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ORIGINAL PAPER

Prevalence of cervical human papillomavirus in Mexico, 2010–2017: analysis of 2.7 million women

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Abstract

Purpose Prevalence of cervical high-risk human papillomavirus (hrHPV) infection varies greatly. Data on distribution of hrHPV infection constitute important evidence for decision-making when implementing HPV testing into cervical cancer screening programs. We estimate the prevalence of cervical hrHPV infection in a large sample of women in a middle-income country and explore variation by age, community marginalization and region in women using public cervical cancer screening services.

Methods Records covering 2010–2017 from a registry of hrHPV test results (Hybrid Capture 2 and polymerase chain reaction) in 2,737,022 women 35–64 years were analyzed. In this observational study, 32 states were categorized into five geographical regions and classified by degree of marginalization. We stratified by test type and estimated crude and adjusted prevalence and rate ratios and used Poisson models and joinpoint regression analysis.

Results Prevalence was higher in women 35–39 years, at 10.4% (95% CI 10.3–10.5) and women 60–64 years, at 10.1% (95% CI 10.0–10.3). Prevalence was higher in the southeast, at 10.5% (95% CI 10.4–10.6). Women living in less marginalized areas had a significantly higher prevalence, at 10.3% (95% CI 10.2–10.4) compared to those in highly marginalized areas, at 8.7% (95% CI 8.5–8.7). HPV16 infection was detected in 0.92% (2,293/23,854) of women and HPV18 infection was detected in 0.39% (978/23,854) of women.

Conclusion Understanding the distribution of HPV prevalence has value as evidence for developing policy in order to improve cervical cancer screening strategies. These results will constitute evidence to allow decision makers to better choose where to focus those resources that they do have.

Keywords Human papillomavirus DNA tests · Prevalence · Mexico · Cervical cancer screening test

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Introduction

Prevalence and distribution of cervical human papillomavirus infection with high-risk types (hrHPV) varies throughout the world. In addition to the impact of HPV vaccination, hrHPV infection may vary by age group, related behaviors, ethnic group, and geographic region or sub-region; some of these characteristics may serve as proxies for other factors, such as screening coverage [1–3]. HPV prevalence in women with normal cytology is 11.4% worldwide, 10.3% in higher-income nations, and 14.3% in lower- and middle-income countries [4]. In general, young women (less than 25 years) have a higher prevalence of hrHPV infection (24%) than older women and prevalence decreases with age, as seen in studies in the United States and in some countries in Asia and Europe, although this decline appears to be less steep in the world's poorest countries [4–6]. However, in some parts of Central and South America, as well as in West Africa, a second increase in hrHPV infection has been reported near menopause, possibly due to a cohort effect and/or to an increase in number of partners among some women in this life period [7–9]. In the Americas, there is a lower prevalence of hrHPV (9.0%) in women aged 45–54 years while in Asia and Europe women in this age group have higher prevalence (10%). Notably, Africa has the highest prevalence (20%) compared to the rest of the world in women in the same age groups [6].

The Mexican cervical cancer program considers women's age when choosing between screening tests: women older than 35 are assigned a hrHPV test (when available) while women under 35 receive cytology. Availability of HPV testing may vary annually; in years the program has insufficient resources, an insufficient number of hrHPV tests are distributed and thus states may be forced to screen women with cytology only. HPV-positive women should return for second visit for cytological triage, after which only those with a cytological diagnosis ≥ ASCUS receive colposcopic evaluation for confirmation and treatment. Women with a histological diagnosis of ≥ CIN 2 are sent to a dysplasia clinic for medical treatment or an oncology center. Mexican national guidelines recommend that HPV-negative women return for screening after 5 years.

In Mexico, beginning in 2012 the bivalent HPV vaccine was included as a nationally required vaccine for girls in elementary school (ages 9–13) or who are 11 years old and not in school. HPV vaccination of girls is funded by the government and offered for free; adult women can access vaccination at private health services [10]. The data base analyzed in this study does not provide information on whether women are vaccinated against HPV but it is likely that few of the women were vaccinated given their ages. The nonavalent vaccine is not currently available in Mexico, except for use in clinical trials.

In Mexico an overall prevalence of hrHPV of 9.4% to 11.0% has been reported, although there is only data for limited regions of the country and for short time periods with the highest prevalence in women younger than 35 years [5, 11–13]. HPV16 and HPV18 prevalence have only been studied in a small proportion of Mexican women.

Knowledge of hrHPV infection has led to new prevention strategies and to changes in the way screening for cervical and other cancers is organized [14, 15]. Prevalence estimates can inform decision-makers on how to best use limited resources, by allowing them to identify groups or regions in which the population's need for screening is greater, especially in women older than 35 years. Such data on the distribution of infection are useful to improve program approaches to follow-up of cases and also to inform decision-makers in order to design targeted prevention programs that take into account the prevalence in each region [16].

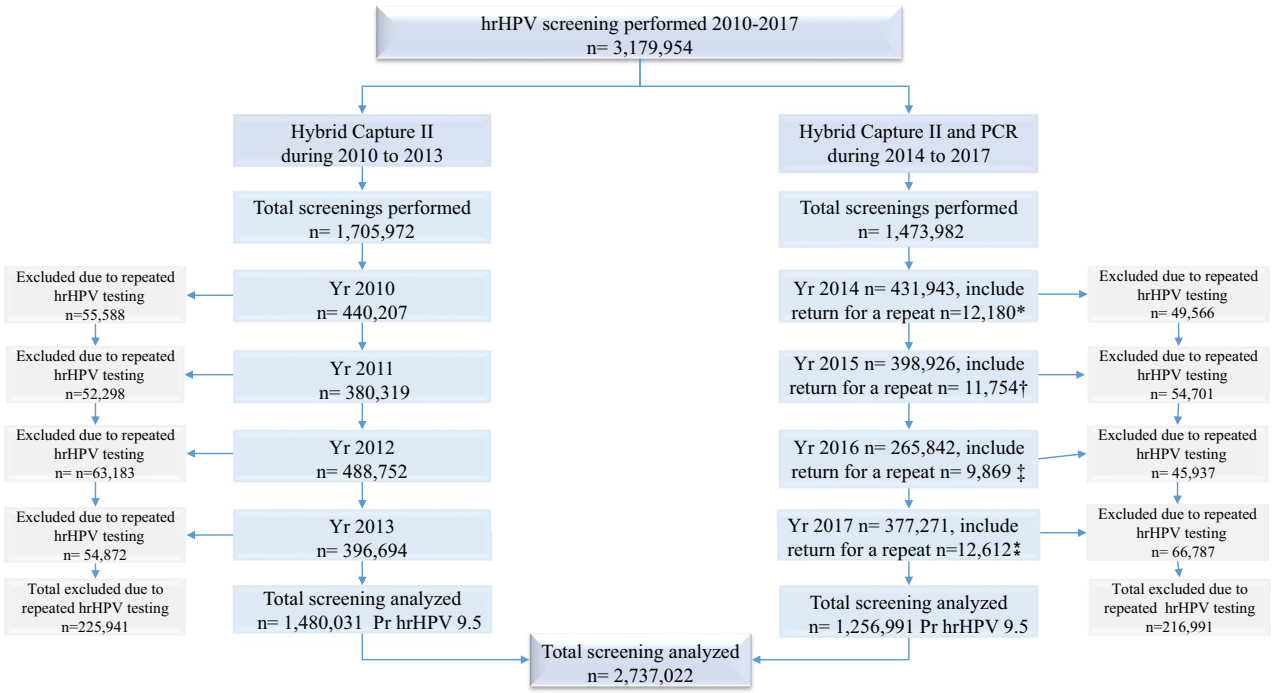
The objective of this paper is to estimate the prevalence of cervical hrHPV infection in a very large sample of women in a middle-income country (Mexico), and explore variation by age, level of marginalization as well as regional differences in infection at the population level in a public cervical cancer prevention program.

Material and methods

In this observational study, records covering 2010–2017 from Mexico's Women's Cancer Information System database on hrHPV test results [Hybrid Capture 2 (HC2) and polymerase chain reaction (PCR)] in women 35–64 years of age were analyzed.

Target population

In Mexico, the Ministry of Health provides free public health services for unemployed or informally employed persons without social security or insurance from another source, who represent 38–40% of the population [17]. This healthcare system has a cancer registry with information from cytology-based cervical screening and after 2010 hrHPV-based screening at a population level as well as data on clinical follow-up and diagnostic confirmation. Only the data for women who actually use the program are included in the registry [18]. The estimated target population is around 10 million women aged 35–64 who should undergo screening. Figure 1 shows that between 2010 and 2017, 3,179,954 hrHPVscreens were performed. During the first 4 years of study data (2010, 2011, 2012, 2013), we included positive or negative results for only one screen



• Women screened in 2010 and who returned for a repeat in 2014. † Women screened in 2011 and who returned for a repeat in 2015. ‡ Women screened in 2012 and who returned for a repeat in 2016. ⁑ Women screened in 2013 and who returned for a repeat in 2017

Fig. 1 Consort diagram

per woman per calendar year. Thus, for women screened in 2010, re-screenings in 2011–2013 were not included in the analysis. At the end of the 5 year period, women who had completed 5 years between screenings were then included in the denominator for the next 5 year period. In the next time period, the same procedure was followed to analyze results for only one screen per woman per calendar year, until the woman completed a 5-year period.

We excluded from the analysis women who sought a repeat screen before 5 years had passed since the first screening. So, those excluded were women who sought screening due to being referred by a health professional or who were self-referred, before 5 years had passed since their previous screen. Women with hysterectomy were included in the analysis only when the hysterectomy was performed after her first screening took place; in these cases, the screening data were included for the year before the hysterectomy took place. The consort diagram (Fig. 1) shows what population was eliminated each year and why.

Link Plus version 2.0, a probabilistic record linkage software developed at the Centers for Disease Control and Prevention (CDC), was used to identify duplicate records [19]. Link Plus was programmed based on the selected phonetic coding system (Soundex), to search for partial, approximate or fuzzy matches.

Study population

A total of 2,737,022 electronic records (corresponding to one hrHPV test result per woman) were obtained from the registry database and used in the analysis. Results from women with a hysterectomy were excluded from the analysis. The National Institute of Public Health of Mexico's Research Ethics Committee approved the study (number 1004).

hrHPV test

hrHPV-based screening recorded in the registry includes results from two types of automated platforms, which are based on the hrHPV DNA extraction techniques used during the study:

1. Hybrid Capture® 2 High-Risk HPV DNA Test® (HC2), a hybridization assay with antibody capture and signal amplification that uses detection by chemiluminescence gives qualitative results on the presence or absence of one or more of 13 hrHPV types (HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [20]. Between 2010 and 2017, women were screened with the HC2 test.
2. Roche cobas® 4800 HPV Test uses polymerase chain reaction (PCR) to give qualitative results to detect HPV

16, HPV 18 and a pool of 12 other hrHPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) [21]. The PCR platform was progressively introduced by an increasing number of states starting in 2014 but it was not until 2017 that there was a representative sample of PCR results in all of Mexico's 32 states. When PCR started operating in all states, the number of HC2 tests decreased progressively.

The cervical cancer detection program gradually scaled-up PCR and scaled-down HC2 beginning in 2014; each year more laboratories with the PCR platform were established in the program. However, for a short period, in some states in Mexico the screening program used both screening tests (some of each for different women) in women from the same communities and the same year. However, we feel that differences in hrHPV estimation between types of screening platform (PCR or HC2) are not relevant to our analysis, and we have included the results from both types of screening.

Covariates

Degree of marginalization (five levels, very high to very low) is a measure that includes indicators which provide data about services that are lacking and other aspects related to poverty, including lack of access to education, inadequate housing and crowding, insufficient income, among other indicators. Mexico's 32 states were grouped into five geographical areas (north, center-north, center, center-south and southeast). The supplementary Fig. 1, shows a map of Mexico with the borders of the geographic regions identified and a colored heat-map of the marginalization strata used for the analysis [22, 23].

Statistical analysis

For the initial descriptive analysis, we calculated the median and interquartile range for age at screening, as well as frequencies and proportions for categorical variables (marginalization, geographic region and year of screening). Age at screening was divided into 5-year groups (35–39, 40–44, 45–49, 50–54, 55–59 and 60–64). We performed stratified analyses by type of test (HC2 and PCR). We analyzed results from the 32 states, grouped into the five geographical regions. We estimated the prevalence of hrHPV infection and its regional distribution, divided into quartiles.

We used Poisson models with robust standard errors to estimate hrHPV prevalence. To consider the role of other variables, we adjusted estimated prevalence by age, geographic region (where screening was performed), degree of marginalization and year of screening. Using these models, we obtained adjusted prevalence and prevalence ratios with 95% confidence intervals (CI) [24, 25]. Analyses were performed in the Stata statistical package version 14.2 (STATA Corporation, College Station, TX, USA).

Women who were HPV positive from 2010 to 2013 are included once in the denominator and women who were ever positive are considered once in the numerator. As the consort diagram (Fig. 1) shows, women who are screened 5 years after the first screening are included in the denominator again, and if they had a positive screening result are included in the numerator.

The average annual percent change and 95% CI of hrHPV infection using the HC2 test during 2010–2017 were estimated using joinpoint regression with maximum joinpoint of zero (Joinpoint Regression Software, version 4.7.4 Feb 2019). Thus we fitted a regression line between the natural logarithm of multivariable-adjusted hrHPV prevalence and time [26]. In order to examine annual percent change correlates, we stratified the analysis by age, geographic region and degree of marginalization. The level of significance was 0.05.

Results

Approximately 27.3% of the target population (35–64 year-old) was included in the analysis. During 2010–2017, 259,882/2,737,022 hrHPV positive cases were detected, a prevalence of 9.5% (95% CI 9.46–9.55) of all women who had at least one screening visit. The HC2 test detected 236,028/2,488,620 positive cases and the PCR test detected 23,854/248,402 positive cases, representing a prevalence of 9.5% and 9.6%, respectively.

Table 1 shows the study population's characteristics by type of test and for each of the covariates. The age distribution the women for whom screening results were analyzed does not represent that of the larger target population. While the most frequently screened group were women aged 35–44 years, women in the 60–64 year age group were the least screened with either type of test. Median age was 44 years for HC2 and 45 years for PCR, with an interquartile range (IQR) of 12 for both tests. The center region had the lowest number of HC2 tests (16.7%) and the north-center the highest (23.8%), while for the PCR test, the north had the lowest number of tests (0.6%) and the north-center had the highest (33.9%). A higher proportion of women residing in municipalities with a very low degree of marginalization (42.0% for HC2 and 37.8% for PCR) were screened, compared with women residing in areas with a high degree of marginalization (6.4% for HC2 and 5.6% for PCR).

To reduce the risk of underestimating the true HPV prevalence, we included in the analysis only one screening test for each woman in the years 2010 to 2013; women who returned after 5 years for screening were included in the analysis of the next 5 years of data (2014–2017). Crude and

Table 1 Characteristics of screened women from 2010 to 2017, $n = 2{,}737{,}022$

	Women screened HC2 only		Women screened PCR only	
	$n = 2{,}488{,}620$	%	$n = 248{,}402$	%
Year				
2010–2013	1,480,031	54.1	–	–
2014–2017	1,008,589	36.8	248,402	9.1
Age group				
35–39	706,362	28.4	76,494	30.8
40–44	579,163	23.3	55,225	22.2
45–49	462,636	18.6	43,917	17.7
50–54	353,451	14.2	34,225	13.8
55–59	242,607	9.7	23,941	9.6
60–64	144,401	5·8	14,600	5.9
Geographical region				
North	427,844	17.2	1,540	0.6
North-Center	592,341	23.8	84,247	33.9
Center	414,655	16.7	58,699	23.6
South-Center	483,571	19.4	71,298	28.7
Southeast	570,209	22.9	32,618	13.1
Marginalization				
Very-high	159,141	6.4	13,995	5.6
High	188,876	7.6	17,305	7.0
Medium	688,693	27.7	68,050	27.4
Low	406,633	16.3	55,075	22.1
Very-low	1,045,277	42.0	93,977	37.8

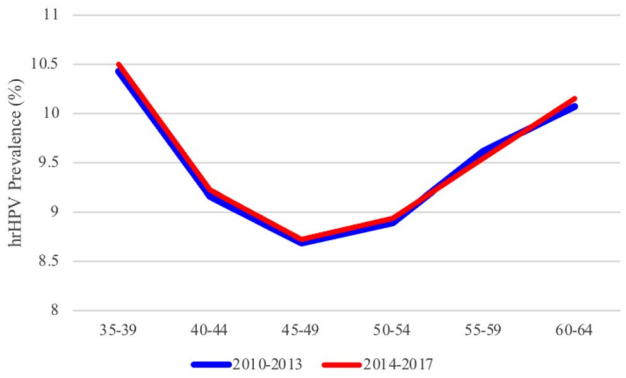


Fig. 2 hrHPV prevalence by age group by period 2010–2013 and 2014–2017

adjusted prevalence was higher in the youngest and oldest age groups (35–39 and 60–64 years), compared with the intermediate groups, with bimodal U-shaped growth, which was even higher among the 35–39 year group (Fig. 2). There was a subsequent decrease after age 40 and a slight increase after age 55 (Table 2).

Table 2 Demographic characteristics associated with HrHPV prevalence in screened women, 2010–2017, $n = 2{,}737{,}022$

	No. of women	Prevalence of hrHPV, % (95% CI)		PR[b]
	Screened	Crude	Adjusted[a]	(95% CI)
Year of screening				
2010–2013	1,480,031	9.5 (9.4–9.6)	9.5 (9.4–9.6)	1 (1.0–1.1)
2014–2017	1,256,991	9.5 (9.4–9.6)	9.5 (9.4–9.6)	1 (1.0–1.1)
Age group				
35–39	782,856	10.4 (10.3–10.5)	10.4 (10.3–10.5)	1 (Ref)
40–44	634,388	9.2 (9.1–9.2)	9.1 (9.0–9.2)	0.8 (0.8–0.8)
45–49	506,553	8.7 (8.6–8.8)	8.7 (8.6–8.8)	0.8 (0.8–0.8)
50–54	387,676	8.9 (8.8–9.0)	8.9 (8.8–9.0)	0.8 (0.8–0.8)
55–59	266,548	9.6 (9.5–9.7)	9.6 (9.5–9.8)	0.9 (0.9–0.9)
60–64	159,001	10.1 (10.0–10.3)	10.2 (10.1–10.4)	0.9 (0.9–0.9)
Geographical region				
North	429,384	10.2 (10.1–10.3)	9.3 (9.2–9.4)	1 (Ref)
North-center	676,588	8.5 (8.4–8.6)	8.3 (8.2–8.4)	0.9 (0.9–0.9)
Center	473,354	9.2 (9.1–9.3)	8.7 (8.6–8.8)	0.9 (0.9–0.9)
South-center	554,869	9.4 (9.3–9.5)	9.9 (9.8–10.1)	1.0 (1.0–1.0)
Southeast	602,827	10.5 (10.4–10.6)	11.3 (11.2–11.4)	1.2 (1.2–1.2)
Marginalization				
Very-high	173,136	8.7 (8.5–8.8)	7.9 (7.7–8.0)	1 (Ref)
High	206,181	9.0 (8.9–9.2)	8.4 (8.2–8.5)	1.1 (1.0–1.1)
Medium	756,743	8.6 (8.5–8.7)	8.4 (8.3–8.5)	1.0 (1.0–1.1)
Low	461,708	9.4 (9.3–9.5)	9.5 (9.4–9.6)	1.2 (1.1–1.2)
Very-low	1,139,254	10.3 (10.2–10.4)	10.8 (10.7–10.9)	1.3 (1.3–1.3)

[a]Model-predicted prevalence adjusted by age, geographical regions, marginalization and year of screening

[b]*PR*, prevalence ratio. Adjusted for the variables shown in table and year of screening

The adjusted prevalence of hrHPV infection by geographical region was slightly higher in the southeastern part of the country in women screened, at 11.3% (95% CI 11.2–11.4). When comparing regions, there were no significant differences in terms of a positive hrHPV result except for in the

southeast. Supplementary Fig. 2 shows hrHPV prevalence in Mexico's 32 states, classified in quartiles. hrHPV prevalence does not vary significantly in the 2010–2017 period.

Regarding the degree of marginalization, prevalence was higher in women with very low marginalization, at 10.3% (95% CI 10.2–10.4), compared with 8.7% (95% CI 8.6–8.8) in women with very high degree of marginalization.

A total of 248,402 women were examined using PCR. Overall hrHPV infection prevalence was 9.6% (23,854 women). HPV16 infection (alone or with other hrHPV) was detected in 0.92% (2,293 women), HPV18 infection (alone or with other hrHPV) was detected in 0.39% (978) of participants, while another 12 hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) were detected in 7.5% of women using the PCR HPV DNA assay. Prevalence by HPV genotype is summarized in Table 3.

In Mexico, the average annual percentage change (AAPC) in rate of hrHPV prevalence from 2010 to 2017 for the 40–44 and 45–49-year age groups was higher (0.3%) compared to that of the 50–54 and 55–59-year age group (−1.0%). The average APC in the southeast was lower (−0.3%) compared with the other geographical regions. The average APC in women living in states with a high degree of marginalization was lower (−0.8%) compared with women living in areas with a high degree of marginalization (0.8%) (Table 4).

Table 4 Annual percent change in hrHPV prevalence, Mexico 2010–2017

	Average annual prevalence	Segment 1, 2010–2017 AAPC (95% CI)
Overall	8.4	0.1 (−0.3 to 0.4)
Geographical region		
North[†]	9.3	0.1 (−0.3 to 0.5)
North-center	8.3	0.9 (0.1–1.7)
Center	8.7	0.4 (1.1–7.1)
South-center	9.9	0.2 (−0.8 to 1.2)
Southeast	11.3	−0.3 (−0.7 to 0.1)
Marginalization		
Very-high	9.3	−0.1 (−0.8 to 0.6)
High	8.3	−0.8 (−1.8 to 0.1)
Medium	8.7	−0.3 (−0.7 to 0.2)
Low	9.9	0.8 (−0.2 to 1.8)
Very-low	11.3	0.5 (−0.1 to 1.0)
Age group		
35–39	10.4	0.2 (−0.2 to 0.6)
40–44	9.2	0.3 (−0.3 to 0.9)
45–49	8.7	0.3 (−0.3 to 1.0)
50–54	8.9	−1.0 (−0.9 to 0.7)
55–60	9.6	−1.0 (−0.7 to 0.5)
60–64	10.1	0.1 (−0.7 to −0.9)

Age-adjusted prevalence rates and average annual percent change (AAPC) for HrHPV: Mexico 2010–2017

CI confidence interval

*Statistically significant ($p<0.05$)

[†] North geographical region had two trend segments (2010–2012, 2012–2016)

Discussion

A systematic review for literature published from 1995 to 2005 found that cervical HPV prevalence in women with normal cytology was 10.4% overall and highest in women younger than 35 years, with decreases in prevalence in women of older age [1]. A study of 15 regions worldwide found that cervical HPV prevalence peaked below age 25 or 35 in various regions while prevalence in three regions in Latin America also showed a second peak in older women. In this analysis, cervical HPV prevalence was low in all ages in two regions in Asia but was high in the poorest parts of Asia studied as well as in Nigeria [13].

Table 3 HPV genotype results in screened women, 2016–2018, by PCR test, $n=248,402$

HPV typing	Frequency	Prevalence	95% CI for PR
HPV 16 (single infection)	2,293	0.92	(0.85–0.96)
HPV 18 (single infection)	978	0.39	(0.36–0.41)
HPV 16 & HPV 18 as co-infections	66	0.03	(0.02–0.04)
Other HR HPVs (31,33,35,39,45,51,52,56,58,59,66,68)	18,578	7.48	(7.37–7.58)
Other HR + 16	1,267	0.51	(0.48–0.53)
Other HR + 18	580	0.23	(0.21–0.25)
Other HR + 16 + 18	92	0.04	(0.02–0.05)
Sum[a]	23,854	9.60%	(9.48–9.71)

HPV human papillomavirus, *HR* high risk

[a]Sum of all HPV types. HPV 16/18 coinfected women are a separate category

This is the first population-based study in Mexico to examine the differences in prevalence of hrHPV infection at the national level. Previous research has focused on describing the prevalence of infection and associated cervical lesions, mainly in small areas limited to the center of the country [27–30]. The findings on hrHPV prevalence were consistent with studies conducted on much smaller sample sizes, where an overall prevalence of 9.3% was found [28]. In this analysis, both crude and adjusted rates show prevalence has a bimodal distribution in terms of age. This is consistent with previous research in the region, where these two prevalence peaks have been found [5, 13, 31, 32]. Torres-Ibarra et al. reported an overall prevalence of 11% with the PCR test, for the state of Tlaxcala, with a U-shaped prevalence in the same age groups as in our national analysis. Our results found a prevalence of 10.6% in that same state, around the same year with the same test [12].

Many factors of hrHPV prevalence in young women have been described, which are the main determinants of higher prevalence in this age group [33]. Most of the time these are transitory infections that will clear up quickly, in around 12–24 months [34]. Not all women with positive results will develop persistent infections, e.g., most of these HPV infections will clear [31, 35].

In women over 55, enormous variability in hrHPV prevalence between regions has been found. The available evidence on higher prevalence in older women points to different etiologies; among the most consistent explanations is a lowered immune response due to physiological changes, limiting the ability to eliminate infections. That is, immunosenescence favors the presence of infections in a period of latency, which may become active at any time with different triggers (anatomical, physiological, hormonal changes) [5]. Another possible interpretation is the existence of cohort-specific differences in sexual behaviors, such as differing partner acquisition patterns [36]. Finally, another possible explanation for the increased prevalence in this group is re-exposure through new sexual partners which in association with the above factors or independently, may be the cause of a relatively high peak in prevalence among adult women [35].

We consider the results in women over 55 obtained in this analysis to be due to a mixture of these three major explanations, as it is difficult to attribute the results to a single cause, since they are all interrelated [2, 3, 37, 38]. Also, the results in terms of prevalence by age group are consistent with inter-regional variations similarly present in other countries [13, 29, 37, 39, 40].

Differences in prevalence between countries and regions may occur because of the variability of methodologies used in the detection of hrHPV DNA. However, in some regions, differences in prevalence may be real and be due to the variability in characteristics associated with hrHPV infection in different populations, such as age, geographic region, gynecological history, prolonged hormonal contraception use, and smoking [6, 41].

Northern Mexico generally has lower levels of poverty and marginalization. Hypothetically, the sexual behaviors of women in this area may have different characteristics from those of women in the center and south of the country (where there is more poverty and marginalization). Related to this is that a higher prevalence of hrHPV was found in women living in states with lower levels of marginalization (whether they were in the northern part of the country or not), compared to women living in highly marginalized states. These results seem controversial since the most economically and culturally disadvantaged women are considered to be at greater potential risk for developing any pathology, including cervical cancer, due to multifactorial causes [42–44]. Women in the study who lived in highly marginalized areas were screened less than women in areas with low levels of marginalization. However, we do not know if these women are at higher risk and therefore could skew the results. Although very few studies have documented the relationship between hrHPV infection and economic status, in 2013 researchers in Costa Rica found an increased risk of hrHPV in women with a high socioeconomic status [31]. Researchers in China in 2019 published a meta-analysis with studies of their region and found a higher prevalence in women of medium and high economic status [43]. Another study reported a slightly higher prevalence in urban populations 14.8% (95% CI 12.8–16.8) versus those in rural areas with a prevalence of 13.7% (95% CI 11.1–16.2) [13]. These results could be due to differences in sexual practices related to socioeconomic level. Our results are consistent with these findings.

In Mexico, the use of hormonal contraception in sexually active women has been found to be lower in populations without any education (62%), compared with those having basic schooling or more (74%). While 66.7% of women of childbearing age living in rural areas reported use of hormonal contraception, 75% of those in urban areas reported using this type of contraception. According to a recent estimate, in Mexico hormonal contraception use increased from 30% in 1976 to 73% in 2014 among sexually active women, which may have impacted the change in HPV prevalence over time [44]. We do not have information on whether the women included in this data base report higher condom use in marginalized areas of Mexico (compared with for example oral contraception); however, in a population-based national health survey done in 2012, women living in more marginalized areas used 7.1% less modern contraception in general than women living in less marginalized areas (and 10% less women living in rural areas use modern contraception than those in urban areas) [45].

International migration on both Mexico's northern and southern borders could also be an influential factor in hrHPV prevalence. This migration could lead to changes in partner acquisition; similar changes in sexual behavior may have led to increased HPV prevalence after the so-called "sexual revolution" in the United States [46]. An additional explanation for these findings is that some states in Mexico have few or no municipalities classified as highly marginalized; thus, in those states, most women being screened live in communities with low to medium marginalization. Also the women living in areas with high marginalization encounter more economic, structural and socio-cultural barriers to getting a gynecological test such as an HPV test, or access to medical services in general [47]. While some women may go for a screening test, others who should be screened (among whom there might be a higher HPV prevalence) may not receive testing.

A potential limitation of this study is that women are screened more frequently than stipulated by policy (once a year or more often, instead of every 3 years after two negative test results); this could have skewed the results towards lower coverage of women at higher risk of cervical HPV. However, we sought to correct this by eliminating duplicate testing results using appropriate software.

We opted to combine HPV DNA detection results for women, whether the hybrid capture (HC2) or PCR testing technique was used. Although PCR is usually more sensitive than HC2 [48], the overall prevalence for HPV determined using either technique did not differ significantly, since prevalence for PCR was 9.6% (PCR 95% CI 9.48–9.71) and for HC2 was 9.5% (95% CI 9.4–9.6). In order to explore this further, we did a comparison of the data from one state (Jalisco, in the North-Center of the country), for women 45–49 years: while in 2015 when HC2 was being used HPV prevalence was 9.1% (95% CI 8.1–10.1), in 2017 when PCR was used prevalence was 9.4% (95% CI 8.2–10.6).

The impact of HPV vaccination is an important factor to take into account when evaluating cervical cancer prevention programs [49]. The database used for our analysis does not include whether women are vaccinated. Mexico began HPV vaccination in girls in 2012, but adult women are not included in the public vaccination program and only have access to HPV vaccines if they can pay for them in private healthcare. The women included in this analysis use public healthcare and are not likely to have the income necessary to cover the cost of an HPV vaccine. HPV vaccination coverage among adult women in Mexico is very low; for example, in one state (Tlaxcala, in the Center-South of the country) coverage is only 0.3%. Given the low coverage of HPV vaccination among adult women in Mexico, we conclude the impact on our study results is likely to be insignificant.

We were unable to include additional factors influencing cervical HPV prevalence such as women's individual socioeconomic level since this data was not included in the registry we analyzed. Nevertheless, we feel that the large sample size and the fact that the data are population-based are strengths of this analysis, which make it relevant in spite of having limited variables on factors potentially associated with cervical HPV prevalence.

The national registry we analyzed includes only women without access to a social security healthcare institution (generally available only to formal employees and their cohabiting partners). Thus, this sample may not be representative of all Mexican women at the national level. However, many characteristics of women with and without access to social security healthcare do not differ, such as age or area of residence.

Conclusion

Understanding the distribution of HPV prevalence has value as evidence for developing policy in order to improve cervical cancer screening strategies, as well as possible vaccine implementation policies [50]. Prevalence results from this study provide relevant information about the distribution of hrHPV in a representative population of Mexico, mainly of women without healthcare coverage from the social security system or private insurance.

The implementation of HPV screening technologies has the potential to prevent cervical and other cancers; however most of the world's countries face challenges in taking advantage of innovations such as HPV screening tests or vaccines [51]. Middle- and lower-income countries especially need to resolve organizational barriers that reduce the effectiveness of these technological innovations. An essential first step is to provide decision-makers, healthcare leaders and those implementing new screening options at all levels with information about the multiple benefits of HPV testing including performance, safety and cost-effectiveness [52]. It will also be necessary to resolve issues related to training personnel, space in facilities for testing, as well as purchasing and distributing supplies [53]. Finally, where feasible, expanded HPV vaccination schemes rolled out in combination with HPV testing will offer the possibility of an increased decline in cancer incidence, especially cervical cancer which continues to have a significant negative impact on many of the world's women. These results constitute evidence that will allow decision makers to better choose where to focus those resources that they do have.

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Data availability Anonymized data that are minimally required to replicate the outcomes of the study will be made available upon reasonable request to the corresponding author, and following approval by the participating sites.

Declarations

Conflict of interest The authors declare no potential conflicts of interest. Only Dr. Franco reports grants and personal fees from Merck, outside the submitted work; In addition, Dr. Franco has a patent Methylation markers in cervical cancer pending.

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