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COST-EFFECTIVENESS OF USING HUMAN PAPILLOMAVIRUS 16/18 GENOTYPE TRIAGE IN CERVICAL CANCER SCREENING

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Abstract

Objective—Testing for human papillomavirus (HPV) 16 and 18 genotypes, which are known to cause more than 65–70% of invasive cervical cancer cases, may allow clinicians to identify women at highest risk for underlying high-grade dysplasia missed by Pap cytology. Our objective was to determine the cost-effectiveness of adding HPV-16 and 18 genotype triage to current cervical cancer screening strategies in the United States.

Methods—We developed a lifetime Markov model to assess the cost-effectiveness of adding HPV genotyping to current cervical cancer screening algorithms. All costs were estimated from a payer perspective in 2007 U.S. dollars. Outcome measures included lifetime risk of cervical cancer, quality-adjusted life-years saved (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results—In our model, the use of HPV genotype triage prevented 51–73 deaths per 100,000 women screened compared to screening using liquid-based cytology (LBC) followed by HPV triage and 4–26 deaths compared to co-screening with LBC and HPV. Use of HPV genotyping to triage all high-risk HPV-positive women every three years had an ICER of \$34,074 per QALY compared to HPV and LBC co-screening. HPV genotyping with co-screening was the most effective strategy and had an ICER of \$33,807 per QALY compared to HPV genotyping for all high-risk HPV-positive women.

Conclusion—The addition of HPV-16 and -18 genotype triage to current adjunctive HPV screening with LBC is a cost-effective screening strategy in the United States.

Introduction

Virtually all cases of cervical cancer are caused by persistent infection with specific high-risk (HR) types of human papillomavirus (HPV). (i) The most common HPV genotypes detected in invasive cancers are HPV type 16 (HPV-16) and HPV-18, which are present in

approximately 65-70% of invasive cervical cancer cases. (ii,iii) HPV-16 has been shown to be more persistent and more often associated with high-grade cervical lesions than other high-risk HPV types. (iv,v,vi) Although HPV-18 is the second most common type in invasive cervical cancer, precancerous lesions associated with HPV-18 are often underrepresented, possibly because these lesions are harder to detect with cervical screening. (iii,iv,v)

Current guidelines in the United States recommend screening annually with conventional cervical cytology or every two years using liquid-based cytology (LBC). (vii) For women 30 years of age or older, cervical screening can be performed every three years using conventional cytology or LBC combined with a HR HPV DNA test. (vii,viii) HPV DNA testing is considerably more sensitive than cytology at detecting high-grade cervical intraepithelial neoplasia (CIN) (ix,x,xi,xii,xiii) but is somewhat less specific due to the detection of transient HPV infections that may not progress to cervical lesions. (iv) As more women are vaccinated against HPV, the positive predictive value of current screening strategies is expected to decrease, resulting in additional testing and follow-up. (iii,xiv,xv) Several authors have proposed the use of HPV genotyping tests to address some of these concerns. (iv,v,vi,xiv,xvi) Using HPV genotyping to triage HPV-positive women may increase the specificity of HPV DNA testing thereby reducing referrals for colposcopies and treatment while still maintaining a high sensitivity. (iv,xiv) Women positive for HPV-16 or -18 could be followed more aggressively than women positive for other HR HPV types. (iv,vi)

Several studies have documented the cost-effectiveness of HPV DNA testing as a primary screening test or to triage equivocal cytology (atypical squamous cells of undetermined significance (ASC-US)) results. (xvii,xviii,xix) However, the cost-effectiveness of using HPV genotyping tests has not been established. As screening algorithms incorporating HPV genotyping tests are considered, it would be helpful to understand the economic implications of this approach. The purpose of our study was to determine the cost-effectiveness of adding HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States.

Methods

We developed a lifetime Markov Monte Carlo model to assess the cost-effectiveness of adding HPV genotyping tests to current cervical cancer screening algorithms. We assumed that all women would undergo biennial LBC testing until age 30. After age 30, we compared the following screening strategies (refer Supplemental Digital Content 1 for detailed screening algorithms):

- Screening using LBC every 2 years;
- Screening using LBC every 2 years, followed by HPV DNA testing for all patients with equivocal results on cytology (ASC-US);
- Primary screening using HPV DNA testing every 3 years, followed by cytology for all patients with positive result on HPV;

- Screening using a combination of simultaneous cytology and HPV DNA testing every 3 years;
- Screening using a combination of simultaneous cytology and HPV DNA testing every 3 years, with reflex HPV genotyping and more intensive follow-up for HPV types 16/18;
- Screening using HPV DNA testing followed by reflex HPV genotyping for all HPV-positive women and more intensive follow-up for HPV types 16/18.

Detailed methods regarding our core cervical cancer screening model have been published previously. (xvii) Briefly our model follows a hypothetical cohort of 100,000 U.S. women over their lifetimes, starting at age 13 years. The natural history of cervical neoplasia was modeled using 18 distinct Markov health states representing type-specific HPV infection, CIN, and invasive cervical cancer (Figure 1). Women could transition between health states at the end of each month. All modeling was conducted using TreeAge Pro 2007 release 1.5 (TreeAge Software, Williamstown, MA).

The natural history of HPV infection, CIN, and cervical cancer was based on data from the published literature. The type-specific incidence of HPV infection was based on data from a recent study among 18- to 70-year-old women in the United States.(xx) During the course of the model, women with persistent HPV infection could develop CIN or invasive cervical cancer based on conditional probabilities that depended on the woman's age and underlying HPV type (Table 1). (ii,vi,xxi,xxii,xxiii,xxiv,xxv,xxvi,xxvii,xxviii,xxix)

We stratified the 13 known HR HPV types into three categories: HPV-16 only, HPV-18 only, and other HR HPV types (including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). We combined data from several studies to evaluate the risk of progression and regression of HPV and CIN based on the underlying HPV category (ii,vi,xxiii,xxvii,xxviii). (Additional data are available from the authors). Given the limited data on the impact of HPV co-infection, we assumed that the risk of disease progression and regression for patients with co-infection was the same as patients infected with the most aggressive HPV type only. For instance, a patient infected with HPV-16 and HPV-18 had a risk of progression and regression similar to a patient infected with HPV-16 only. We also assumed that in patients with non-16/18 HR HPV infection, disease progression and regression rates were identical for patients infected with single versus multiple HPV types. The rate at which women progress from FIGO (International Federation of Gynecology and Obstetrics) stage I through stages II, III, and IV invasive cervical cancer was assumed to be independent of the type of the underlying HPV infection. In a few cases, we used cytology test results as a proxy for the histological diagnosis. In these cases, we have assumed that a cytological diagnosis of low-grade squamous intraepithelial lesions (LSIL) correlates with CIN 1 and high-grade squamous intraepithelial lesions (HSIL) with CIN 2/3.

Screening and treatment protocols were based on recently published consensus guidelines. (vii, viii) The sensitivity and specificity of LBC and HPV tests were based on clinical studies and meta-analyses in the published literature. (xxx, xxxi, xxxii) In the genotyping strategies, we assumed that patients who have normal cytology, a positive HPV result, and

are HPV-16 or -18 positive will receive immediate colposcopy and biopsy, while those who are HPV-16 and -18 negative will have repeat LBC and HPV tests in one year.

All costs were estimated from a health-care payer perspective in 2007 U.S. dollars. Detailed micro-costing methods were used to identify the total direct medical cost of screening and treating CIN and invasive cervical cancer. Unit costs were obtained from the 2007 Medicare fee schedules (Table 2). Primary outcome measures included quality-adjusted life-years saved (QALYs), incremental cost-effectiveness ratios (ICERs), and lifetime risk of cervical cancer. Disease-specific utilities were used to incorporate quality-of-life decrements. (xxv)

We conducted extensive sensitivity analyses to assess the impact of all parameters on the overall cost-effectiveness results. The range of values used for sensitivity analysis was based on published literature and clinician input as shown in Table 1.

Results

The model was calibrated to match the age-specific prevalence of HPV infection to within +/- 0.5 percentage points of the data in the literature (Figure 2). We then matched model predications to the overall prevalence of HPV-type-specific CIN and cervical cancer (Table 3). The margin of error (standard deviation) was less than 0.02% of total lifetime cost per patient and less than 0.01% of the average life expectancy. The model predicted an average annual incidence of nine cervical cancer cases per 100,000 women screened using LBC every 2 years. (xxvi)

Table 4 shows the lifetime incidence of cervical cancer cases and cervical cancer-related deaths per 100,000 women. Screening for cervical cancer and its precursors prevented 770-940 cervical cancer cases and 640-740 cervical cancer-related deaths per 100,000 women screened. The average annual incidence of cervical cancer ranged from six to nine cases per 100,000 women for the various screening strategies. Compared to screening using LBC followed by HPV triage every two years, HPV genotyping reduced the incidence of cervical cancer by 12-23% and prevented an additional 51-73 deaths per 100,000 women depending upon genotyping strategy. Compared to co-screening with both LBC and HPV, use of the genotyping test prevented an additional 4-26 deaths per 100,000 patients.

In the absence of screening, women lived an average of 28.59 discounted QALYs (Table 5). Screening using LBC only every two years, increased life expectancy by 28 days at an incremental cost of \$19,321 per QALY. Current clinical practice of LBC with HPV triage for equivocal pap smears was the next most effective strategy, with an incremental cost of \$21,304 per QALY. HPV testing as a primary screening test with LBC triage for all HPV-positive women was a highly cost-effective strategy with an ICER of \$2,618 per QALY. Compared to HPV with LBC triage, co-screening with LBC and HPV testing every three years increased quality-adjusted life expectancy (QALE) to 28.67 years resulting in an ICER of \$17,204 per QALY. Use of HPV genotyping for all HR HPV-positive women every three years was more effective and had an ICER of \$34,074 per QALY compared to co-screening. Adding HPV genotyping to HPV and LBC co-screening was the most effective strategy and

had an ICER of \$33,807 per QALY, compared to using HPV genotyping for all HR HPV-positive women in the absence of cytology screening.

We compared current clinical practice with HPV and LBC co-screening to HPV genotyping with HPV and LBC co-screening in one-way sensitivity analysis. The tornado diagram in Figure 3 shows the range of ICERs for key variables in the model. The vertical line represents the base-case analysis ICER. A wide horizontal bar indicates that the associated variable has a large effect on the results of the model. Model results were sensitive to HPV incidence rate, relative risk of progression of CIN for HPV-16 and -18, and the risk of progression to cervical cancer for all HPV types. Cost of the HPV tests and the cost of colposcopy and biopsy also had a significant impact on the ICERs. Overall, the HPV genotyping strategies remained cost-effective. The model results were also sensitive to the sensitivity and specificity of LBC and HPV tests. Increasing the sensitivity of the cytology test by more than 10% or decreasing the sensitivity of the HPV test by more than 15% increased the ICER of the genotyping strategy to more than \$100,000.

Discussion

We found that adding HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States resulted in fewer cervical cancer-related deaths, longer QALE, and higher costs. Using the 2007 U.S. per capita gross domestic product as a threshold for defining cost-effectiveness (xxxiii), HPV genotyping was very cost-effective when used to triage HR HPV-positive women.

Results from a large cohort study demonstrated that identification of women who were positive for HPV-16 was a better predictor of progression to CIN3 or cervical cancer than a cytological diagnosis of LSIL. (vi) The authors have suggested that HPV genotyping may identify women at the greatest risk of developing CIN3 and cancer and may allow less aggressive management of women with non-16/18 HR HPV infections and have called for evaluations of the cost-effectiveness of this approach. Based on a Pub Med search (1966-May 2009; English language; search terms: “HPV”, “genotyping”, and “cost-effectiveness”), we believe this is the first study to assess the cost-effectiveness of cervical cancer screening algorithms incorporating HPV genotyping. One of the strengths of the modeling approach that we used is the ability to determine the impact of HPV genotyping on survival and cost-effectiveness over a woman’s lifetime, a length of follow-up that is impractical for a clinical trial.

Although HPV DNA testing in the United States is currently used either to triage equivocal cytology or as a primary screening test in conjunction with cytology, the International Agency for Research on Cancer (xxxiv) and other authors (xxxi) have endorsed the use of HR HPV testing alone as an option for primary cervical cancer screening, and ongoing clinical studies are investigating the effectiveness of this approach. (xvi) One of the strengths of our model is that it compares the current use of HPV DNA testing as an adjunct to cytology to the potential use of HPV DNA testing as a primary screening tool as well as HPV DNA testing in conjunction with HPV genotyping.

Our study has several limitations. First, because the use of HPV genotyping has not yet been incorporated into current cervical cancer screening guidelines in the United States, we chose two possible HPV genotyping scenarios to include in the model – as a triage test for HPV-positive, cytology-negative women and as a triage test for HPV-positive women who received HPV testing alone for primary screening. These screening algorithms are consistent with other recently proposed HPV genotyping algorithms (iv,vi). However, there are other potential screening algorithms and other possible applications of HPV genotyping, such as its use as a primary screening test or for post-treatment monitoring for recurrence (xvi), which were not included in this model. Second, we have not incorporated the impact of HPV vaccination on the screening strategies evaluated in our model. However, given the recent introduction of HPV vaccination in the United States for women aged 11-26 years, the cohort in our model that is eligible for HPV genotype triage (women age 30+) today represents an unvaccinated group in the US. In addition, our results probably reflect a conservative evaluation of the cost-effectiveness of HPV testing given the likely negative impact that HPV vaccination will have on the performance of cytology relative to that of HPV testing, though this hypothesis will require further research. (xv)

Third, there are limited data available on the risk of progression and regression of HPV and CIN for specific HPV genotypes and for patients infected with more than one HPV genotype. As shown in Table 3, the prevalence of CIN 2,3 and invasive cervical cancer predicted by the model closely match the data in the literature. In addition, we tested all assumptions through extensive sensitivity analysis and our results remained consistent over a range of plausible values. Finally, because a standard reimbursement for the HPV genotyping test has not yet been established, we assumed a cost of \$100 for the test in the model, which is approximately two times the cost of the standard HPV test available today. Although the model results were sensitive to the cost of both the standard HPV test and the HPV genotyping test, we found that the HPV genotyping strategies remained cost-effective throughout the range of test costs we evaluated in sensitivity analyses (standard HPV test cost ranged from \$37 to \$61 and HPV genotyping test cost ranged from \$75 to \$125).

Additional clinical studies are needed to refine our understanding of the effect of different HPV genotypes on the risk of progression and regression of HPV and CIN, as well as to determine the clinical effectiveness of using HPV DNA testing alone and using HPV genotyping in conjunction with HPV DNA testing and/or cytology for primary cervical cancer screening. Our analysis provides evidence of the cost-effectiveness of HPV genotyping based on currently available data. These findings will require confirmation when additional clinical and cost data become available.

In our model, the addition of HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States was clinically effective and very cost-effective. Policymakers should consider the use of HPV genotyping triage as one strategy to increase the positive predictive value and cost-effectiveness of current cervical cancer screening algorithms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Schematic representation of the model.

Figure 2. Prevalence of HPV infection in the US. Dotted line denotes data from the literature & solid line denotes model prediction

Figure 3.

Tornado Diagram: One-way sensitivity analysis showing the range of incremental cost-effectiveness ratios comparing LBC and HPV co-screening with genotyping and LBC and HPV co-screening. The vertical dotted line represents the base-case analysis ICER.

Table 1

Input variables and sources*

Clinical variable	Base-case value	Range	Source
Population variables			
Annual hysterectomy rate [†] (%)	0.02 – 1.17		Keshavarz (2002)
Age-specific prevalence of HR HPV infection ^{†‡} (%)	4 – 31	0.5 – 2x baseline	Apple
Probability of disease progression			
HPV infection progressing to CIN 1 (%)	8.1	5.4-15.0	Ho (1998)
Prevalence of LSIL among patients with non 16/18 HR HPV infection (%)	14	0.5 – 2x baseline	Herrero (2005)
RR of LSIL among patients with HPV-16 infection [§]	1	“	Assumption
RR of LSIL among patients with HPV-18 infection [§]	1	“	Assumption
HPV infection progressing to CIN 2,3 (%)	0.56	0.54-1.5	Ho (1998), Myers (2000)
Prevalence of CIN 2,3 among patients with non 16/18 HR HPV infection (%)	4	0.5 – 2x baseline	Khan (2005)
Progression from CIN 1 to CIN 2,3 [†] (%)	1.7 – 5.7	1.7-8.3	Myers (2000)
Annual rate of progression among patients with non 16/18 HR HPV infection	0.09	0.5 -2x baseline	Khan (2005)
RR of CIN 2,3 in patients with HPV-16 infection [§]	4.6	“	Khan (2005)
RR of CIN 2,3 in patients with HPV-18 infection [§]	2.5	“	//
Progression from CIN 2,3 to cervical cancer (%)	3.8	3.0-6.2	Sanders (2003)
Incidence rate of cervical cancer in the United States (per 100,000 women)	9.4	0.5 – 2x baseline	Saraiya (2007)
Prevalence of HPV-16 in patients with cervical cancer (%)	59	55-63	Clifford (2003), Munoz (2003)
Prevalence of HPV-18 in patients with cervical cancer (%)	13	11-15	
Prevalence of non 16/18 HR HPV types in patients with cervical cancer (%)	28	22-34	
Probability of cervical cancer progression (%)[‡]	43.7-68.3	40-70	Myers (2000), Sanders (2003)
Probability of disease regression			
Age-specific probability of regression of HPV infection [†] (%)	3.3 – 37.3	1.7-60.0	Myers (2000), Ho (1998)
Rate of clearance of non 16/18 HR HPV infection	1.29	0.5 – 2x baseline	Trottier (unpublished manuscript)
RR of clearance of HPV-16 infection [§]	0.85	“	Trottier
RR of clearance of HPV-18 infection [§]	0.96	“	Trottier
Regression of CIN 1 [†] (%)	2.7 – 14.2	2 – 16	Sanders (2003)
Patients regressing to HPV infection without lesion (%)	10	0 – 20	Sanders (2003), Myers (2000)
Regression rate of LSIL among patients with non 16/18 HR HPV infection	0.98	0.5 – 2x baseline	Schlecht (2003)
RR of regression of LSIL in patients with HPV-16 [§]	0.91	“	“
RR of regression of LSIL in patients with HPV-18 [§]	0.91	“	Assumption
Regression of CIN 2,3 [†] (%)	3.7 – 5.8	3-7	Sanders (2003), Myers (2000)

Clinical variable	Base-case value	Range	Source
Patients regressing to normal (%)	45	40-50	“
Patients regressing to HPV infection without lesion (%)	5	0-10	“
Patients regressing to CIN 1 (%)	50	40-60	“
Regression rate of HSIL among patients with non 16/18 HR HPV infection	0.77	0.5 – 2x baseline	Schlecht (2003)
RR of regression of HSIL in patients with HPV-16 [§]	0.27	“	“
RR of regression of HSIL in patients with HPV-18 [§]	0.27	“	“
Annual symptom detection probability for cervical cancer (%) [‡]	15-90	12-93	Sanders (2003)
5-year survival rates (% alive at 5 years) [‡]	85-12	84-10	NCDB commission on cancer (2006)
Disease-specific utilities			Sanders (2003)
HPV infection	1	0.8-1	
CIN 1	0.97	0.8-1	
CIN 2,3	0.97	0.5-1	
Invasive cervical cancer [‡]	0.79-0.62	0.25-1	
Initial efficacy of treatment (%)			Karyn Goodman (personal communication), Assumption
CIN 1	98	95-100	
CIN 2	95	90-98	
Invasive cervical cancer [‡]	90-15	10-100	
Probability HPV persists after effective treatment (%)			Sanders (2003)
CIN 1	10	0-25	
CIN 2,3	10	0-25	
Invasive cervical cancer	0	---	Assumption
Screening tests (%)	Sensitivity	Specificity	
Liquid-based cytology (ASCUS or worse)			
CIN 1 or worse	43	85	Ratnam (2000)
CIN 2,3 or worse	53	96	Cuzick (2006)
HPV positive			
CIN 1 or worse	57	96	Bigas (2005)
CIN 2,3 or worse	96	91	Cuzick (2006)

* All variables are annual unless otherwise noted. HR denotes high risk, HPV human papillomavirus, CIN cervical intraepithelial neoplasia, LSIL low-grade squamous intraepithelial lesion, RR relative risk, FIGO International Federation of Gynecology and Obstetrics, HSIL high-grade squamous intraepithelial lesion, NCDB National Cancer Database, and ASCUS atypical squamous cells of undetermined significance.

[‡] These data vary based on age. The range of values is shown.

[‡] These data also vary by HPV type.

[§] Compared to patients with non 16/18 HR HPV infection

// Estimated using a Markov model to match the incidence of CIN 2,3 and cervical cancer in the United States

¥ These data vary based on cervical cancer stage (FIGO I, II, III or IV)

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Table 2Cost variables^{*}

Variable	Base-case value
Cost per clinic visit for routine screening	\$66
Cost per clinic visit for repeat screening	\$97
<i>Diagnostic test costs</i>	
Liquid-based cytology	\$28
HPV DNA testing	\$49
Linear array [†]	\$100
Colposcopy only	\$172
Colposcopy with biopsy	\$399
Colposcopy with endocervical curettage	\$424
<i>Treatment costs</i>	
LLETZ	\$1,279
Conization	\$1,768
Cryosurgery	\$212
Total abdominal hysterectomy	\$35,402
Vaginal hysterectomy	\$35,241
Radical abdominal hysterectomy	\$36,176
Chemotherapy	\$5,062
Radiotherapy (EBRT)	\$10,509
Radiotherapy (EBRT with brachytherapy)	\$17,778
<i>Treatment costs based on stage of disease</i>	
CIN 1 and CIN 2,3	\$1,086
FIGO stage I cancer	\$53,621
FIGO stage II cancer	\$26,206
FIGO stage III and stage IV cancer	\$26,014

^{*} All costs are in 2007 USD and are based on 2007 Medicare reimbursement unless otherwise noted. HPV denotes human papillomavirus, LLETZ large loop excision of the transformation zone, EBRT external beam radiation therapy, CIN cervical intraepithelial neoplasia, and FIGO International Federation of Gynecology and Obstetrics.

[†] The cost of the linear array is an assumption.

Table 3

Model validation results – prevalence of CIN 2,3 and invasive cervical cancer among women screened using LBC every 2 years*

Parameter	Data from:		
	Literature	Model	Source
Prevalence of CIN 1 cases among patients with HR HPV infection (%)	14	13	Herrero (2005)
Prevalence of CIN 2,3 cases among patients with HR HPV infection (%)	4	4.5	Khan (2005)
CIN 2,3 cases caused by HPV-16 (%)	41	43	Khan (2005)
CIN 2,3 cases caused by HPV-18 (%)	10	10	Khan (2005)
CIN 2,3 cases caused by non 16/18 HR HPV (%)	49	47	Khan (2005)
Annual incidence of cervical cancer in the United States (per 100,000 women)	9.4	9.2	Saraiya (2007)

* CIN denotes cervical intraepithelial neoplasia, HR high-risk, and HPV human papillomavirus.

Health and economic outcomes – Lifetime incidence of disease per 100,000 women, costs, QALE, and ICER compared to next most effective strategy *

Table 4

Strategy	Cervical cancer cases	Cervical cancer deaths	Annual incidence of cervical cancer	Costs (\$)	QALE (years)	ICER (\$/QALY)
No screening	1,383	894	20.64	\$86,700	28.5866	--
LBC only (2 year interval)	615	259	9.17	\$88,162	28.6623	\$19,321
LBC with HPV triage (2 year interval)	574	231	8.56	\$88,221	28.6651	\$21,304
HPV with LBC triage (3 year interval)	527	193	7.86	\$88,226	28.6670	\$2,618
HPV and LBC co-screening (3 year interval)	502	184	7.49	\$88,303	28.6714	\$17,204
HPV genotyping for HR HPV-positive women (3 year interval)	507	180	7.57	\$88,340	28.6725	\$34,074
HPV genotyping with co-screening (3 year interval)	444	158	6.62	\$88,407	28.6745	\$33,807

* ICER denotes incremental cost-effectiveness ratio, QALE quality-adjusted life expectancy, QALY quality-adjusted life year, LBC liquid-based cytology, HPV human papillomavirus, and HR high-risk.