

Clinical and Budget Impact of Primary HPV Genotyping for Cervical Cancer Screening in Peru

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Abstract

Introduction: Cervical cancer is an important public health topic in Peru as it is the second leading cause of oncology-attributed mortality among women in the country. Conventional cytology was previously the standard method for cervical cancer screening, but recognized to have low test sensitivity in detecting pre-cancerous lesions. After a growing number of countries have implemented human papillomavirus (HPV) testing as part of a primary screening approach in order to reduce the incidence of cervical cancer, Peru did the same issuing the 2017 national guidelines. The objective of this study was to compare, from the Peruvian public payer perspective, the clinical and budget impact of conventional cytology versus HPV testing with genotyping or co-testing (cytology and HPV testing with genotyping) for primary cervical cancer screening.

Methods: A decision analytic model was used to estimate the clinical and budget impact of each screening approach over a ten year period. A Markov model was used to simulate the natural history (progression and regression) of HPV and project the annual incidence of cervical cancer. The analysis was conducted on a hypothetical cohort of 4,000 women between 30 and 65 years eligible for cervical cancer screening. Epidemiological and clinical data were derived from the published literature and from the Addressing THE Need for Advanced HPV Diagnostics (ATHENA) trial. The analysis included cervical cancer screening, diagnosis, and treatment costs from the national Reimbursement Tariff Listing of the Seguro Integral de Salud (SIS), Peru in addition to Peruvian gynecologic oncologists opinion when SIS costs were not available. One-way sensitivity analysis was conducted on all model inputs to evaluate the impact of uncertainty on results.

Results: In the base-case analysis, 58.6%, 83.7% and 90.5% of CIN2 and CIN3 pre-cancer lesions were detected among women by conventional cytology, HPV test with genotyping and co-testing (cytology and HPV test with genotyping) respectively. Relative to conventional cytology, introduction of HPV test with genotyping is estimated to reduce the annual incidence of cervical cancer from 3.3 per 100,000 to 2.7 per 100,000 with an incremental budget impact of 0.62 USD per screened woman per year. A co-testing approach was estimated to reduce the annual incidence to 2.5 per 100,000 with budget impact of 1.37 USD per screened woman per year.

Conclusions: HPV primary screening with genotyping, either implemented alone or as part of a co-testing approach, improves early cervical cancer detection and reduces cervical cancer incidence and associated mortality with minimal budget impact on a per screened woman per year basis. Including HPV primary screening with genotyping for the screening of women aged 30 to 65 years may be a cost-beneficial approach to reduce cervical cancer incidence among women in Peru.

Keywords: Cervical Cancer; Budget Impact; HPV Primary Screening; Peru

Abbreviations: ATHENA: Addressing THE Need for Advanced HPV Diagnostics; SIS: Seguro Integral de Salud; HPV: Human Papillomavirus; CIN: Cervical Intraepithelial Neoplasia; USD: United States Dollars; ICC: Invasive Cervical Cancer; LSIL: low-grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion; ASC-US: Atypical Squamous Cells of Undetermined Significance

Background

Cervical cancer is an important public health topic in Peru due to high incidence; it is the second leading cause of oncology-attributed mortality among women in the country [1]. Some of the primary reasons for high disease incidence and mortality may

be due to: 1) low population coverage of cervical cancer screening programs, 2) use of conventional cytology as primary screening method and 3) poor follow-up of women with abnormal cytology results.

Numerous studies have demonstrated that conventional

cervical cytology has low sensitivity, ranging from 45% to 70% for the detection of pre-cancerous lesions [2-6]. Specifically in Peru, a published study showed that cervical cytology was only 42% sensitive in detection of invasive cervical carcinoma (ICC) [7]. The evidence suggests that one in three cervical cancer cases occur among women with previously “normal” cytology results [8,9]. Even in developed countries, where conventional cytology has helped to reduce the incidence of cervical cancer, it has been observed that there is a limitation to further reduce this incidence due to low cervical cytology test sensitivity [10,11].

The human papillomavirus (HPV) has been determined to cause up to 90-95% of cervical cancer cases [12]. Women infected with high-risk strains, such as HPV 16 and/or 18 are at increased risk of developing high-grade cervical intraepithelial neoplasia (CIN), a precursor to ICC [13]. HPV testing has demonstrated higher sensitivity than conventional cytology in the detection of pre-cancerous lesions (CIN2 and CIN3)[14]. For this reason, an increasing number of countries and professional guidelines are recommending primary cervical cancer screening with HPV testing either alone as an alternative to cytology testing, or as part of a complementary testing approach with cytology (“co-testing”)[15-19]. Substantial evidence demonstrates that early identification and treatment of pre-cancerous lesions, especially at CIN2 stage, is associated with reduced incidence of cervical cancer and subsequent mortality [20,21].

Recently in Peru, the Ministry of Health approved new guidelines recommending HPV primary testing of women 30 to 49 years old, when available in the health establishment [22]. Although this is a significant advancement, the population coverage is limited (30 to 49 years) and does not include all women at risk. The objective of this study was to compare, from the Peruvian public payer perspective, the clinical and budget impact of implementing HPV testing with genotyping, versus co-testing (cytology and HPV testing with genotyping) and conventional cytology for primary cervical cancer screening of women age 30 to 65 years in Peru in order to really include in the study all the women that are at risk and not only those between 30 to 49 years old.

Methods

Model Structure

A decision analytic model was developed using Microsoft® Excel 2010 and used to estimate the clinical outcomes and costs of three different cervical cancer screening strategies:

1. Conventional cytology every year as the primary screening method. In women with atypical squamous cells of undetermined significance (ASCUS), cervical cytology is repeated in 6 months. Any result worse than low grade squamous intraepithelial lesion (LSIL) leads to colposcopy. Women with negative results return for routine cervical cancer screening annually (Figure 1A).
2. Co-testing every five years. Women testing positive for HPV types 16 and/or 18 are sent to colposcopy, whereas women positive for HPV but negative for HPV types 16 and 18 repeat

co-testing in 12 months. Women with normal cytology and negative HPV test return for screening in five years (Figure 1B).

3. HPV test with genotyping every five years. This approach utilizes HPV test with genotyping as the primary screening modality. Women who are HPV negative return for routine screening in five years. Women who are HPV types 16 and/or 18 positive are referred for immediate colposcopy. HPV positive women who are HPV types 16 and 18 negative have reflex cytology performed on the residual sample. A cytology result of ASCUS or worse leads to immediate colposcopy, whereas women with normal results from cytology return for follow-up testing in 12 months (Figure 1C).

A Markov model was included as part of the analysis to project the progression and regression of HPV infection to pre-cancerous lesions (CIN2 and CIN3) and cervical cancer. The model comprised of eight mutually exclusive health states: well / HPV negative, HPV positive (non high-risk strains), HPV positive (high-risk strains 16 and 18), CIN1, CIN2, CIN3, ICC, and cervical cancer attributed death. The model implemented one-month transition cycles to project the annual incidence of cervical cancer over a ten year period among the cohort of women within each screening approach. This Markov model was previously described in detail by Wright, et al. 2016, including transition probabilities derived from the published literature [23].

Model Inputs

Population

For this analysis, we used a hypothetical cohort of 4,000 women between 30 and 65 years eligible for cervical cancer screening. The population size (4,000) reflects the total number of women who were screened in 2015 in the obstetrics & gynecology department at hospital nacional dos de mayo, lima, Peru. The cohort entered the decision model based on the selected screening approach and moved through the model based on disease prevalence and the probability of each testing approach to identify disease (test performance). The analysis did not take into account vaccination and we assumed that women were not vaccinated in this study population. We assumed 80% patient compliance with follow-up testing at routine screening intervals based on data from the hospital nacional dos de mayo.

Clinical Inputs

The test performance of the different screening strategies were derived from the Addressing THE Need for Advanced HPV Diagnostics (ATHENA) study, a prospective three-year cervical cancer screening trial designed to compare the cobas® HPV test (Roche Molecular Diagnostics, Pleasanton, CA, USA) both alone and in combination with cervical cytology among women 21 years and older in the United States (Table 1) [24]. In the base-case analysis, colposcopy was assumed to have 100% sensitivity and specificity. Epidemiological data inputs, such as prevalence of CIN1, CIN2, CIN3, ICC, and prevalence of high-risk HPV infection were obtained from the published literature, with as many inputs derived from local studies in Peru as available and presented in (Table 2) [25,26].

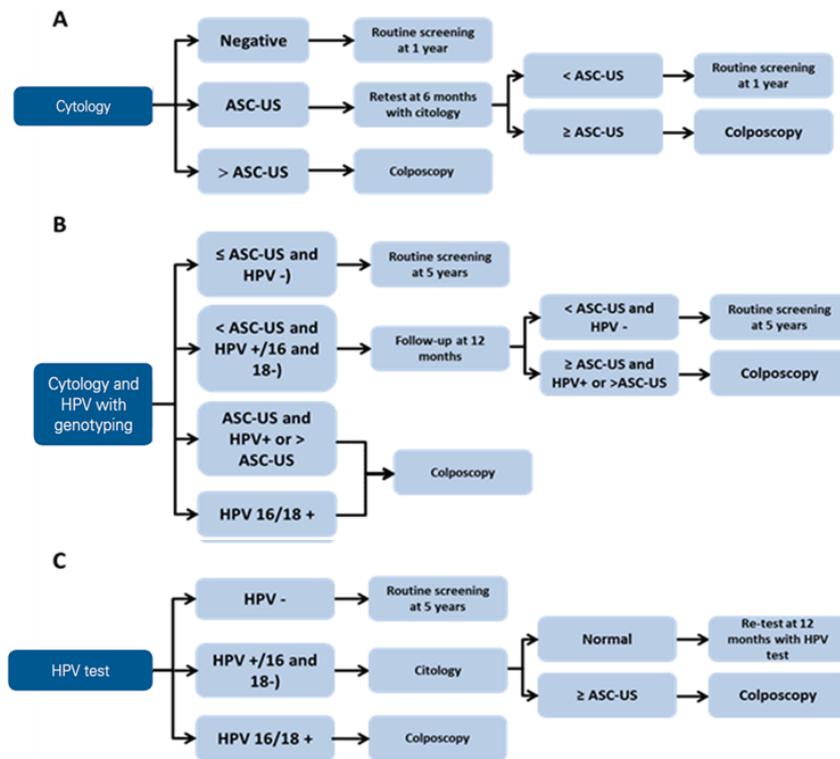


Figure 1: Different screening algorithms used in the study. ASC-US: atypical squamous cells of undetermined significance; HPV: Human Papillomavirus; HPV+ refers to high-risk human papillomavirus; HPV 16/18: refers to two high-risk HPV types, HPV16 and 18.

Table 1: Sensitivity and specificity of cervical cytology, HPV test with genotyping, and colposcopy

Sensitivity and specificity of cervical cytology (ASCUS)		
Parameter	Base-case Input	Reference
Sensitivity for CIN2	53.20%	[24]
Sensitivity for CIN3	57.70%	[24]
Sensitivity for ICC	57.70%	[Assumed equivalent to CIN3]
Specificity of cervical cytology (ASCUS)	73.40%	[24]
Sensitivity and specificity of cervical cytology (LSIL)		
Sensitivity for CIN2	34.10%	[ATHENA trial; unpublished data on file from general population]
Sensitivity for CIN3	35.40%	[ATHENA trial; unpublished data on file from general population]
Sensitivity for ICC	35.40%	[Assumed equivalent to CIN3]
Specificity of cervical cytology (LSIL)	91.00%	[ATHENA trial; unpublished data on file from general population]
Sensitivity and specificity of HPV test with genotyping		
Sensitivity for CIN2	63.60%	[24]
Sensitivity for CIN3	72.00%	[24]
Sensitivity for ICC	72.00%	[Assumed equivalent to CIN3]
Specificity of HPV test with genotyping	85.20%	[24]
Sensitivity and specificity of colposcopy		
Sensitivity for CIN2	100%	[Assumed]
Sensitivity for CIN3	100%	[Assumed]
Sensitivity for ICC	100%	[Assumed]
Specificity of colposcopy	100%	[Assumed]

Table 2: Prevalence of CIN1, CIN2, CIN3 and Invasive Cervical Cancer among women aged 30 to 65 years old

Parameter	Base-case Input	Reference
CIN 1 prevalence	7.6% (76/1000)	[25]
CIN 2 prevalence	0.2% (2/1000)	[25]
CIN 3 prevalence	0.4% (4/1000)	[25]
ICC prevalence	0.9% (9/1000)	[25]
Prevalence of hrHPV	12.6% (126/1000)	[25]
Prevalence of HPV16 and/or 18	6.6% (66/1000)	[26]

CIN: Cervical Intraepithelial Neoplasia; ICC: Invasive Cervical Cancer; hrHPV: High-risk Human Papillomavirus; HPV16 and/or 18: Human Papillomavirus types 16 and/or 18. [25,26].

Cost Inputs

The cost inputs for screening, diagnosis and treatment procedures (direct medical costs) reflect the reimbursed rates to hospitals by the Seguro Integral de Salud (SIS) and were obtained from the official tariff listing or from physician interviews at the Hospital Nacional Dos de Mayo when costs were not available in the tariff listings. Hospital practice for the treatment for pre-cancerous lesions (CIN) is to perform cold-knife conization or LEEP (loop electrosurgical excision) depending on each case. The base-case cost estimate of treating ICC reflects the weighted average treatment cost by cancer stage distribution and assumes that patients with stage 1 are treated with radical hysterectomy and patients diagnosed with stage 2 or greater are treated with concurrent chemotherapy (cisplatin 40mg/m2 IV once weekly for maximum six doses) and radiotherapy [27]. All costs were converted to 2016 USD (1 USD=3.3 PEN) and presented in (Table 3). Costs were not discounted per budget impact analysis best practice guidelines [28].

Table 3. Direct medical costs (2016 USD)

Parameter	Base-case Input (USD)	Reference
Conventional cytology	3.03	Hospital tariff listing (SIS)
Office visit (routine/repeat screening)	2.36	Hospital tariff listing (SIS)
Office visit (diagnostic)	2.36	Hospital tariff listing (SIS)
HPV test with genotyping	54	Hospital tariff listing (SIS)
Colposcopy and biopsy	19.97	Interviews to gynecologic oncologists of Hospital Nacional Dos de Mayo
CIN treatment	244.57	Interviews to gynecologic oncologists of Hospital Nacional Dos de Mayo

CIN: Cervical Intraepithelial Neoplasia; HPV: Human Papillomavirus; ICC: Invasive Cervical Cancer

Sensitivity Analysis

One-way sensitivity analysis (OWSA) was conducted to evaluate the impact of uncertainty on the results by varying each clinical input ±20% and each cost input ±50% individually while keeping constant all other parameters.

Results

Base-case Clinical Impact Results

Based on a hypothetical cohort of 4,000 women, the base-case analysis estimated that after two screening cycles, 58.6% of CIN2 and CIN3 were detected following screening with cervical cytology, whereas 83.7% and 90.5% were detected by HPV with genotyping and co-testing, respectively (Table 4). Only 45.3% of cervical cancer cases were detected following cytology testing, 86.3% detected following HPV primary screening, and 91.3% of cases were detected following co-testing (Table 4).

The annual cervical cancer incidence per 100,000 women was reduced from 3.3 cases with cytology to 2.7 and 2.5 cases following HPV test with genotyping and co-testing, respectively (Table 5). Consequently, the projected annual cervical cancer mortality rate was reduced from 0.03% with cytology screening to 0.005% following HPV test with genotyping.

Table 4: Base-case Results – Cervical cancer cases detected with each screening approach in the hypothetical selected cohort

Screening Approach	CIN2 and CIN3 detected (%)	ICC detected (%)
Conventional cytology	58.6	45.3
HPV test with genotyping	83.7	86.3
Co-testing with genotyping	90.5	91.3

Table 5: Base-case Results - Cervical cancer incidence and mortality projected with each screening approach in the hypothetical selected cohort

Screening Approach	Annual incidence of cervical cancer per 100,000	Annual cervical cancer mortality per 100,000
Conventional cytology	3.3	31.5
HPV test with genotyping	2.7	5.4
Co-testing with genotyping	2.5	3.6

Base-case Budget Impact Results

The total annual cost to the SIS of implementing cervical cancer screening for 4,000 women at one hospital, taking into account the cost of screening tests, diagnosis, and treatment procedures were 50,253 USD with cytology screening approach, 52,735 USD with HPV test with genotyping, and 55,725 USD with co-testing approach (Table 6). In high disease prevalence settings, more infections are detected with higher sensitivity HPV testing

and therefore additional treatment costs are incurred with HPV testing strategies. However, these treatment costs are offset by reductions in cervical cancer incidence and mortality. Relative to current cytology screening practices, implementing HPV primary screening at one hospital (4,000 women) is projected to have budget impact to the SIS of 0.62 USD per screened woman per year while a co-testing approach is estimated to have budget impact of 1.37 USD per screened woman per year (Table 6).

Table 6: Base-case Results – Budget impact of each screening approach for a cohort of 4,000 women (2016 USD) in the hypothetical selected cohort

Screening Approach	Total annual cost (USD)	Incremental total annual cost (versus cytology)	Total annual cost per screened woman	Incremental total annual cost (versus cytology) per screened woman
Conventional cytology	50,253	-	12.56	-
HPV test with genotyping	52,735	2,482	13.18	0.62
Co-testing with genotyping	55,725	5,472	13.93	1.37

Sensitivity Analysis

The OWSA results showed that the prevalence of ICC, the cost of treating ICC, and the cost of HPV test with genotyping were the parameters that had greatest impact on results (Figures 2-3). In the base-case analysis, ICC prevalence was estimated at 0.9% (9/1000) based on the published literature and resulted in total annual costs ranging from 50,253 to 55,725 USD across the three different screening strategies for a cohort of 4,000 women (Table 6). However, when ICC prevalence was explored in OWSA ($\pm 20\%$; 0.7% to 1.1%) (7/1000 to 11/1000), the variability in total annual costs increased between 45,000 to 57,000 USD across the three different screening strategies (Figures 2a,b,c). Subsequently, the cost of treating ICC was also impactful on results. When the parameter was varied $\pm 50\%$ (1,084 to 2,168 USD), the total

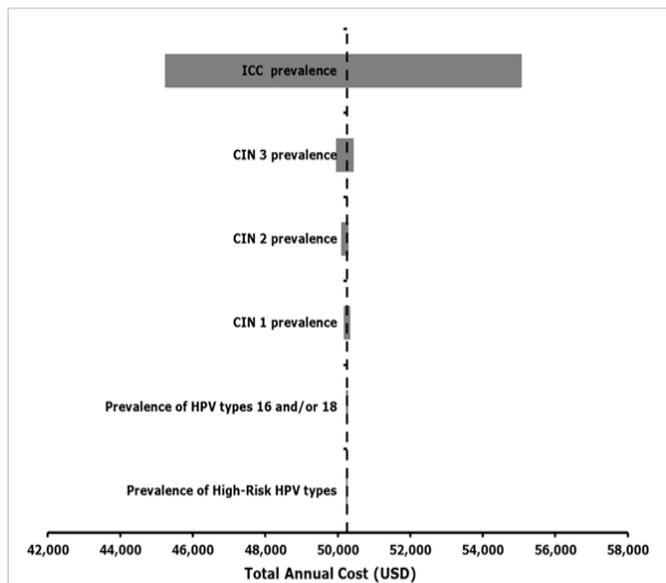


Figure 2a: OWSA results when clinical inputs varied $\pm 20\%$ from base-case for cervical cytology approach

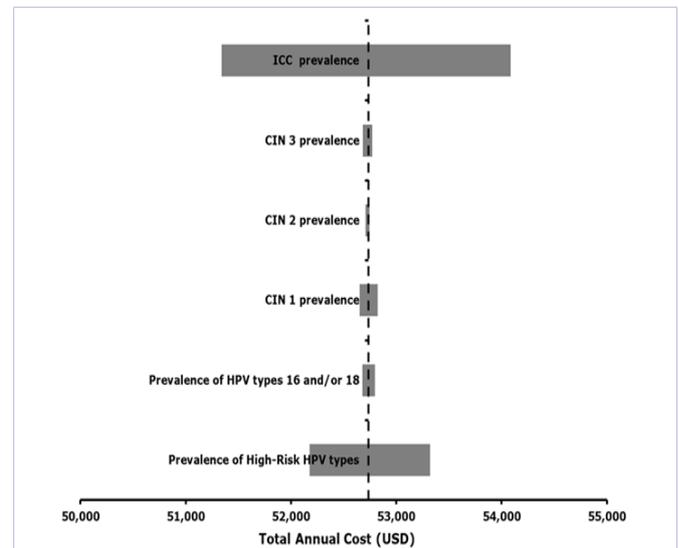


Figure 2b: OWSA results when clinical inputs varied $\pm 20\%$ from base-case for HPV with genotyping approach

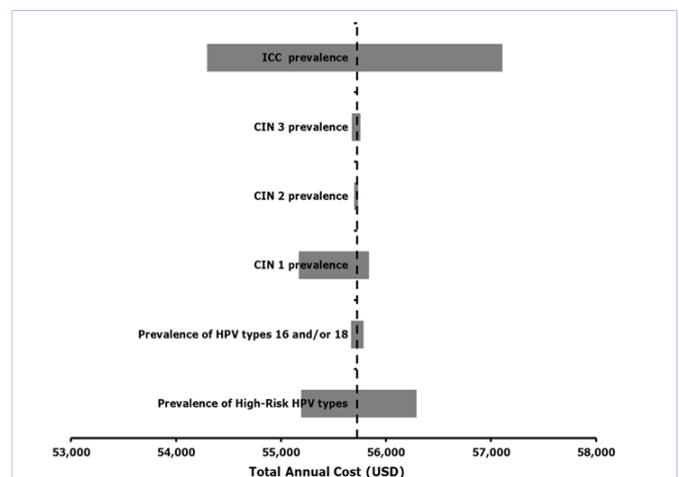


Figure 2c: OWSA results when clinical inputs varied $\pm 20\%$ from base-case for co-testing approach

annual costs ranged between 38,000 to 64,000, and similarly, when the cost of HPV test with genotyping was varied $\pm 50\%$ (27

to 81 USD), total annual costs ranged between 31,000 to 77,000 USD across the three screening strategies (Figures 3a,b,c).

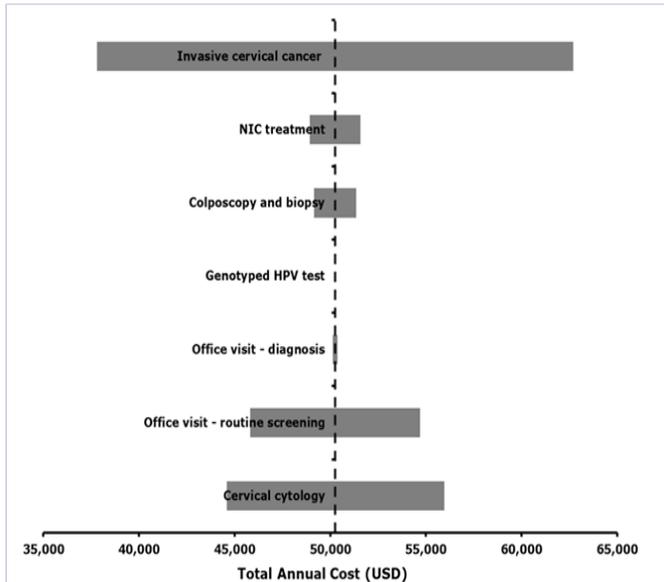


Figure 3a: OWSA results when cost inputs varied $\pm 50\%$ from base-case for cervical cytology approach

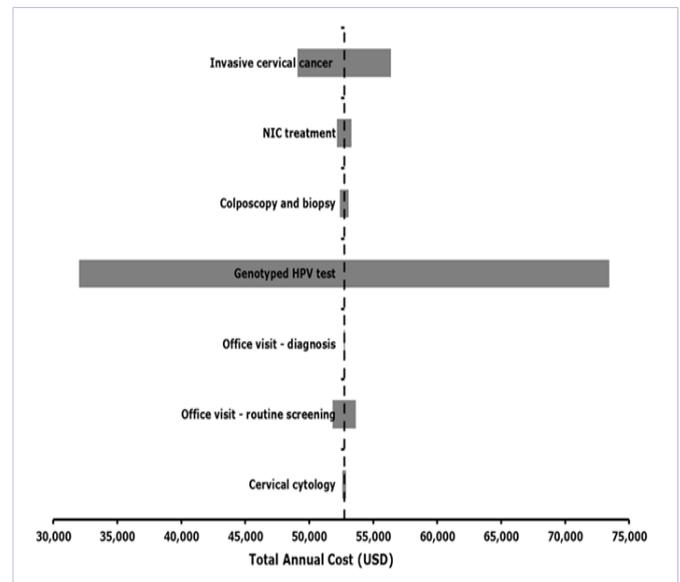


Figure 3b: OWSA results when cost inputs varied $\pm 50\%$ from base-case for HPV with genotyping approach

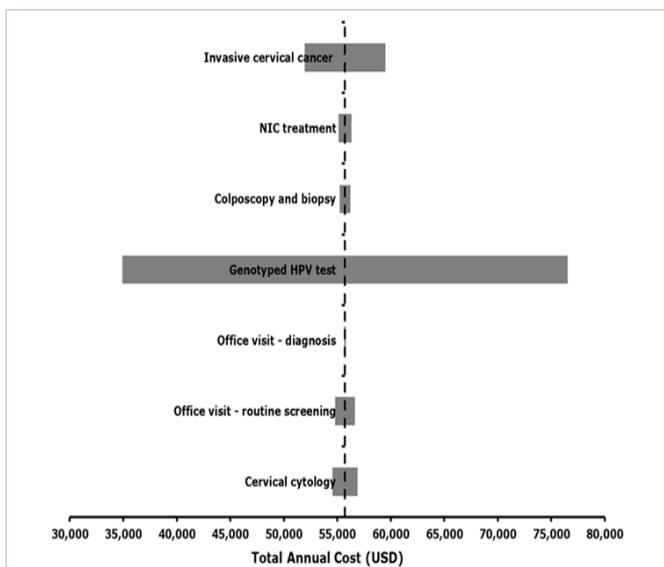


Figure 3c: OWSA results when cost inputs varied $\pm 50\%$ from base-case for co-testing approach

conventional cytology (current practice) compared to HPV test with genotyping alone or as part of a co-testing approach among a broader population of women 30 to 65 years old. Among the analytic cohort of 4,000 women, the study showed that the introduction of HPV test with genotyping either alone or as a co-testing for cervical cancer screening, yields important clinical benefits through higher test sensitivity and detection of a larger percentage of CIN2 and CIN3 pre-cancerous lesions relative to conventional cytology. When pre-cancerous lesions are detected early, they are more likely to be successfully treated with high recovery rates and survival [20,21]. Subsequently, the results showed that the improved screening modality reduced the annual incidence of cervical cancer and associated mortality over a ten year period. Although the magnitude of clinical and budget impact estimated in this study was based on a hypothetical cohort of 4,000 women, if HPV testing were to be implemented as part of organized national screening programs across multiple hospitals, these results suggest that HPV primary screening could significantly reduce the burden of cervical cancer among women in Peru with relatively minimal budget impact to the public payer on a per screened woman per year basis.

Discussion

The Ministry of Health in Peru recently approved new national guidelines recommending HPV test cervical cancer as the primary screening for women between 30 to 49 years old [22]. Furthermore, the test is already being reimbursed by the SIS. This represents a significant advancement; however, the benefited population is limited and does not include all women at risk. In this analysis, we used a decision analytic model to estimate the clinical and budget impact to the Peruvian public healthcare payer of primary cervical cancer screening using

The greater sensitivity of HPV test with genotyping in detecting pre-cancerous lesions (CIN2 and CIN3) has been shown to reduce cervical cancer incidence when used as primary screening in several clinical trials [24,29,30,31]. Budget impact analyses conducted in other countries have similarly demonstrated that the use of HPV test with genotyping as primary screening is clinically beneficial and associated with lower costs than cervical cytology alone [23,32]. Additionally, some studies have also demonstrated that using HPV test with genotyping as primary screening in cervical cancer prevention programs is more cost-

effective than with cervical cytology alone [33,34]. Based on these evidence and similar, many countries have changed screening practices and adopted guidelines like those from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American Society for Clinical Pathology (ASCP), the U.S. Preventive Services Task Force (USPSTF), the American College of Obstetricians and Gynecologists (ACOG), among others, that recommend using HPV test with genotyping for primary screening of cervical cancer for women between 30 to 65 years of age [15-19]. All these discussed evidences and guidelines consider and demonstrates the clinical benefit and the cost-effectiveness of screening women between 30 to 65 years, and not only those between 30 to 49 years old, being this the reason why this study has considered 30 to 65 years as the appropriate range for the study. Furthermore, as far as we are aware, this is the first budget impact analysis conducted from a Peruvian public health perspective to assess the clinical and budget impact of HPV test with genotyping for cervical cancer screening.

There are some limitations worth noting, especially in the availability of data to inform base-case inputs. The test performance data used in the base-case analysis were derived from a U.S. clinical trial (ATHENA). Although we do not believe that test performance should vary between geographies or between cultures, local data are not available to confirm this assumption. We used epidemiology, clinical, and cost inputs from local studies and available data sources. However, recognizing limited data and the variability between healthcare system infrastructures and population demographics across Peru, the base-case inputs are associated with a level of uncertainty. The results of modeling are limited by the accuracy of data inputs. We performed OWSA to evaluate the impact of parameter uncertainty on the results and to understand the most influential parameters in the analysis; however the results may be more relevant to the urban areas of Peru, such as Lima, where specialized healthcare and routine cervical cancer screening may be more accessible.

Conclusion

This analysis suggests that HPV primary screening with genotyping, either implemented alone or as part of a co-testing approach, improves early cervical cancer detection and reduces cervical cancer incidence and associated mortality with minimal budget impact to the Peruvian public healthcare payer on a per screened woman per year basis. Including HPV primary screening with genotyping for the screening of women aged 30 to 65 years may be a cost-beneficial approach to reduce cervical cancer incidence among women in Peru.

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Mindy Cheng are employees of Roche Diagnostics. All other authors are scientific collaborators and were not paid in any way by Roche Diagnostics for their scientific and expert contributions to this study.

Author contributions

The method proposed in this paper was suggested by Sixto Sánchez and David Callejas. David Callejas and Mindy Cheng identified data inputs and performed the analysis. All authors reviewed the analysis and interpreted results. Sixto Sánchez and David Callejas drafted the manuscript; Mindy Cheng provided technical writing and editing support. All authors reviewed the drafts and read and approved the final manuscript. As gynecologic oncologists, Urso Parra and Victor Cubas gave technical assistance in the area.

Conflict of interest

The health economic models described were developed and owned by Roche. David Callejas and Mindy Cheng are employed by Roche Diagnostics, manufacturer of the cobas® HPV Test. All other authors are scientific collaborators and were not paid in any way by Roche Diagnostics for their contributions to this study.

References

1. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence World Wide in 2012. Globocan, International Agency for Research on Cancer (IARC). World Health Organization (WHO); 2012.
2. Coste J, Cochand-Priollet B, de Cremoux P, Catherine LG, Cartier I, Molinie V, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ*. 2003;326(7392):733. Doi: 10.1136/bmj.326.7392.733
3. Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 2007;357(16):1579-88. Doi: 10.1056/NEJMoa071430
4. Petry KU, Menton S, Menton M, van Loenen-Frosch F, de Carvalho Gomes H, Holz B, 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):1570-1577. Doi: 10.1038/sj.bjc.6600918
5. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, 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):765-774. Doi: 10.1093/jnci/djj209
6. Taylor S, Kuhn L, Dupree W, Denny L, De Souza M, Wright TC Jr. Direct comparison of liquid-based and conventional cytology in a South African screening trial. *Int J Cancer* 2006;118(4):957-962. Doi: 10.1002/ijc.21434
7. Almonte M, Ferreccio C, Winkler JL, Cuzick J, Tsu V, Robles S, et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer* 2007;121(4):796-802. Doi: 10.1002/ijc.22757

8. Leyden WA, Manos MM, Geiger AM, Weinmann S, Mouchawar J, Bischoff K, et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst.* 2005;97(9):675-683. Doi: 10.1093/jnci/dji115
9. Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst.* 2008;100(9):622-629. Doi: 10.1093/jnci/djn099
10. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin no. 109: Cervical cytology screening. *Obstet Gynecol.* 2009;114(6):1409-1420. Doi: 10.1097/AOG.0b013e3181c6f8a4
11. Naucler P, Ryd W, Törnberg 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. Doi: 10.1093/jnci/djn444
12. Alguilar A, Pinto JA, Araujo J, Williams Fajardo, Leny Bravo, Luis Pinillos, et al. Control of cervical cancer in Peru: Current barriers and challenges for the future (Review). *Mol Clin Oncol* 2016;5(2):241-245. Doi: 10.3892/mco.2016.926
13. Santos C, Muñoz N, Klug S, et al. HPV types and cofactors causing cervical cancer in Peru. *Br J Cancer.* 2001;85(7), 966–971. Doi: 10.1038/sj.bjc.6691948
14. Bulk S, Bulkman NW, Berkhof J, Rozendaal L, Boeke AJ, Verheijen RH, et al. Risk of high-grade cervical intra-epithelial neoplasia based on cytology and high-risk HPV testing at baseline and at 6-months. *Int J Cancer.* 2007; 121(2):361-367. Doi: 10.1002/ijc.22677
15. Torné A, Del Pino M, Cusidó M, Alameda F, Daniel A, Javier C, et al. Guía de cribado del cáncer de cuello de útero en España. *Rev Esp Patol.* 2014;47(1):1-43. Doi: 10.1016 / S1699-8855 (14) 70203-X
16. Test de VPH. Ministerio de Salud de la República Argentina. 2017.
17. Mateus LF. Netherlands to Start First HPV Primary Screening Program. *Cervical Cancer News.* 2015
18. Saslow D, Solomon D, Lawson HW, Maureen K, Shalini K, Jonna C, et al; ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62(3):147-172. Doi: 10.3322/caac.21139
19. Cervical cancer: screening. US Preventive Services Task Force. 2012.
20. Del Mistro A, Matteucci M, Insacco EA, et al. Long-Term Clinical Outcome after Treatment for High-Grade Cervical Lesions: A Retrospective Monoinstitutional Cohort Study. *BioMed Research International* 2015;2015:8. Doi: 10.1155/2015/984528
21. Survival rates for cervical cancer, by stage, 2016. American Cancer Society. 2016.
22. Guía de Práctica Clínica para la Prevención y Manejo del Cáncer de Cuello Uterino. Ministerio de Salud. 2017.
23. Wright T, Huang J, Baker E, Garfield S, Hertz D, Cox JT, et al. The Budget Impact of Cervical Cancer Screening Using HPV Primary Screening. *Am J Manag Care.* 2016;22(3):e95-e105.
24. Cox JT, Castle PE, Behrens CM, Sharma A, Wright TC Jr, Cuzick J, et al. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: Results from the ATHENA HPV study. *Am J Obstet Gynecol* 2013;208(3):184.e1-11. Doi: 10.1016/j.ajog.2012.11.020
25. Almonte M, Ferreccio C, Gonzales M et al. Risk Factors for H-R HPV Infection and Cofactors for High-Grade Cervical Disease in Peru. *Intl J of Gynecological Cancer.* 2011;21(9):1654-1663. Doi: 10.1097/IGC.0b013e3182288104
26. Bruni L, Barrionuevo-Rosas L, Albero G, et al. Human Papillomavirus and Related Diseases Report. Peru. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). 2017.
27. NCCN Clinical Practice Guidelines in Oncology. Cervical Cancer. Version 1.2018
28. Sullivan SD, Mauskopf JA, Augustovski F, et al. Principles of good practice for budget impact analysis II: Report of the ISPOR Task Force on Good Research Practices – Budget Impact Analysis. *Value Health.* 2007;10(5):336-347. Doi: 10.1111/j.1524-4733.2007.00187.x
29. 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.e1-11. Doi: 10.1016/j.ajog.2011.07.024
30. Castle PE, Stoler MH, Wright TC, Abba S, Teresa LW, Catherine MB. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: A subanalysis of the ATHENA study. *Lancet Oncol.* 2011;12(9):880–890. Doi: 10.1016/S1470-2045(11)70188-7
31. Ronco G, Dillner J, Elfström 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):524-532. Doi: 10.1016/S0140-6736(13)62218-7
32. Arbyn M, Haelens A, Desomer A, et al. Cervical cancer screening program and human papillomavirus (HPV) testing, part ii: update on HPV primary screening – Summary. *Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE)* 2015; Doi: D/2015/10.273/16
33. Huh W, Williams E, Huang J, et al. Cost Effectiveness of Human Papillomavirus-16/18 Genotyping in Cervical Cancer Screening. *Appl Health Econ Health Policy.* 2015;13(1):95–107. Doi: 10.1007/s40258-014-0135-4
34. Vijayaraghavan A, Efrusy MB, Goodman KA, Santas CC, Huh WK, et al. Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening. *Gyn Oncol.* 2010;119(2):237–242. Doi: 10.1016/j.ygyno.2010.07.004