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ORIGINAL PAPER

A pilot study of HPV DNA and cytology testing in 50,159 women in the routine Mexican Social Security Program

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Abstract
Introduction We present a large feasibility evaluation of high-risk HPV (HR-HPV) DNA testing and cervical cytology as a primary screening strategy for cervical cancer precursor lesions in Mexican women, as part of a routine cancer control program (CCP).
Methods A community-based study was carried out in 50,159 women aged 20–70 years who visited the CCP in 12 federal entities located in Northern, Central, and Southern Mexico, including a total of 48 primary health care units of the *Instituto Mexicano del Seguro Social* (IMSS). Cervical specimens for cytology and HR-HPV tests were collected at baseline. Women with cytological abnormalities (ASCUS or greater) were referred to colposcopy for further evaluation and treatment if necessary. A subset of HR-HPV-positive women without cervical lesions, in Morelos state, were tested again for HR-HPV DNA within a year, and repeat-positive women were referred to colposcopy.
Results HR-HPV prevalence among all women was 8.6% (95% CI: 8.3–8.9). Prevalence by age group was 12.2% (95% CI: 11.0–13.3) before 30 years of age and decreased to 7.4% (95% CI: 6.7–8.0) between 46 and 50 years of age. A second minor prevalence peak (8.1%; 95% CI: 7.2–9.0) was observed in women more than 55 years of age. Overall prevalence of cytological abnormalities was relatively low (2.2%; 95% CI: 2.0–2.3) with the highest frequency of abnormal cytology (ASCUS or greater) in the 41–45 year age group (2.5%: 95% CI 2.1–2.7). No correlation between cervical abnormalities and HR-HPV prevalence, by region, was observed. A total of 370 (0.7%) women had an abnormal cytology as well as a positive HR-HPV result; 736 (1.5%) had an abnormal cytology and a negative HR-HPV test; 3,941 (7.9%) women had a positive HR-HPV test and a normal cytology; and 45,112 (89.9%) women were negative in both tests. The first two groups were immediately referred to colposcopy, 72.7% of the women from the cytology-positive and HR-HPV-positive group and 58.0% from the cytology-positive and HR-HPV-negative group successfully completing evaluation. Among the 269 cytology-positive and HR-HPV-positive women, 53 (19.7%) CIN2/3+ cases were detected, whereas among the 427 cytology-positive and HR-HPV-negative participants, only 13 (3.0%) CIN2/3+ cases were documented. In Morelos state, a sample of 287 women with a negative cytology smear and a positive HR-HPV test at baseline were re-screened after ~12 months, by means of cytology and HR-HPV testing. Among these women, 106 (36.9%) were again HR-HPV positive and were referred to colposcopy. Of whom, 76 (71.7%) were successfully

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evaluated; among these women, 9 CIN2/3+ (11.8%) were documented. Sensitivity of cervical cytology for detecting histologically confirmed CIN2/3+ cases was only 40.0% (95% CI 38.5–41.4) compared to 93.3% (95% CI 92.5–94.0) for HPV DNA testing considering the additional cases detected among women with persistent HPV infection. The specificity of cytology was 97.0 vs. 89.2% for the HPV DNA test.

Discussion Population-based programs using HR-HPV testing can improve cervical cancer prevention and control in Mexican and other populations where cytological screening is inadequate for detecting precursors of cervical cancer.

Keywords HPV testing · Mexico · Cervical cytology · Cancer

Introduction

Low coverage of cervical cancer screening in economically poor and marginal areas is a conditioning factor for high incidence and mortality rates for cervical cancer [1–3]. In addition in poor regions Papanicolaou (Pap) smears have generally proven to be ineffective [4], frequently due to inadequate sampling of the specimen [5], poor fixation and/or staining and lack of competencies and abilities in cytotechnologists who are generally poorly trained and misinterpret the diagnosis [6]. The consequence is a very high number of false-negative results [7]. Furthermore, there are geographical and cultural barriers that reduce accessibility and acceptance of Pap sampling [8], and for this reason, it is more efficient to implement a screening strategy that employs a test with the highest clinical sensitivity, thus allowing an extension of the screening interval. The fact that cervical cancer occurs only in women who have been persistently infected with high-risk HPV led to the development of novel prevention strategies with new technologies besides traditional cervical cytology [9]. At present, there are sensitive molecular biology methods that dramatically increase the possibilities for identifying precursor lesions that appear before invasive cancer [10].

Currently available epidemiological evidence that includes hundreds of smaller observational studies and 6 large completed randomized controlled trials, plus several more underway, is clearly sufficient to recommend HR-HPV testing as a primary detection strategy for cervical cancer precursor lesions [11–16]; however, there is now a need to provide evidence of the actual performance of HPV DNA testing in the local population context to allow an efficient move to mass HPV screening programs [17]. There is an overwhelming amount of evidence showing that the Hybrid Capture 2 HPV test (HC2) has much higher sensitivity and has greater flexibility than the Pap smear, since it requires less technical resources, is semi-automated and highly reliable [18], and its interpretation is not subjective. The fact that simultaneous Pap and HPV testing (co-testing) can identify virtually all high-grade lesions and invasive cancers is an additional advantage. However, the incremental sensitivity offered by Pap cytology is small and may not be cost-effective in parallel with HPV testing. Perhaps a more efficient approach is to conduct an initial HPV test and employ the Pap test in reflex to decide which women need colposcopy; an approach that should be evaluated in several randomized, controlled trials on different continents before it can be considered for large-scale implementation [19, 20]. With regard to co-testing, women who are negative for both tests could be screened with lesser frequency, which may result in greater screening compliance. Several scientific reports have emphasized that HR-HPV testing at the primary health care level could be more sensitive [21], reproducible and cost-effective [22] for cancer detection than cytology testing and colposcopy [23–25]. In spite of the above evidence, there is much resistance to include HPV DNA testing in cervical cancer prevention and control population–based programs [26, 27].

We report initial results of a pilot study of HPV DNA testing in the context of a routine social security program for cancer control. The purpose of the pilot was to evaluate actual performance of the HPV test in a diversity of settings prior to large scale introduction for routine screening in Mexico. Our data support the implementation of a population-based program with HR-HPV screening and also demonstrate the deficiencies in the existing Pap cytology testing program in Mexico.

Methods

Study population

A community-based intervention was conducted simulating actual conditions of a cancer control program (CCP) within the Mexican social security IMSS system. Women aged 20 to 70 years who spontaneously visited the CCP in the following federal entities comprised the study population: Northern and Southern México City, State of México, Guerrero, Michoacán, Morelos, Jalisco, Nuevo León, Oaxaca, Querétaro, Veracruz and Yucatán. Eligible women without a history of hysterectomy or uterine myomatosis were approached to participate in the study.

States were selected to include areas in the North, Center, and South of the country, representing high, medium and low risk for cervical neoplasia and each state included several primary health care units (family medicine

units). All women attending the cervical cancer prevention program for a Pap smear screening were invited to participate in the study; most accepted, so a sample of 51,168 women was formally recruited. Women older than 70 and younger than 20 years were excluded from analysis ($n = 65$), as well as those with incomplete data for name and IMSS registration ($n = 569$). We also excluded from analysis participants with an unsatisfactory Pap smear at baseline and those we were unable to recruit for a new Pap test ($n = 375$). After exclusions, a total of 50,159 women remained with complete data for baseline analysis. Informed consent was obtained so that HR-HPV-positive women without cervical lesions would accept HPV DNA re-testing within a year and colposcopic evaluation if necessary. The research and ethics committees at the National Public Health Institute and the IMSS approved the study.

Cervical cytology assessment

During the recruitment visit, health providers performed a pelvic examination to obtain a cervical specimen for a Pap smear, following standard procedures. Cervical cytology was taken and diagnosed according to the official Mexican guideline for cancer prevention and control in Mexico under established institutional quality control standards. The current Mexican diagnostic classification for the Pap smear corresponds to WHO classification (Normal, Atypical, Mild dysplasia, Moderate dysplasia, Severe dysplasia, Carcinoma in situ, Invasive squamous-cell carcinoma, and Adenocarcinoma). Basic information on demographics was collected: age, socio-demographic characteristics and gyneco-obstetric history assessed as part of the institutional Pap test form. All women with cervical cytology abnormalities, atypical or higher, corresponding to ASCUS or higher on the Bethesda System [28], were referred to colposcopy for additional diagnostic procedures, regardless of HR-HPV testing results.

HR-HPV testing

At the same recruitment visit, after the Pap smear sample collection, a second cervical specimen was collected for HR-HPV testing, using a conical cytobrush (Qiagen Inc., Gaithersburg, MD) that was preserved in a specimen transport media test tube. Cervical specimens were kept at room temperature (between 13 and 32°C) and delivered once a week to the HPV laboratory at the National Institute of Public Health, where they were stored at 4–8°C, until analyzed by HC2 according to the manufacturer's instructions. This test utilizes in vitro nucleic acid hybridization and signal amplification in a chemiluminescent microplate format for qualitative detection of 13 types of high-risk HPV DNA (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) [29].

Data analysis

We estimated the binomial 95% CI for HR-HPV prevalence and cervical cytology abnormalities by age groups and geographical areas [30]. Spearman correlation coefficients of cytology abnormalities and HR-HPV prevalences according to region were estimated. To evaluate the different alternatives of cervical cancer screening, the sensitivity, specificity, positive predictive values (PPV), were estimated for HR-HPV and cervical cytology tests, in the state of Morelos. Stata version 10.1 was used to perform estimates (Stata Corp. College Station, TX, USA).

Results

High-risk HPV prevalence

The study's baseline included 50,159 women registered in IMSS in 12 geographical areas in Mexico. Overall, HR-HPV prevalence in women aged 20 to 70 years was 8.6% (95% CI, 8.3–8.9%). With respect to HR-HPV prevalence by age group, this was the highest before 30 years of age (12.2%; 95% CI, 11.0–13.3%). As age increased, HR-HPV prevalence decreased, reaching 7.4% (95% CI, 6.7–8.0%) between 46 and 50 years of age. A small second prevalence peak was seen after 56 years of age [8.1%; 95% CI, 7.2–9.0%] (Table 1).

Among the 12 geographical regions studied, the lowest HR-HPV prevalence was in Nuevo León at 7.5%, whereas Morelos state had the highest with 11.3% (Fig. 1).

Cervical cytology abnormalities

Overall, cytology abnormalities were 2.2% (95% CI, 2.0–2.3%). The highest frequency of cytology with ASCUS+ was found in women aged 41 to 45 years, at 2.5% (95% CI, 2.1–2.7%), and the age group with the lowest rate of ASCUS+ was in women aged 60–70 (1.6%); however, no trend was observed by age. The region with the lowest ASCUS+ rate was Nuevo León with 0.3% and the highest rate was observed in Oaxaca with 6.3% (Fig. 1). No statistically significant correlation between HR-HPV prevalence and rate of cytology abnormalities ASCUS+ was observed (Spearman $r = 0.42$; $p = 0.167$; Table 2).

Figure 2 shows the distribution of participating women according to cervical cytology and HR-HPV results. From the total sample of 50,159 screened women, 370 women had an abnormal cytology as well as a positive HR-HPV

Table 1 Age-specific prevalence of HR-HPV positivity and cytological abnormalities in 50,159 women in Mexico

Age	*n*	HR-HPV positivity	95% Confidence interval	Abnormal cytology ASCUS+	95% Confidence interval
20–30	3,320	405 (12.2)	11.0–13.3	76 (2.3)	1.7–2.7
31–35	10,499	1,031 (9.8)	9.2–10.3	207 (2.0)	1.7–2.2
36–40	10,066	829 (8.2)	7.6–8.7	242 (2.4)	2.1–2.7
41–45	8,405	685 (8.2)	7.5–8.7	207 (2.5)	2.1–2.7
46–50	6,872	509 (7.4)	6.7–8.0	166 (2.4)	2.0–2.7
51–55	5,481	417 (7.6)	6.9–8.3	107 (2.0)	1.5–2.3
56–60	3,633	295 (8.1)	7.2–9.0	60 (1.7)	1.2–2.0
60–70	1,883	140 (7.4)	6.2–8.6	30 (1.6)	1.0–2.1
Total	50,159	4,311 (8.6)	8.3–8.9	1,095 (2.2)	2.0–2.3

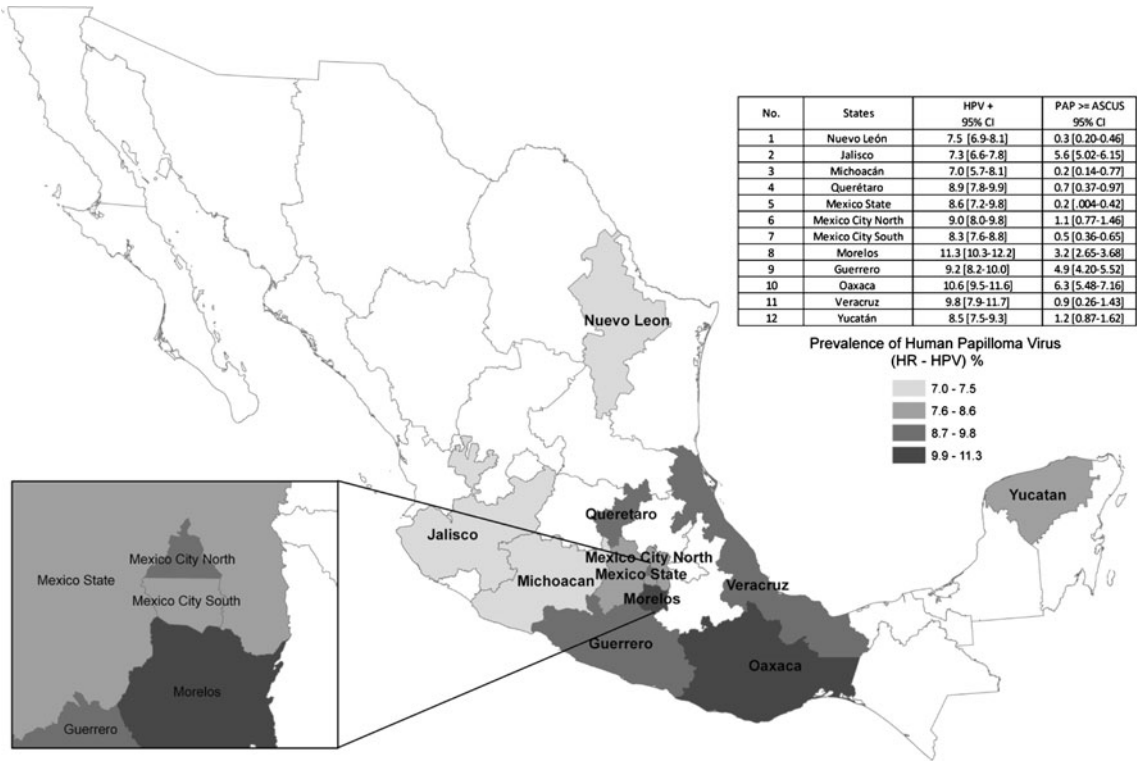

Fig. 1 High-risk HPV prevalence in 12 Mexican States

result, representing 0.7% of the sample. An additional group of 736 had an abnormal cytology and a negative HR-HPV test (1.5% of the sample). A total of 3,941 (7.9%) women had a positive HR-HPV test and a normal cytology; the remaining 45,112 women were negative in both tests (89.9%; Fig. 2) and were referred back to routine screening.

All women with cytological abnormalities were immediately referred for a colposcopy evaluation and histological confirmation; 269 women from the first group (Pap positive and HR-HPV positive), and 427 from the second group (Pap positive and HR-HPV negative) were fully evaluated (72.7 and 58.0%, respectively). Among the Pap-positive and HR-HPV-positive women, 53 CIN2/3+ cases were detected (equivalent to a combined test PPV of 19.7%), and among the Pap-positive and HR-HPV-negative group only 13 CIN2/3+ cases were positive (PPV 3.0%).

HR-HPV persistence and CIN among women with normal cytological results

Among the entire sample, 3,941 (7.86%) women were HR-HPV positive and had normal cervical cytology; this group was indicated for re-screening in ~1 year by Pap

Table 2 Performance of cervical cytology and HR-HPV testing for the detection of CIN2/3+ Morelos state

Cervical cytology	Positive	Negative		Performance of cervical cytology	
				Sensitivity	Specificity
Positive	6	134	140		
Negative	9	4,269	4,278	40.0%	97. 0%
Total	15	4,403	4,418	CI 95% 38.5–41.4	CI 95% 96.5–97.5
HR-HPV testing	Positive	Negative		Performance of HR-HPV testing	
				Sensitivity	Specificity
Positive	14	484	498		
Negative	1	3,919	3,920	93.3%	89. 2%
Total	15	4,394	4,418	CI 95% 92.5–94.0	CI 95% 88.3–90.1

PPV positive predictive value, *NPV* negative predictive value

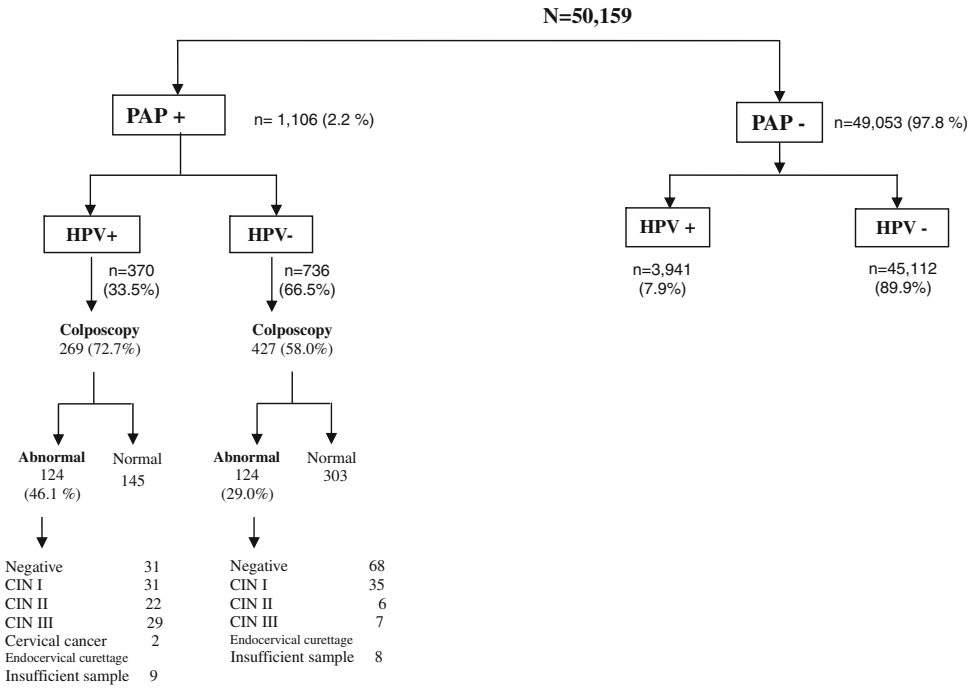

Fig. 2 HPV testing and Pap test in the Mexican social security context, $n = 50,159$

and HR-HPV testing. A total of 1,868 (47.3%) women were successfully re-screened and 768 presented a persistent HR-HPV-positive result (41.1%).

In Morelos women with 1-year persistent HR-HPV infection were referred to colposcopy for further evaluation, diagnostic confirmation, and treatment if necessary. We did not follow-up all 1-year HR-HPV repeat-positive and Pap-negative women in the other regions with colposcopy, instead most women were evaluated using longer followup intervals (results to be presented later). Two hundred and eighty-seven participants in Morelos were successfully assessed for HR-HPV persistence and 106 HR-HPV positives (36.9%) were detected. Seventy-six of these women were successfully evaluated under colposcopy (71.7%) and 8 CIN2/3 cases and 1 invasive cancer were histologically confirmed, representing a PPV of 11.8% for CIN2/3+ (Fig. 3).

Performance of cervical cytology and HR-HPV testing for detection of CIN2/3+, in Morelos

Sensitivity of cervical cytology for detecting histologically confirmed CIN2/3+ cases was only 40.0% (95% CI 38.5–41.4) compared to 93.3% (95% CI 92.5–94.0) for HPV DNA testing considering the additional cases detected among women with persistent HPV infection. The specificity of cytology was 97.0% (CI 96.5%−97.5%) vs. 89.2% (CI 88.3%−90.1%) for HR HPV DNA testing.

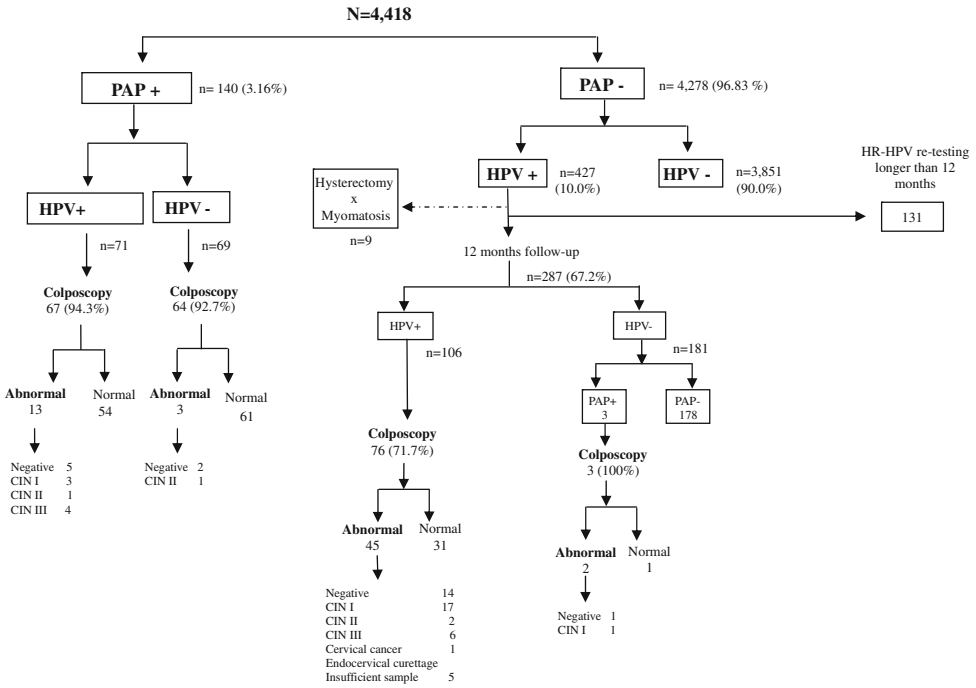

Fig. 3 HR-HPV testing and Pap test in the Mexican social security context in Morelos state, $n = 4{,}418$

Discussion

Our findings offer strong evidence to justify implementation of population-based programs using HPV DNA screening because in Mexican women the number of cytology tests has increased in recent years but efficacy in identification of precursor cervical cancer lesions has remained poor.

Cervical cytology screening has greatly reduced invasive cervical cancer incidence in industrialized countries. However, this approach requires repeated Pap testing at short intervals, confirmation of abnormalities by colposcopy, biopsy collection and histological confirmation in order to treat cancer precursor lesions. This kind of program is highly expensive and not affordable by many developing countries. For this reason, new secondary prevention alternatives for cervical cancer are needed, with greater sensitivity, to aid in improving cervical cancer screening in population-based programs for specific populations.

New technological developments should be used in countries with high incidence and mortality rates for cervical cancer. HR-HPV testing has proven to be a highly sensitive screening tool for cervical cancer precursor lesions and has been successfully used in diverse clinical settings; clinical trials and epidemiological studies have demonstrated the suitability of testing for HR-HPV in population-based programs in women older than 35 years of age [31, 32]. There is also evidence showing that HR-HPV testing increases the positive predictive value for identifying CIN2/3+ in cases diagnosed with atypical squamous cells [33]. Although cervical cytology is a highly effective screening test in registry-based population-based programs with wide coverage and frequent screening intervals, a single test has low sensitivity for identifying clinically significant lesions; it is estimated that 25 to 50% of all patients could have false-negative results on a single Pap test [34]. This finding is compounded in the Mexican context, as has been documented in this study and referred to recently as a national public health problem [35]. In this context as previously reported, women with negative Pap smears and HPV tests could benefit from greatly increased time intervals between screenings, with an estimated 43% reduction in future cervical cytologies in particular populations [36].

The National Health System in Mexico has an infrastructure to test 4 million women annually, for a population at risk of $\sim$20 million. In fact, the conditions prevailing in the cervical cancer prevention and control programs of mid-income countries make HR-HPV testing a more cost-effective strategy, when compared to cervical cytology testing in large part because of the comparable safety of substantially longer (5–10 year) HPV screening intervals [37].

During the last 20 years, diverse approaches of cost-effectiveness studies for cervical cancer prevention alternatives have been implemented. Analyses have focused on identifying an optimal periodicity for screening, particularly the ages to start and end such screening. HR-HPV testing in women older than 30 years is widely recommended; however, indispensable clinical guidelines for diagnosis and follow-up are lacking, and these depend on

HPV prevalence and available resources in various geographical areas [38].

Experts have still not defined the best follow-up strategy for women with abnormal Pap smears and positive HR-HPV tests after colposcopy and CIN-negative biopsy. For this reason, our study may provide evidence for developing guidelines for diagnosis and clinical management, particularly in very high-risk geographical areas [39]. In fact, HR-HPV testing as a screening strategy is more cost-effective in populations having a very high risk for cervical cancer [40, 41].

Our study is designed to provide evidence for the most effective primary screening strategy for cervical cancer. Initial results support the rationale for introduction of HPV DNA testing into routine screening in Mexico. Our estimates of the prevalence of overall HR-HPV persistence (3.6%) are ~60% higher than the rate of overall cytological abnormalities (2.2%); however, this modest increase should be manageable by appropriate follow-up algorithms. Although small, the sub-study in Morelos shows that 11.8% of women cytologically negative but HR-HPV persistent, 1 year apart, were detected with CIN2/3 or cancer. Since only the HR-HPV-positive women are retested in 1 year and the Pap-negative and HR-HPV-negative women are given an extended screening interval, our proposed HPV testing algorithm appears to represent a more effective use of screening resources.

In the Mexican context, if cervical cytology were implemented in HR-HPV-positive women with immediate referral to colposcopy for cytology abnormalities and repeat HR-HPV testing for Pap-negative and HR-HPV-positive women, the accuracy of detecting high-grade lesions may be improved. Additionally, in a captive population such as women covered by social security in Mexico, there is an opportunity to create an epidemiological surveillance registry of women infected with HR-HPV and an automated monitoring system to follow changes in the HPV epidemic in the coming era of widely disseminated prophylactic HPV vaccination [42].

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