Age patterns of human papillomavirus infection as primary screening test for cervical cancer and subsequent triage with visual inspection in Honduras

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Abstract

Objective. To evaluate age patterns in human papillomavirus (HPV) prevalence and visual inspection with acetic acid (VIA) positivity among women participating in cervical cancer screening in Honduras. **Materials and methods.** Data on the HPV status (*care*HPV) and subsequent VIA in HPV-positive women were retrieved from three provinces within the Public Health Sector. **Results.** Between 2015 and 2018, 60 883 women aged 15-85 years were screened. HPV was detected in 15%, with variation by age, peaking at 20-24 years (27.8%) decreasing to 16% at 30-49 years. Differences in point age–specific HPV prevalence were observed between provinces, but with similar age pattern. VIA was positive in 24.5% of the women aged 30-44 years. **Conclusions.** The age pattern of the HPV prevalence supports starting HPV testing at age 30+. The low positivity of VIA in ages close to menopause suggest underdetection of cervical lesions in this age group.

Keywords: screening; cervical cancer; human papillomavirus; visual inspection

Sandoval M, Holme F, Lobo S, Slavkovsky R, Thomson KA, Jeronimo J, Figueroa J, de Sanjose S. Patrones de edad de infección por el virus del papiloma humano como prueba primaria en el tamizaje de cáncer de cuello uterino y triaje posterior con inspección visual en Honduras. Salud Publica Mex. 2020;62:487-493.
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Resumen

Objetivo. Evaluar la prevalencia del virus del papiloma humano (VPH) y la positividad a la inspección visual con ácido acético (IVA) de cáncer cervicouterico, según edad en mujeres tamizadas en Honduras. **Material y métodos.** Se extrajo información sobre la prueba de VPH (*care*HPV) y de IVA en tres provincias en el ámbito de la Atención Pública en Salud. **Resultados.** Durante 2015-2018, 60 883 mujeres de 15-85 años fueron tamizadas, 15% fueron VPH positivas con valores máximos en mujeres de 20-24 años (27.8%), con una disminución a 16% entre 30-49 años. Se observaron diferencias mínimas entre provincias, con un patrón de edad similar. La IVA fue positiva en 24.5% en mujeres de 30-44 años, con una posterior disminución. **Conclusiones.** La curva de prevalencia del VPH respalda el tamizar con VPH a los 30+ años. La baja positividad de la IVA en edades cercanas a la menopausia sugiere una subdetección de lesiones cervicales en este grupo.

Palabras clave: tamizado; cáncer de cuello uterino; virus del papiloma humano; inspección visual

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Cervical or vaginal detection of high risk human papillomavirus (HPV) is a key marker of women at risk of cervical cancer.[1] HPV prevalence is a function of incidence and persistence of infection and has been shown to be highly variable by geographic region.[2,3] The main determinants of HPV prevalence are age, sexual behavior, host control of the virus, vaccination, and the censoring effects of treatment in places that have widespread cervical screening.[4] While infection is highly prevalent in young women after onset of sexual activity, by age 30 a decline in HPV detection is generally observed in in many populations. This inflection point is used to target HPV detection as the best available tool to identify women at risk of cervical cancer due to persistent infection.[5] Latent infection and reactivation at older ages may also be observed; the causes still remain unknown and have been shown to vary considerably by geography.[2] Identifying the country- or region-specific pattern of HPV burden by age may assist targeting HPV-based cervical cancer screening interventions. Ideally HPV tests should be performed when the infection is more likely to be a persistent one, but early enough to allow detection of precancerous lesions. Generally, the ideal moment to initiate HPV screening is considered to be when the HPV prevalence drops and stabilizes. This turning point varies across populations.[2,4]

Honduras, like its neighbouring countries, has an estimated annual incidence of cervical cancer of 19 per 100 000 women; however, little is known about the age-specific prevalence of HPV infection in this population.[6] While preparing for the introduction of HPV-based approaches to cervical cancer screening, it is important to appropriately anticipate the volume of women that may be HPV-positive, so that management of subsequent triage and/or treatment can be adequately planned. Further, a more complete picture of HPV infection age-patterns may provide parameters to better understand the global nature of HPV infection and the impact of HPV vaccination in future screening cohorts.[7-9] Additionally, it is relevant to evaluate the differences of age at the triage step in settings where a second test is used to detect precancerous lesions among HPV-positive women. When using HPV as the primary screening test, a certain proportion of women may not develop disease as they may clear the infection. While some countries, like El Salvador, may opt to treat all HPV-positive women after a visual assessment for treatability (VAT),[10] others recommend a triage test to reduce potential overtreatment.[11] Common triage approaches in low resource settings include the Papanicolaou test and the visual inspection with acetic acid (VIA). Importantly, the overall performance of the screening procedure will combine the accuracy of the primary screening test with that of the triage test. Unfortunately, both the Papanicolaou test and the VIA have a lower average sensitivity than the HPV test. It is therefore possible that a considerable number of true precancerous lesions are being overlooked as a consequence of drops in sensitivity in the triage step. Efforts are underway to identify improved algorithms.[12] In Honduras, triage of HPV-positive women was carried out using VIA, considering both HPV- and VIA-positive women as eligible for treatment. We report the age distribution of HPV screening tests and VIA triage tests during the introduction of HPV testing as part of the Scale-Up project. This analysis took place within the Scale-Up project, a collaboration between the Ministry of Health (MOH) and the Program for Appropriate Technology in Health (PATH) to introduce and scale-up screening with HPV tests in three selected regions of Honduras.[13]

Materials and methods

Details of Scale-Up project methods have been reported previously. [13] In brief, the Scale-Up project introduced vaginal self-sampling and *care*HPV, a low-cost human papillomavirus (HPV) test, as the primary approach for cervical cancer screening in selected public health centers in El Salvador, Guatemala, Honduras, and Nicaragua, reaching over 300 000 women by 2019, of whom 13.4% were identified as HPV positive.

Specifically in Honduras, Scale-Up areas were selected by the MOH aiming to facilitate successful introduction of HPV tests. Also selected were areas suspected to have high burden of cervical cancer cases, a significant population density, a reasonable access to follow-up and treatment services, ease of access for monitoring activities carried out by project and MOH workers, and a demonstrated interest in implementing HPV testing by local health leadership. The selected areas were the Metropolitan Region of Tegucigalpa (Tegucigalpa), El Paraíso and Copán. The three areas include an estimated average female population of 448 948 residents aged 15 years or older. While the site criteria tended to favor more dense, urban areas, Copán is mainly a rural area with a difficult-to-reach population.

The screening assay used was *care*HPV (Qiagen, Hilden, Germany), a signal-amplification batch diagnostic test for high-risk HPV DNA detection. The test allows qualitative detection of 14 highrisk types of HPV DNA in cervical and vaginal specimens. Qiagen and PATH trained local laboratory microbiologists, cytologists, and technicians to run the test. Samples were either self-collected or provider-collected. Both were obtained by using the brush and transport media recommended by Qiagen.

Screening with HPV tests was highly recommended for women aged between 30 and 64 years living in Tegucigalpa and the provinces of El Paraíso or Copán. Screening outside this age group was discouraged but is sometimes still practiced. Overall, 88.9% of the women targeted by the Scale-Up project and screened during 2015-2018 had HPV. Women were opportunistically screened primarily in public clinics, and a small proportion of women were contacted during community outreach campaigns at health fairs, at the markets, and in the form of home visits. Screening was largely done through HPV testing of provider-collected samples until 2017; thereafter, women in Tegucigalpa were primarily encouraged to collect their own vaginal samples while provider-collected sampling continued to be the primary strategy in the remaining provinces. Women who screened negative for HPV were instructed to return for retesting in five years, while screen-positive women were referred for a triage step. Women with a visible transformation zone received VIA as triage; otherwise, they were referred for triage at a colposcopy clinic in the referral hospitals. HPV data were collected from those laboratories of the public health system that participated in the Scale-Up project. In the absence of HPV tests, Honduras recommends primary screening with VIA. Data on the VIA results were extracted from medical records at clinics in Tegucigalpa and El Paraíso. No triage data were available for Copán. All the screening and triage activities were carried out by the services provided by the MOH and supervised during the process with the assistance of a country-based non-governmental organization, the Honduran Association for Family Planning (ASHOPLAFA), in discussion with PATH. All data for analysis were de-identified in Honduras after duplicates were removed. An aggregated Excel file was generated for the purpose of this analysis and used to generate the figures. This analysis received non-research determination by PATH's Research Determination Committee.

Available data included province of residence, age at screening, and HPV and VIA results (if HPV positive). Prevalence estimates with 95% confidence intervals (CI), tests for heterogeneity, and linear trends are provided. When prevalence was 0, a one-sided test with a 97.5%CI was provided. Stata version 15.1 (StataCorp, College Station, TX) was used for the analysis.

Results

During 2015-2018, a total of 60 883 women aged 15 to 85 years were screened in three districts in Honduras: 60.8% in Tegucigalpa, 21.2% in Copán, and 18.0% in El Paraíso. The mean age was 43.2 years (standard deviation [SD] 3.2). A total of 9 002 women across all age groups were HPV positive (14.8%; 95%CI=14.5-15.1). HPV positivity varied by age, following a U-shape curve with high prevalence before age 34 and a slight rebound among women aged 70+ years (table I). Women with missing age record did not differ in HPV prevalence from the average estimate. HPV positivity was 19.5% among women aged 30 to 34 years, which was the largest age group, representing 23.7% of all women screened.

Figure 1 shows the age-specific HPV positivity across the three districts. Overall HPV prevalence was 15.0% (95%CI=15.1-15.8) in Tegucigalpa (95%CI=15.1-15.7), 12.9% (95%CI=12.2-13.4) in El Paraíso, and 13.9% (95%CI=12.7-15.1) in Copán. Tegucigalpa had a prevalence ratio of 1.19 times higher compared to El Paraíso and 1.10 times higher compared to Copán (figure 2). Tegucigalpa showed higher prevalence estimates in all age groups up to age 55. From age 65 onwards, estimates were more uncertain, although Tegucigalpa consistently had higher prevalence estimates than El Paraíso, while Copán had higher prevalence estimates than Tegucigalpa.

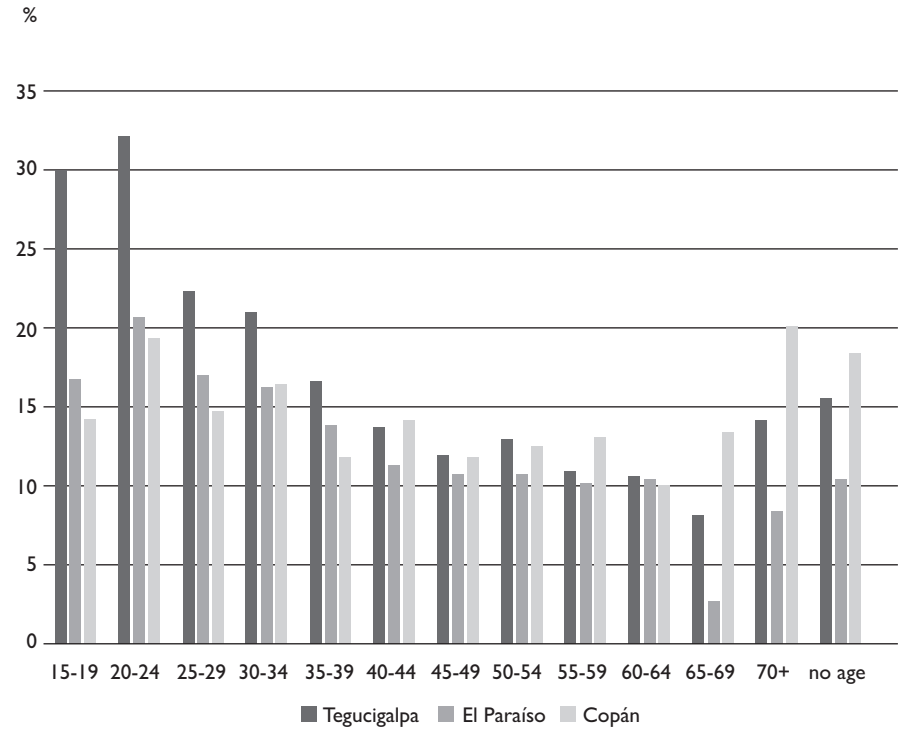
Table I

Women screened with HPV and HPV positivity by age group in three Honduran districts, Tegucigalpa, El Paraíso and Copán, from 2015-2018. Honduras, 2019

Age group	*Total screened N*	*HPV positive N*	*Percent HPV positive within age group %*
15-19	63	14	22.2 (12.7-34.4)
20-24	291	81	27.8 (22.8-33.3)
25-29	1 024	213	20.8 (18.3-23.4)
30-34	14 443	2 823	19.5 (18.9-20.2)
35-39	11 748	1 842	15.7 (15.0-16.3)
40-44	9 689	1 275	13.2 (12.5-13.8)
45-49	7 810	912	11.7 (10.9-12.4)
50-54	6 532	813	12.4 (11.6-13.3)
55-59	4 864	527	10.8 (10.0-11.7)
60-64	3 251	342	10.5 (9.4-11.6)
65-69	252	20	7.9 (4.9-12.0)
70+	86	12	14.0 (7.4-23.1)
Missing age	830	128	15.4 (13.0-18.1)
Total	60 883	9 002	14.8 (14.5-15.1)

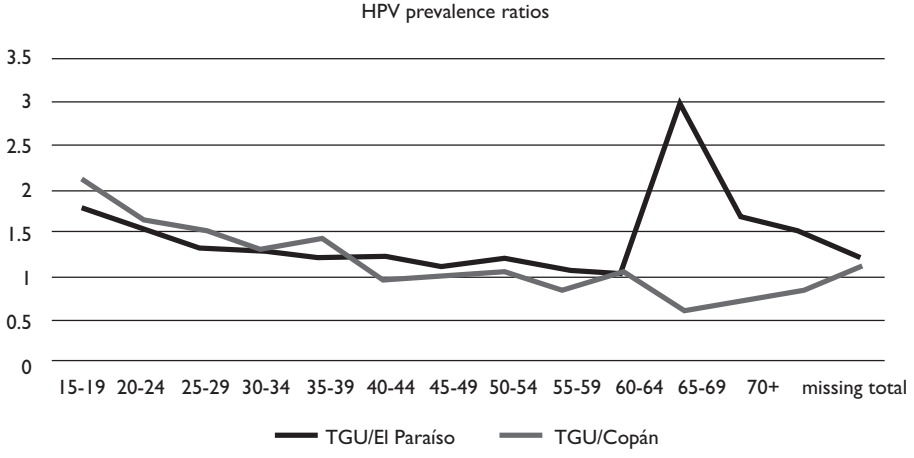
HPV: human papillomavirus

χ^2 test for heterogeneity 410.4 $p<0.0001$. No linear trend identified.



HPV: human papillomavirus

Figure 1. HPV positivity by age group among 44 313 women HPV screened for cervical cancer in Tegucigalpa, El Paraíso, and Copán districts during 2015-2018. Honduras, 2019



HPV: human papillomavirus
TGU: Tegucigalpa

Figure 2. HPV prevalence ratios between Tegucigalpa and El Paraíso and between Tegucigalpa and Copán. Honduras, 2019

HPV positivity was stable through the period 2015-2018, with a range of 13 to 14%, and non-differential prevalence was observed in 2017; self-sampling was introduced in Tegucigalpa with an uptake of 45% of all tests.

Table II shows the age distribution of women triaged with VIA in Tegucigalpa and El Paraíso. The proportion of HPV-positive women completing VIA triage decreased with age (*p* value for linear trend= 0.022). Among all women undergoing VIA triage, 1 746 (20.5%; 95%CI=19.6-21.3) were considered positive for precancerous lesions. The majority of VIA-positive women (79%) were between 30 and 44 years old; this age group was significantly more likely to be positive than the age group of 45 to 64 years ($p<0.001$).

Table II
VIA-positive triage of HPV-positive women in the Metropolitan Region of Tegucigalpa and El Paraíso, Honduras during 2015-18

Age group	*HPV positive N*	*VIA positive N*	*VIA-positive percentage by age groups %*
15-19	11	0	0.0 (0-28.5)*
20-24	68	17	25.0 (15.3-36.9)
25-29	196	39	19.9 (14.5-26.2)
30-34	2 680	685	25.6 (23.9-27.2)
35-39	1 765	440	24.9 (22.9-27.01)
40-44	1 200	259	21.6 (19.3-24.0)
45-49	871	124	14.2 (11.9-16.7)
50-54	782	100	12.8 (10.5-15.3)
55-59	499	49	9.8 (7.3-12.8)
60-64	327	22	6.7 (4.2-10.0)
65-69	16	1	6.3 (1.5-30.2)
70-74	10	0	0.0 (0-30.8)*
Missing age	106	10	9.4 (4.4-16.7)
Total	8 531	1 746	20.5 (19.6-21.3)

HPV: human papillomavirus
VIA: visual inspection with acetic acid
p value of χ^2 test for heterogeneity <0.0001 and *p* value for linear trend 0.0222.
* One-sided CI at 97.5%

Discussion

For the first time in Honduras, a large number of women have undergone primary screening with an HPV test. This information allowed us to estimate age-specific HPV prevalence patterns in three different provinces. Women attending screening were largely in the screening-age target of 30 to 64 years, but the inclusion of some younger and older participants allowed us to confirm the U shape of the HPV prevalence curve previously observed in other Latin American countries and particularly in Central America.[14] It remains unclear which factors determine the HPV age-related pattern in late adulthood and how they could provide a biological explanation of the differences across world regions.[2] Changes in sexual behavior, immune ability to resolve infections, differential vaginal microbiota, and cohort differences have all been proposed with no definitive explanation to date. Although we identified some differences in the prevalence pattern between the three provinces, they all showed a common pattern of HPV infection being highly prevalent among the younger ages (<24 years) and also at much higher ages (> 70 years). Tegucigalpa, a densely populated urban area, exhibited a higher prevalence of HPV, particularly among the younger age groups. Although we did not have information on sexual behavior, differences in HPV prevalence in urban versus rural populations could potentially be explained by variations in sexual behavior, including earlier age of sexual debut, a larger number of lifetime sexual partners, and greater lifetime geographic mobility.

Two different studies carried out in Brazil identified a significantly higher prevalence of HPV among non-married women aged <25 years residing in urban areas than among women living in rural areas.[15,16] Furthermore, first-time HPV screening may also result in higher HPV prevalence estimates.[4,15] The women included in our study all attended public sector health clinics where screening services are available free of charge. For a large majority, this was likely to be their first HPV screening,[13] and although individual information on previous screening was not available, discussions with providers suggest that most women were being screened for the first time. The prevalence estimates presented here, although based on large numbers, may not fully represent Honduran women overall if those attending private services have a different HPV prevalence. This could be speculated to be lower, if women attending the private services are more likely to be regular users of screening exams.

Among women who were HPV positive, VIA triage was performed by medical doctors, either general

practitioners or gynecologists. VIA positivity was highest in the early target age group of 30 to 44 years and substantially decreased thereafter, consistently with the findings of other studies.[17-19] Raifu and colleagues[18] showed that 49% of the HPV-positive women proved to be VIA positive in physician-performed VIA, while in Honduras positivity was substantially lower (20%). In Rwanda, VIA positivity was detected in 7.6% of women attending screening.[19] While the three studies showed a similar overall HPV prevalence, differences in VIA were striking. Provider performance is likely to be a determining factor in explaining differences across study populations, and questions the true effectiveness of VIA, given a wide range of sensitivities across studies. In order to minimize variability across the different providers using VIA in Honduras, all the professionals involved in VIA followed a training process to refresh or learn how to run VIA. Our results could not be evaluated by the provider as this information was not available.

A meta-analysis comparing studies that used both VIA and an HPV-PCR based test estimated that the pooled sensitivity to detect CIN2+ was 69% (95%CI=54-81), significantly lower than that of HPV tests alone, which was 95% (95%CI=84-98).[20] In a study on the acceptability of thermal ablation in this area,[21] we have identified that 24.1% of both HPV-positive and VIA-positive women harbored a histology proven CIN2+ lesion. In Raifu and colleagues,[18] where all subjects had a biopsy, out of 31 cases of CIN2+, 29 were VIA-positive, suggesting a better performance of VIA than in Sandoval and colleagues.[21] Using self-collected samples with *care*HPV may cause an additional slight reduction in sensitivity, and when adding VIA as triage may together limit the full potential of a screening intervention.[11] The use of low-cost, validated PCR based tests that detect exclusively oncogenic HPV types is strongly preferred. VIA has been used widely as a screening or triage test but given the limited accuracy, it is urgent to provide a better approach that can be cost-effective and logistically acceptable and feasible. While primary screening with accurate HPV tests has been widely accepted as the best screening approach, different low-cost options remain under evaluation on how best to organize the triage of HPV positive women, including enhanced visualization with automatic reading, genotype restriction, or methylation assays. There is an urgency to obtain evidence-based information on these new options in order to guarantee a fully successful screening round.

To conclude, women in Honduras show a U-shaped age distribution of HPV prevalence –a result that confirms current recommendations for starting routine HPV testing at 30+ years of age. Local geographical differences in HPV prevalence are detectable, suggesting behavioral and age-cohort effects that could both reflect sexual conduct and screening access.

Declaration of conflict of interests. The authors declare not to have conflict of interests.

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