Effect of introducing human papillomavirus genotyping into real-world screening on cervical cancer screening in China: a retrospective population-based cohort study

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Abstract

Background: China's Fujian Cervical Pilot Project (FCPP) transitioned cervical cancer screening from high-risk human papillomavirus (HR-HPV) nongenotyping to genotyping. We investigated the clinical impact of this introduction, comparing performance indicators between HR-HPV genotyping combined with cytology screening (HR-HPV genotyping period) and the previous HR-HPV nongenotyping combined with cytology screening (HR-HPV nongenotyping period).

Methods: A retrospective population-based cohort study was performed using data from the FCPP for China. We obtained data for the HR-HPV nongenotyping period from 1 January 2012 to 31 December 2013, and for the HR-HPV genotyping period from 1 January 2014 to 31 December 2016. Propensity score matching was used to match women from the two periods. Multivariable Cox regression was used to assess factors associated with cervical intraepithelial neoplasia of grade 2 or worse (CIN2+). The primary outcome was the incidence of CIN2+ in women aged ⩾25 years. Performance was assessed and included consistency, reach, effectiveness, adoption, implementation and cost.

Results: Compared with HR-HPV nongenotyping period, in the HR-HPV genotyping period, more CIN2+ cases were identified at the initial screening (3.06% *versus* 2.32%; $p < 0.001$); the rate of colposcopy referral was higher (10.87% *versus* 6.64%; $p < 0.001$); and the hazard ratio of CIN2+ diagnosis was 1.64 (95% confidence interval, 1.43–1.88; $p < 0.001$) after controlling for health insurance status and age. The total costs of the first round of screening (US$66,609 *versus* US$65,226; $p = 0.293$) were similar during the two periods. Higher screening coverage (25.95% *versus* 25.19%; $p = 0.007$), higher compliance with age recommendations (92.70% *versus* 91.69%; $p = 0.001$), lower over-screening (4.92% *versus* 10.15%; $p < 0.001$), and reduced unqualified samples (cytology: 1.48% *versus* 1.73%, $p = 0.099$; HR-HPV: 0.57% *versus* 1.34%, $p < 0.001$) were observed in the HR-HPV genotyping period.

Conclusions: Introduction of an HR-HPV genotyping assay in China could detect more CIN2+ lesions at earlier stages and improve programmatic indicators. Evidence suggests that the introduction of HR-HPV genotyping is likely to accelerate the elimination of cervical cancer in China.

Keywords: cervical cancer, genotyping, human papillomavirus, real-world study, screening

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Introduction

Cervical cancer is the third most common cancer among women in the world,[1] and 85% of cases occur in low- and middle-income countries (LMICs).[2] The number of cervical cancer cases was largest in China, with 98,900 new cases and

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30,500 deaths each year[3] due to inadequate screening, low coverage of human papillomavirus (HPV) vaccine and increased HPV infection rates.[4] A recent study found that the age-standardized incidence rate and the age-standardized mortality rate of HPV-attributable cervical cancer were 4.83 and 1.42 per 100,000 person-years in China, respectively. Between 2005 and 2015, these figures showed significant upward trends.[5] The first HPV vaccine was approved for listing in China in 2017, but a considerable amount of time will be required for HPV vaccination to be scaled up across the country.[6] Consequently, screening remains the major prevention strategy. Unfortunately, due to the economic, educational and healthcare status of the population, national programs designed for real-world cervical cancer screening are either lacking or have low coverage rates in China and other LMICs.[7–9] It is integral to global cervical cancer prevention and control to identify a suitable real-world cervical cancer screening strategy in LMICs.

Extensive evidence indicates that cervical cancers and precursors are closely related to persistent infection of high-risk HPV (HR-HPV).[10–14] Therefore, HR-HPV assays are gradually being applied in cervical cancer screening.[15] Prior to 2011, the US Food and Drug Administration (FDA) only approved two HR-HPV assays, including the Hybrid Capture 2 (HC2) (QIAGEN, Gaithersburg, Netherlands) HPV test and Cervista® (Hologic, Bedford, MA, USA) HR-HPV test, which were mainly used to detect HR-HPV without genotyping. These two HR-HPV assays mainly serve for the triaging of patients with equivocal cytology results[15] or can be used for co-testing with cytology for routine cervical cancer screening in women ⩾30 years old.[16] Existing studies[17,18] have already shown the high specificity and sensitivity of the Cervista® HR-HPV assay for cervical cancer screening, similar to those of the HC2 assay.

According to previous studies,[19,20] different HR-HPV genotypes are associated with different precancer and cervical cancer risks, with HPV-16/18 demonstrating the highest cancer risk. In 2011, the US FDA approved the HR-HPV partial genotyping method Cobas HPV (Roche Molecular Diagnostics, Pleasanton, CA, USA), which enables individual genotyping of HPV-16/18, but not 12 other HR-HPV types. The ATHENA study[21] confirmed that an HR-HPV assay plus HPV16 and HPV18 genotyping is a more sensitive and effective cervical cancer screening strategy. Thus, in 2015, the American Society for Colposcopy and Cervical Pathology (ASCCP)[22] proposed that all HPV-16/18-positive women should be directly referred for colposcopy. Accordingly, HR-HPV genotyping assays have been increasingly used for cervical cancer screening.

HR-HPV genotyping assays can determine the specific HR-HPV genotypes, facilitating the triaging of women who have cytological abnormalities or HR-HPV positivity.[23–25] Some evidence suggests that the application of HR-HPV genotyping assay to cervical cancer screening can reduce screening costs,[26,27] especially in resource-poor areas such as China.[28] In recent years, some commercial HR-HPV genotyping kits have been used worldwide,[23–25] serving as a sensitive and reliable method for the detection of all HR-HPV genotypes. In 2009, the National Cervical Cancer Screening Program was launched in China. Fujian province initiated national procedural cervical cancer screening and introduced an HR-HPV genotyping assay for screening in 2014. Fujian, a province with a high prevalence of HR-HPV (18.2%)[29] among the community population in China, was selected for implementation of the Fujian Cervical Pilot Project (FCPP), an 8-year population-based cohort study, to evaluate the program of the large-scale introduction of an HR-HPV genotyping assay for cervical cancer screening. In our previous work and in other studies,[23,24] the HR-HPV genotyping assay was used for the screening of cervical cancer in China and served as a sensitive and reliable method for HPV genotype detection, but the performance of HR-HPV genotyping-based screening in real-world settings is unclear.

In this study, using colposcopy-guided biopsy and the pathology result as the gold standard, we aimed to evaluate the performance of HR-HPV genotyping screening in the detection of cervical precancerous and cancer in real-world settings compared to HR-HPV nongenotyping screening.

Materials and methods

Study population and procedures

This study is a population-based retrospective cohort study of cervical cancer screening in a real-world setting in China. We obtained the results of the initial screening tests and any subsequent

follow-up from the Fujian Province Cervical Lesions Screening Cohorts (FCLSCs). The FCLSCs[29,30] constitute a cervical cancer screening cohort established in Fujian with more than 200,000 cases used to assess the value of introducing HR-HPV testing into screening. The FCLSCs include a provincial-level hospital, nine municipal-level hospitals and more than 500 community health service centers. The FCPP project was initiated on the basis of the FCLSCs. The FCPP project involved 2-year planning (between 1 January 2012 and 31 December 2013) and 3-year screening (between 1 January 2014 and 31 December 2016). On 1 January 2014, FCPP was launched, and all FCLSC institutions changed the primary method of cervical cancer screening from HR-HPV nongenotyping testing to HR-HPV genotyping testing. Women in the FCPP project volunteered to go to a hospital or community health service center for cervical cancer screening. FCPP staff provided medical education and organized follow-up visits for all of the participants through interviews or telephone calls. All of the participants enrolled in this study were recruited from the FCPP. Pre/post-design and propensity score matching (PSM) were used to compare the cost-effectiveness of the HR-HPV nongenotyping and HR-HPV genotyping tests in cervical cancer screening. Nonrandomized methods have been used more frequently over the past few years to assess population health interventions.[31] The PSM was used to ensure comparability of the characteristics of the intervention group and the control group, which is essential for realizing reliable conclusions[32] and is especially suitable for a real-world study in which randomization is not feasible.

HR-HPV nongenotyping combined with cytology co-testing screening procedures

According to the guidelines,[33] before 1 January 2014, HR-HPV nongenotyping combined with cytology co-testing (HR-HPV nongenotyping period) for cervical cancer screening was recommended for women aged ⩾25 years old. Therefore, the study included women who underwent HR-HPV nongenotyping co-testing for primary cervical cancer screening between January 2012 and December 2013. In the initial screening, women with negative cytology and HR-HPV results were instructed to undergo routine screening 3 years later. Women confirmed to be infected with HR-HPV or with cytology demonstrating atypical squamous cells of undetermined significance (ASCUS) underwent co-testing again after 1 year. If the co-testing results were negative at the 1-year follow-up, a second round of screening was performed 3 years later, but if the co-testing results were positive, the patient was immediately referred for colposcopy. Women proved to have HR-HPV infection and cytology demonstrating ASCUS, or cytology classified as low-grade squamous intraepithelial lesions or worse (⩾LSIL), immediately underwent colposcopy and/or biopsy. Women whose histology was proved to be cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) were advised to undergo treatment according to the ASCCP guidelines.[33,34] All of the untreated women were followed up, and a second round of screening was performed 3 years later. A detailed flow chart of the screening procedure is shown in Figure 1.

HR-HPV genotyping combined with cytology co-testing screening procedures

On 1 January 2014, the FCPP project introduced PCR reverse dot blot (PCR–RDB) HR-HPV genotyping and cytology co-testing to women aged ⩾25 years old for primary cervical screening (HR-HPV genotyping period), but women who had undergone HR-HPV nongenotyping screening in the previous phase were still followed up for 3 years, according to the original plan. Women who were included in the HR-HPV nongenotyping period will no longer be recruited into the HR-HPV genotyping period. Between January 2014 and December 2016, two cervically exfoliated cell samples were collected simultaneously from all of the women who underwent primary screening for HR-HPV genotyping testing and cytology testing. Women with negative HR-HPV genotyping and cytology results were instructed to undergo a second routine screening after 3 years. Individuals whose samples were positive for HR-HPV types other than 16 and 18 (non-16/18) or those with cytology demonstrating ASCUS underwent repeat HR-HPV genotyping and cytology assays after 1 year. Women were referred for colposcopy and/or biopsy if tested positive for HR-HPV types 16/18 regardless of the cytology results, tested positive for any types of HR-HPV and had cytology demonstrating ASCUS, or had cytology indicative of an ⩾LSIL regardless of the HR-HPV results. Women with histologically confirmed CIN2+ were advised to undergo treatment according to the ASCCP guidelines.[33,34] The HR-HPV nongenotyping assay and HR-HPV genotyping assay were performed in the same laboratory, and the cytological assay was performed

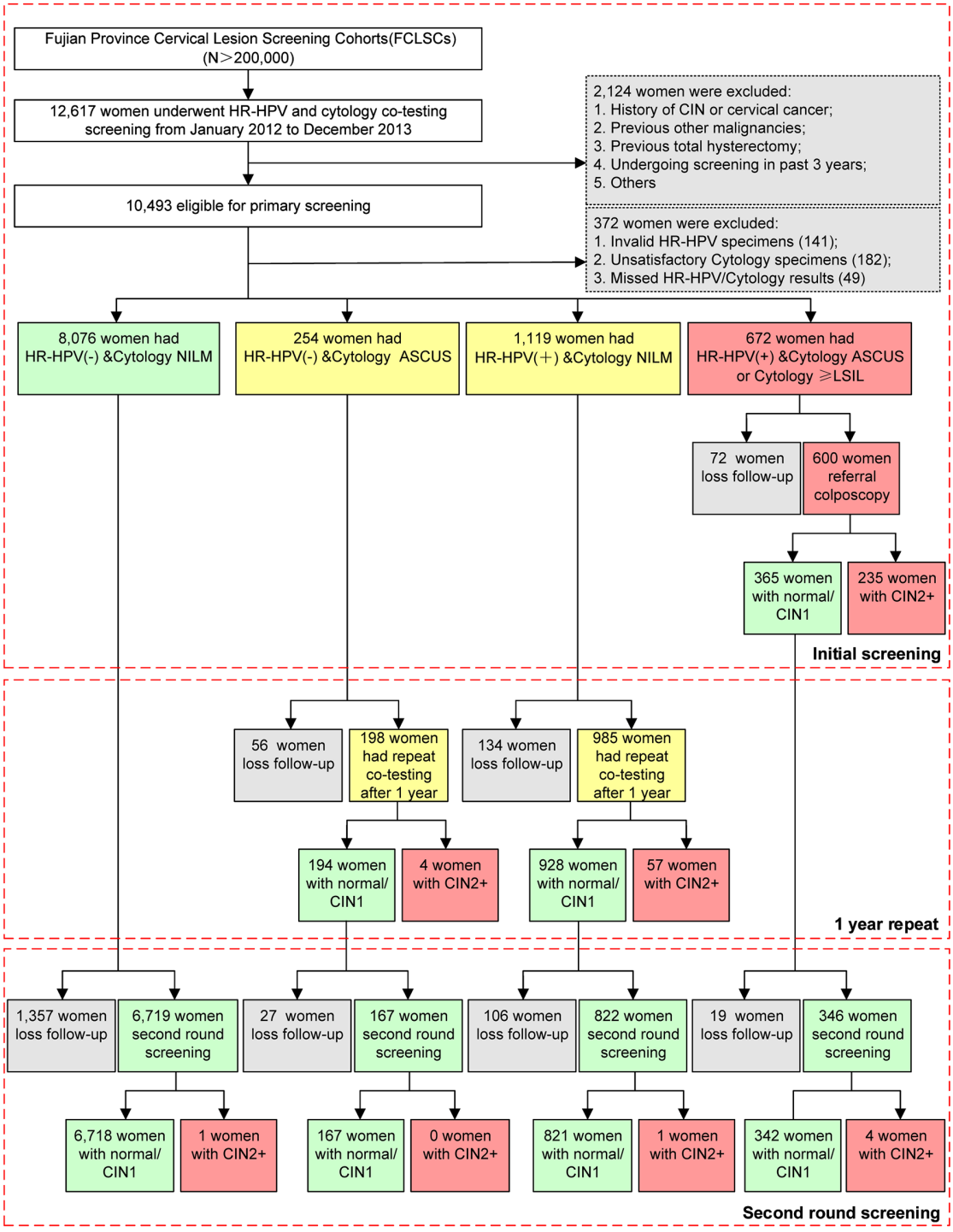

Figure 1. Flow diagram of the screening procedure for women in the nongenotyping period, Fujian 2012–2013. ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia of grade 2 or worse; HR-HPV, high-risk human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

in another pathology department; the laboratory staff responsible for one of these assays was unaware of the results of the other assay(s) when they performed the analyses. All of the untreated women were followed up, and a second round of screening was performed 3 years later. A detailed flow chart of the screening procedure is shown in Figure 2.

Data sources

Since 2010, in the FCLSCs, screening results, diagnosis and treatment have been registered in an automated hospital information system (HIS) for all individuals. The HR-HPV nongenotyping, HR-HPV genotyping and cytology laboratories use the HIS to manage specimen collection, transport, testing and delivery of results to patients. Individual samples were not processed if they did not suit the age range of recommendation or screening frequency. Women were told the reason if there was no analysis and were also reminded of the date of the next HR-HPV test. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital (no. 2014-045), with an exemption from informed consent. No specific consent is needed for statistical analyses of aggregated de-identified data. For this study, the raw data were first extracted from HIS, and patients' identities, including names, screening IDs, patient IDs, and mobile phone numbers, were de-identified. HR-HPV, cytology, colposcopy, biopsy and treatment data that were not registered in the HIS were considered as lost to follow-up.

Outcomes

Primary outcome indicators included reach, coverage, effectiveness, adoption, implementation and cost.[35] Reach was included to assess how the genotyping period screening program achieved high coverage.[35] Coverage was defined as the percentage of women between the age of 25 and 64 years who underwent screening at least once of the estimated target number of women in each period (HR-HPV nongenotyping period, $n = 39{,}790$; HR-HPV genotyping period, $n = 59{,}685$) according to the Sixth National Census 2010.[36] When evaluating effectiveness, the definition of Rabin and Brownson was followed,[37] which refers to the effectiveness of implementing a new intervention in a real-world environment. Effectiveness is defined as the percentage of women with pathologically identified CIN2+ among all of the screened women. The CIN2+ detection rates (per 1000 screened women) in the two periods were calculated at initial screening, at the 1-year follow-up, and in the second round of screening. We also assessed factors associated with CIN2+ detection using hazard ratios (HRs). The proportion of women with detected CIN3+ was also calculated. The gold standard was confirmed by histology.

Adoption was defined as the intention to use the new screening program.[37] We measured the following indicators: the percentage of women aged to meet the recommendation (⩾25 years old) among all women who received screening; and the proportion of over-screened women among all women who conducted screening. Over-screening was defined as more than one screening within 3 years (the initial screening abnormality required repeat after 1 year was not included).

Implementation is defined as the degree to which a program is implemented in the manner originally established.[37] Three outcomes were measured. The first outcome was the quality of the specimens, that is, the percentage of inappropriate cytology specimens among all of the cytological specimens, and the proportion of unqualified HR-HPV samples among all of the HR-HPV samples. The second outcome was the proportion of colposcopy referrals among women with abnormal screening results, and colposcopes consumed per case of CIN2+ were identified in initial screenings. The last outcome was completion of the follow-up, which was reflected by the following parameters: (1) the percentage of women who complied with colposcopy among all of the women who need colposcopy in the initial screening; and (2) the proportion of women who complied with the follow-up after 1 year.

Cost was defined as the cost of performing cervical cancer screenings (per 1000 screened women).[38] The following indicators were calculated: the total cost per 1000 screened women: (1) in the initial screening; (2) in the follow-up after 1 year; and (3) in the first round of screening (includes initial screening and 1-year follow-up); and (4) the cost per identified CIN2+ woman in the first round of screening. To calculate costs in this study, we considered only direct medical expenses and excluded indirect nonmedical expenses. Direct medical expenses are defined as costs (in USD and CNY) that women must pay to the hospital for cervical cancer screening. Unit costs were obtained from the Fujian medical price database.

Statistical analysis

The average age between the HR-HPV nongenotyping period and the HR-HPV genotyping period was compared using a Wilcoxon rank-sum test. Abnormality rates according to the HR-HPV genotyping, HR-HPV, and cytology results were

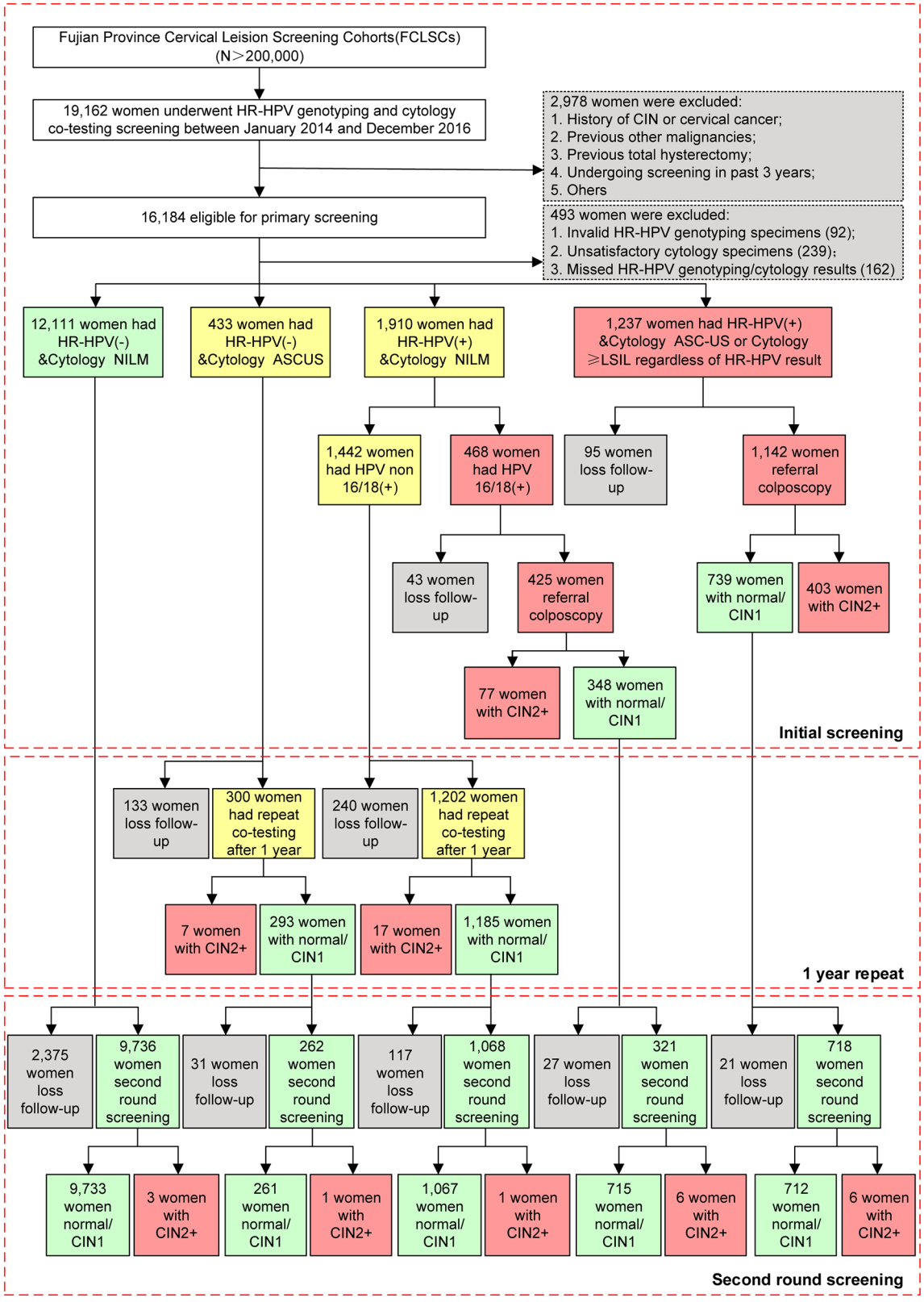

Figure 2. Flow diagram of the screening procedure for women in the genotyping period, Fujian 2014–2016.
ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia of grade 2 or worse; HR-HPV, high-risk human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

Table 1. Sociodemographic characteristics of women screened for cervical cancer, Fujian, 2012–2016.

	Nongenotyping period ($n = 10,121$)	Genotyping period ($n = 15,691$)	p-value
Age (years)	36.26 ± 9.71	37.59 ± 10.04	0.008
25–34 (%)	4504 (44.50)	5907 (37.65)	/
35–44 (%)	3344 (33.04)	5705 (36.36)	/
45–54 (%)	1821 (17.99)	3148 (20.06)	/
55–64 (%)	353 (3.49)	728 (4.64)	/
65 and older (%)	99 (0.98)	203 (1.29)	/
Medical insurance[a]			
Yes (%)	5475 (54.10)	8536 (54.40)	0.726
No (%)	4646 (45.90)	7155 (45.60)	/

Data are presented as *n* (%) or mean ± SD.
[a]Public medical insurance was used during medical visits.

calculated. The performance of detecting CIN2+ or CIN3+ was evaluated in the two periods. A multivariable Cox regression model was used to measure the effect of the HR-HPV genotyping period on CIN2+ detection compared with the HR-HPV nongenotyping period. To minimize the bias in the intervention and control groups, we used PSM to develop a second model. The variables included were age and medical insurance. The PSM system requires that there were no missing values for datasets. For missing data, average imputation was used to process age (9 missing cases), and random imputation was used to process medical insurance (14 missing cases). The nearest-neighbor algorithm was selected as the matching algorithm, and the caliper value was 0.1 SD. All of the analyses were performed using SPSS software, version 24.0 (IBM, New York, NY, USA), MedCalc software, version 18.11.3 (MedCalc, Ostend, Belgium), and R statistical software, version 3.5.2 (Mathsoft, Needham, MA, USA). The significance level was set at a two-tailed p-value < 0.05.

Results

As shown in Table 1, the FCPP project screened a total of 31,779 Chinese women aged ⩾25 years; 12,617 women underwent HR-HPV nongenotyping screening from January 2012 to December 2013, 2496 women were excluded because they did not meet the criteria, and the remaining 10,121 women were the qualified subjects of the HR-HPV nongenotyping period. In addition, 19,162 women were screened for HR-HPV genotyping between January 2014 and December 2016, 3471 women were excluded because they did not meet the requirements, and the remaining 15,691 valid participants were included in the analysis at the HR-HPV genotyping period. The median ages of participants in the two periods were 36.26 and 37.59 years old ($p = 0.008$). Women in the HR-HPV genotyping period had similar rates of public medical insurance to women in the HR-HPV nongenotyping period (54.4% *versus* 54.10%; $p = 0.726$).

The screening effectiveness indicators by different periods are shown in Table 2. The HR-HPV nongenotyping period detected 2.32% (235/10,121), 0.61% (61/10,121) and 0.06% (6/10,121) of CIN2+ women in the initial screening, in the 1-year follow-up and in the second round of screening after 3 years, respectively. Overall, 302 (2.98%) CIN2+ lesions were detected through two rounds of HR-HPV nongenotyping screening, and the positive predictive value (PPV) was 39.17%. In the HR-HPV genotyping period, 3.06% (480/15,691), 0.15% (24/15,691) and 0.11% (17/15,691) of screened women were identified as CIN2+ in the initial screening, in the 1-year follow-up and in the second round of screening, respectively. Overall, CIN2+ lesions were detected in 521 (3.32%) women through two rounds of screening in the

Table 2. The screening performance indicators by genotyping period and nongenotyping period.

	Nongenotyping period	Genotyping period	*p*-value
Total screened women aged 25 years and old	10,121	15,691	/
HR-HPV positive rate	16.50% (15.78–17.22%)	18.90% (18.28–19.51%)	<0.001
Detection by initial screening			
CIN2+ (%)	235 (2.32)	480 (3.06)	<0.001
HSIL(CIN2) (%)	70 (0.69)	142 (0.91)	/
HSIL(CIN3) (%)	96 (0.95)	178 (1.13)	/
Cancer (%)	69 (0.68)	160 (1.02)	/
Detection by follow-up after 1 year			
CIN2+ (%)	61 (0.61)	24 (0.15)	<0.001
HSIL(CIN2) (%)	20 (0.20)	13 (0.08)	/
HSIL(CIN3) (%)	29 (0.29)	8 (0.05)	/
Cancer (%)	12 (0.12)	3 (0.02)	/
Detection by follow-up of second-round screening after 3 years			
CIN2+ (%)	6 (0.06)	17 (0.11)	0.20
HSIL(CIN2) (%)	5 (0.05)	10 (0.06)	/
HSIL(CIN3) (%)	1 (0.01)	6 (0.04)	/
Cancer (%)	0 (0.00)	1 (0.01)	/
Positive predictive value in initial screening (%)	39.17	30.63	<0.001

CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus; HSIL, high grade squamous intraepithelial lesion; HR-HPV co-testing, primarily screens women with both cytology and HR-HPV assays; HR-HPV individual genotyping co-testing, primarily screens women with both cytology and HR-HPV individual genotyping assays.

HR-HPV genotyping period, and the PPV was 30.63%.

The probability of identifying CIN2+ lesions in the HR-HPV genotyping period (HR 1.64, 95% CI, 1.43–1.88; $p < 0.001$) was higher than those in the HR-HPV nongenotyping period after adjusting for medical insurance and age. The probability of being diagnosed with CIN2+ using HR-HPV genotyping had minimum changes after PSM ($HR_{pre\text{-}PSM}$ *versus* $HR_{post\text{-}PSM} = 1.64$ *versus* 1.69; Table 3).

Table 4 shows the key programmatic indicators evaluated by the different periods. This study found that the estimated coverage in the HR-HPV genotyping period (25.95%) was greater than that in the HR-HPV nongenotyping period (25.19%; $p = 0.007$). Regarding adoption, the proportion of screened women's ages meeting the proposed range in the HR-HPV genotyping period was higher than that in the HR-HPV nongenotyping period (genotyping *versus* non genotyping = 92.70% *versus* 91.69%, $p = 0.001$). The proportion of overscreenings during the HR-HPV genotyping period was significantly lower than that during the HR-HPV nongenotyping period (genotyping *versus* nongenotyping = 4.92% *versus* 10.15%; $p < 0.001$).

Among the implementation indicators, the percentage of inappropriate cytology specimens

Table 3. Three-year cumulative risk of CIN2+ with and without propensity score matching.

	Pre-propensity score matching		Post-propensity score matching	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Screening method				
Nongenotyping period	Ref		Ref	
Genotyping period	1.64 (1.43–1.88)	<0.001	1.69 (1.48–1.94)	<0.001
Age (years)				
21–24	Ref		Ref	
25–34	1.39 (0.90–2.15)	0.140	1.44 (0.92–2.24)	0.109
35–44	3.39 (2.23–5.17)	<0.001	3.62 (2.35–5.56)	<0.001
45–54	4.40 (2.87–6.72)	<0.001	4.88 (3.16–7.54)	<0.001
55–64	7.59 (4.86–11.86)	<0.001	8.87 (5.63–13.99)	<0.001
65 and older	3.53 (1.86–6.69)	<0.001	3.98 (2.09–7.59)	<0.001
Medical insurance[a]				
Yes	1.54 (1.34–1.76)	<0.001	1.42 (1.24–1.63)	<0.001
No	Ref		Ref	

[a]Public medical insurance was used during medical visits.
CI, confidence interval; CIN, cervical intraepithelial neoplasia; HR, hazard ratio; Ref, reference.

decreased slightly from 1.73% (HR-HPV nongenotyping period) to 1.48% (HR-HPV genotyping period). However, the proportion of unqualified samples of the HR-HPV test decreased significantly from 1.34% (HR-HPV nongenotyping period) to 0.57% (HR-HPV genotyping period) ($p < 0.001$). The proportion of women who required referral to colposcopy in the HR-HPV genotyping period was significantly higher than that in the HR-HPV nongenotyping period (10.87% *versus* 6.64%; $p < 0.001$) in the initial screening; however, compliance with colposcopy during the HR-HPV genotyping period (92.91%) was higher than that during the HR-HPV nongenotyping period (89.29%; $p = 0.043$). In the HR-HPV genotyping period, 3.55 colposcopies were performed for each CIN2+ cases identified, which was higher than 2.86 in the HR-HPV nongenotyping period ($p = 0.018$). Unexpectedly, the numbers of colposcopies needed to identify one case of cervical cancer were similar in the HR-HPV genotyping and HR-HPV nongenotyping periods (10.66 *versus* 9.74; $p = 0.511$). The percentage of 1-year rescreening during the HR-HPV genotyping period (80.11%) was lower than that during the HR-HPV nongenotyping period (86.16%; $p < 0.001$).

For effectiveness, in the initial screening, the CIN2+ detection rates during the HR-HPV genotyping period (30.59 per 1000 screened women) was significantly higher than that during the HR-HPV nongenotyping period (23.22 per 1000 screened women; $p < 0.001$). However, at the 1-year follow-up, the HR-HPV nongenotyping period detected more previously missed cases of CIN2+ (genotyping period *versus* nongenotyping period = 1.53 *versus* 6.03; $p < 0.001$). Overall, the detection rate of CIN2+ in the HR-HPV genotyping period was similar to that in the HR-HPV nongenotyping period (32.12 *versus* 29.25 per 1000 screened women; $p = 0.194$) in the first round of screening (includes the initial screening and the 1-year follow-up). In the second round of screening, compared with the HR-HPV nongenotyping period, HR-HPV genotyping period had a similar CIN2+ detection rate (1.08 *versus* 0.59 per 1000 screened women; $p = 0.197$).

Table 4. Reach, effectiveness, adoption, implementation and cost measurement in different periods.

Outcomes	Nongenotyping period	Genotyping period	*p*-value
Reach			
Women aged 25–64 years who were screened at least once in each period (%)	25.19 (10,022/39,790)	25.95 (15,488/59,685)	0.007
Effectiveness			
CIN2+ detection rate at initial screening (per 1000 screened women)	23.22	30.59	<0.001
CIN3+ detection rate at initial screening (per 1000 screened women)	16.30	21.54	0.003
CIN2+ detection rate at 1-year follow-up (per 1000 screened women)	6.03	1.53	<0.001
CIN3+ detection rate at 1-year follow-up (per 1000 screened women)	4.05	0.70	<0.001
CIN2+ detection rate at first round screening (per 1000 screened women)	29.25	32.12	0.194
CIN3+ detection rate at first round screening (per 1000 screened women)	20.35	22.24	0.307
CIN2+ detection rate at second-round screening (per 1000 screened women)	0.59	1.08	0.197
CIN3+ detection rate at second-round screening (per 1000 screened women)	0.10	0.45	0.236
Overall CIN2+ detection rate after two rounds of screening (per 1000 screened women)	29.84	33.20	0.133
Overall CIN3+ detection rate after two rounds of screening (per 1000 screened women)	20.45	22.69	0.230
Hazard ratio	Reference	1.69 (1.48–1.94)	<0.001
Adoption			
Women of the recommended age screened in each study period (%)	91.69 (11,569/12,617)	92.70 (17,692/19,085)	0.001
Women who were over-screened in each period (%)	10.15 (1174/11,569)	4.92 (871/17,692)	<0.001
Implementation			
The percentage of invalid cytology specimens among all cytological specimens (%)	1.73 (182/10,493)	1.48 (239/16,184)	0.099
The proportion of unqualified HPV samples among all HPV samples (%)	1.34 (141/10,493)	0.57 (92/16,184)	<0.001
Referral to colposcopy at initial screening	672 (6.64%)	1705 (10.87%)	<0.001
Colposcopes consumed per one case of CIN2+ identified at initial screening	2.86 (672/235)	3.55 (1705/480)	0.018
Colposcopes consumed per one case of CIN3+ identified at initial screening	4.07 (672/165)	5.04 (1705/338)	0.011

(Continued)

Table 4. (continued)

Outcomes	Nongenotyping period	Genotyping period	*p*-value
Colposcopes consumed per one case of CC identified at initial screening	9.74 (672/69)	10.66 (1705/160)	0.511
Follow-up: proportion of referral colposcopy among women with positive screening (%)	89.29 (600/672)	91.91 (1567/1705)	0.043
Follow-up: repeat co-testing after 12 months[a] (%)	86.16 (1183/1373)	80.11 (1502/1875)	<0.001
Cost[b]			
Cost per 1000 screened women at initial screening	¥ 392,829 ($56,931)	¥ 413,896 ($59,985)	<0.001
Cost per 1000 screened women at 1-year follow-up	¥ 57,232 ($8294)	¥ 45,705 ($6624)	<0.001
Total cost per 1000 screened women at first round screening[c]	¥ 45,0061 ($65,226)	¥ 45,9601 ($66,609)	0.293
Cost per identified CIN2+ women at first round screening	¥ 15,437 ($2237)	¥ 14,309 ($2074)	0.013

[a]HR-HPV-positive women with normal cytology or HR-HPV-negative women with ASCUS cytology who were followed up after 12 months (nongenotyping period), and women positive for non-16/18 HR-HPV types with normal cytology or HR-HPV-negative with ASCUS cytology (genotyping period).
[b]Cost refers to all medical direct costs consumed by the screened woman in the hospital; the price of the HR-HPV genotyping test and HR-HPV test is RMB ¥180 (US$ 26.1) per person per time, and the price of cytology is RMB ¥180 (US$ 26.1) per person per time, the price of colposcopy is RMB ¥150 (US$ 21.7) per person per time. The equivalent value between the RMB ¥ and the USD was calculated at 6.9 : 1.
[c]Total cost of initial screening and follow-up after 1 year.
ASCUS, atypical squamous cells of undetermined significance; CC, cervical cancer; CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus.

The cost of the initial screening in the HR-HPV genotyping period was slightly higher than that in the HR-HPV nongenotyping period (US$59,985 *versus* US$56,931 per 1000 screened women; $p < 0.001$). However, the cost of the 1-year follow-up was slightly lower than that of the HR-HPV nongenotyping period (US$6624 *versus* US$8294 per 1000 screened individuals; $p < 0.001$). In summary, in the first round of screening, the cost of the HR-HPV genotyping period was similar to that of the HR-HPV nongenotyping period (US$66,609 *versus* US$65,226 per 1000 screened women; $p = 0.293$). Especially during the HR-HPV genotyping period, the cost of identifying a case of CIN2+ per round of screening was lower than that during the HR-HPV nongenotyping period (US$2074 *versus* US$2237; $p = 0.013$).

Discussion

This study is a systematic analysis of the impact of incorporating HR-HPV genotyping into public health policy for cervical cancer screening in Fujian, China. Our findings indicate that the introduction of HR-HPV genotyping in China is a viable and effective screening strategy for cervical cancer screening. This is especially important given that the World Health Organization has launched a global appeal to eliminate cervical cancer.[39] According to the FCPP project, we found that more CIN2+ lesions were detected during the HR-HPV genotyping period than during the HR-HPV nongenotyping period, especially in the initial screening (3.06% *versus* 2.32%); CIN2+ could be identified earlier and could facilitate access to early treatment or follow-up in the HR-HPV genotyping period. The HR-HPV genotyping period allowed direct referral to colposcopy of HPV-16/18-positive with normal cytology women; this procedure added an additional 19.1% (77/403) to the detection of CIN2+ lesions during the initial screening, confirming the importance of the HR-HPV genotyping program in the early detection of lesions. The effect analysis indicates that HR-HPV genotyping co-testing is a strategy to reduce the inefficient components of the screening program.[21] Thus, HR-HPV genotyping has been regarded as an opportunity for the improvement of screening organizations.

The worry is that the increased rate of detection of CIN2+ may result in an overdiagnosis for patients who do not progress to cervical cancer.[40] Although this content was not evaluated in our

study, there are some evidences that indicates that the increased sensitivity of the HR-HPV genotyping assay to CIN2+ reflects early detection, not overdiagnosis.[40,41] Castle and colleagues[21] pointed out that the HR-HPV genotyping assay can prevent more cancer than a nongenotyping screening strategy; though some CIN2+ lesions do not progress, a small increased number of women treated with CIN should also be received to achieve that benefit. In FCPP, the introduction of HR-HPV genotyping can immediately identify more CIN2+ women in the initial screening, which constitutes an early diagnosis of CIN2+, effectively reducing the morbidity of cervical cancer in LMICs. In addition, the FCPP project strictly stipulates that only women who have been confirmed to be CIN2+ by histopathology can be treated.

It has been pointed out that combined HR-HPV and cytology screening can overconsume medical resources.[42] However, it has been reported that the negative rate of HR-HPV in cervical cancer patients can be as high as 19.4%[43] to 23.3%[44] Combined HR-HPV and cytology screening can improve the detection rate of HPV-negative cervical cancer women and reduce missed diagnosis. Especially in LMICs such as China, screening for cervical cancer is mainly an opportunistic screening, and the screening intervals of most women are longer and random. According to the above circumstances, the choice of co-testing screening program will help eliminate cervical cancer as early as possible in LMICs.

Low screening coverage in LMICs is a serious public health problem. Our study showed an increase in screening coverage after introduction of an HR-HPV genotyping program because the performers conducted cervical cancer health education for women during the implementation process, and several academic conferences on cervical lesion screening and diagnosis were held each year in Fujian to improve the screening coverage. Screening coverage was also influenced by women's economics, knowledge, religious beliefs and health policies.[45] Our research also found that the coverage rate in Fujian is only 26%, and rural areas have significantly lower than urban areas, which provides a reference for health managers to develop policies to enlarged the screening coverage. Because clinician-collected screening limits coverage, especially in rural areas where transportation is not convenient, it has been reported that self-collection screening can improve screening coverage;[45] despite our study does not analyze these data, self-collection screening may improve screening coverage in rural areas of China.

The adoption rate of screening guidelines directly affects screening effectiveness. Low compliance with guidelines can lead to waste of health resources and over-screening,[46,47] especially in LMICs. This study found that after the HR-HPV genotyping was introduced, the rate of the inside of the recommended age range for screening was increased, while the over-screening rate decreased. This may be due to the education of our researchers regarding the screening guidelines through the organization of meetings and online publicity, and screening specimens will not be processed if the recommended frequency or age range was not satisfied. Some studies[46,47] have suggested that by reducing the rate of noncompliance and over-screening in the screening guidelines, the harm caused by incorrect screening can be reduced, and more medical resources are used in those women that have never been screened, which could achieve a higher cost efficiency.

Over-referral colposcopy is a major problem in the HR-HPV genotyping period.[48] Over-referral depends on screening procedures, and the incidence is high when all HR-HPV-positive women are referred to colposcopy.[49] In the FCPP Project, all HPV-16/18-positive women were referred to colposcopy regardless of cytology results. Although the rate of colposcopy referral was higher in the HR-HPV genotyping period than in the HR-HPV nongenotyping period in the initial screening ($p < 0.001$), in subsequent rounds, referral will be similar to the HR-HPV nongenotyping period.[40] Women with a positive HPV-16/18 but normal cytology had a higher risk of CIN3+ compared with other types,[50] and all HPV-16/18-positive women in the FCPP who are referred to colposcopy can be considered as early detection of cervical cancer. Although the rate of colposcopy referral increased, the completion of colposcopy was higher in the HR-HPV genotyping period than in the HR-HPV nongenotyping period ($p = 0.043$). Studies in LMICs such as China have demonstrated lower colposcopy implementation rates after screening abnormalities (70.3–75.7%).[51,52] In the FCPP, we have developed rigorous procedures to support further referral and follow-up of screening positive women. A provincial-level colposcopy center was established in Fujian to cope with the increase in colposcopy, and the provincial-level colposcopy

center regularly conducts refresher courses for colposcopists. Therefore, in HR-HPV genotyping period, the use of colposcopy may be more reasonable for providing services to high-risk women (i.e. HPV-16/18-positive individuals). However, the impact of colposcopy services should be closely monitored at each setting with the introduction of HR-HPV genotyping. The HR-HPV genotyping period may also have a negative psychosocial impact in HPV-16/18-positive women. To reduce this effect, FCPP organizers should educate HR-HPV-infected women in a timely manner, telling them that HR-HPV infection is common and that an HR-HPV-positive diagnosis does not mean cancer.

The rate of unqualified specimens affects the accuracy of screening results and the compliance of screened women. Our study showed that the genotyping period had reduced the number of unqualified specimens for cytology, while the rate of unqualified specimens for HR-HPV genotyping assay had significantly decreased from 1.34% to 0.57%. The possible reason is the regular training of the specimen collection staff, and the other reason is that the HR-HPV genotyping assay used by the FCPP project is a PCR-based method, with a higher sensitivity,[53] which improves the success rate of HR-HPV genotyping detection on specimens with low cell volume. Therefore, we recommend the PCR-based HR-HPV genotyping assay for cervical cancer screening in LMICs due to the large differences in technical skills among their gynecologists.

The follow-up of cervical cancer screening is difficult in LMICs. Our data found that the rate of implementation in women who need to be rescreened after 1 year fell in the HR-HPV genotyping period. There are two possible reasons for this difference. The first is that the rescreening rate decreased after 1 year by women with cytology ASCUS and HR-HPV genotyping negativity, and the incidence of cervical cancer in HR-HPV-negative women is very low; additionally, the HR-HPV genotyping assay we introduced is based on a PCR method, and the miss rate is lower.[53] This may cause gynecologists to reduce health education and follow-up education for screened women. The second reason may be that women who have entered the HR-HPV genotyping period know with which genotype they have been infected and that the highest-risk types of HPV-16/18 are referred directly to colposcopy. Our study found that the colposcopy referral rate for HPV-16/18-positive women was as high as 91.7% (784/855), while some women who are non-HPV-16/18 positive may have relaxed their vigilance and did not continue follow-up after 1 year. Through this study, we found that after the introduction of the HR-HPV genotyping testing, it is necessary to improve the retest rate of women with cytological ASCUS and HR-HPV-negative/non-HPV-16/18-positive results and cytologically normal cells after 1 year.

Cost is an important indicator to consider when formulating a screening strategy, especially in LMICs, where resources are relatively scarce.[54] Our study found that the cost of the initial screening for the HR-HPV genotyping period was increased, but the cost of the 1-year follow-up was significantly reduced. In short, there is no increase in the cost of performing a round of screening. Because of the implementation of the HR-HPV genotyping, more CIN2+ lesions were detected; therefore, the cost of each confirmed CIN2+ lesion is reduced (US$2237 *versus* US$2074). This may be a more cost-effective alternative to cervical cancer screening strategies for China, with its low screening coverage and large population.

There are some limitations to our research. First, the women we included in the study based on the HR-HPV nongenotyping screening program covered only 2 years, shorter than the screening interval, which may cause over-screening to be underestimated. Second, our research data come from a retrospective cohort. Although PSM has been used to control the measured confounders, it is impossible to control unmeasured confounders. Therefore, our study may be affected by selectivity bias. Finally, the participants in the two screening periods in our study are from different times, which may have an impact on the results of the study. Because there may be other differences in health policies between the two periods in addition to different screening procedures, this may lead us to overestimate the advantages of introducing the HR-HPV genotyping program.

Conclusion

This is the first report of results of the implementation of HR-HPV genotyping using real-world data and extensive follow-up in China. The introduction of an HR-HPV genotyping program increased the earlier detection of CIN2+ lesions in China without increasing costs. Our research

provides key evidence for the introduction of HR-HPV genotyping in LMICs. Further research is needed to understand the long-term clinical results.

Author contributions

BD and PS conceived and designed the research; BD, HZ and YS analyzed the data, wrote the paper, and prepared figures and tables; BD, XM, YK and DP performed the experiments; PS, FX, YL and HX recruited the patients and acquired the samples and patient metadata; BD and PS were responsible for funding; BD, HZ, XM, YS, HG, YC and PS helped to analyze the data and reviewed drafts of the paper; PS supervised the research; and PS, HZ and BD reviewed and revised the paper. All authors approved the submitted version of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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