-76)	Cone	conventional
Leguevaque P et al. [31]	Eur J Surg Oncol	2010	France	PCR (GP5+6+)	6	352	73	LEEP	NA
Kang WD et al. [18]	Int J Gynecol Cancer	2010	Korea	HC2,PCR (HDC)	3-24	672	>24	LEEP	NA
Heymans J et al. [19]	Int J Cancer	2011	Belgium	PCR (E6/E7)	6	63	24	Cone	LBC
Valasoulis G et al. [20]	Gynecol Oncol	2011	Greece	PCR (MY09/11)	6	188	14	LEEP	LBC
Torne A et al. [29]	BJOG	2012	Spain	HC2	6	109	24	LEEP	LBC
Ryu A et al. [32]	J Gynecol Oncol	2012	Korea	HC2	3	183	25.3±13.3	LEEP	LBC
Söderlund-Strand A et al. [21]	J Med Virol	2013	Sweden	PCR (GP5+6+)	6	142	36	LEEP	conventional

HC, hybrid capture; LBC, liquid based cytology; LEEP, loop electrosurgical excision procedure; NA, not available; PCR, polymerase chain reaction.
*These studies were included in the pooled analysis to compare the performance of HPV testing and cytology in detecting residual or recurrent diseases after treatment for cervical intraepithelial neoplasia grade 2 or 3 (CIN 2 or CIN 3).

http://dx.doi.org/10.3802/jgo.2016.27.e3