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Effectiveness and feasibility of HPV self-sampling for coverage of cervical cancer screening on internet-based

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Abstract
Objectives: To assess self-sampling HPV testing combining with the internet may serve as a primary cervical cancer screening method in low-resource settings, and to establish an internet self-sampling cervical cancer screening-management model.
Methods: 20,136 women aged 30~59 years with vaginal self-sampling HPV testing as primary screening on internet-based was performed in 13 provinces, municipalities of China. The women who participated in the screening registered on the screening website. A questionnaire was investigated the acceptance of self-sampling after self-sampling.
Results: Among 20103 women with qualified samples, 35.81% of them was remote areas, 37.69% of them was never-screened, 59.96% of them under-screened, 18.54% with a primary school education or below and overall high-risk HPV prevalence was 13.86%. In 8136 respondents, 95.97% of women felt self-collection was easy to operate, 84.61% had no discomfort when using a self-sampling brush, 62. 37% women were more likely to choose self-sampling for cervical cancer screening in the future, 92. 53% were willing to introduce to others around them. Multivariate analysis showed that the reliability of self-sampling and the easy degree of sampling were the independent influencing factors of selecting self-sampling ($p<0.05$), while no statistical significance was found in different age, education, occupation, gravidity, medical insurance, age of sexual initiation ($p>0.05$).
Conclusions: The Internet-facilitated self-HPV-testing screening and management model for cervical cancer prevention with large sample study is feasible and effective and can be used as a supplement to the traditional screening, especially in marginal areas with few medical resources, finally the coverage of cervical cancer screening will be significantly improved.

Keywords: human papillomavirus, self-sampling, cervical cancer screening, internet-based, screening coverage

Introduction

Cervical cancer is the most diagnosed cancer and the leading cause of cancer death in women in many countries, the vast majority of which are in developing countries [1]. It is also the leading cause of cancer-related death in Chinese women under 50 of age [2]. However, a review on multiple studies showed that the cervical cancer screening coverages from 2013 to 2014 in China were from 12%-67% in different regions, [3] although cervical cancer screening as the national program have been implemented for more than 12 years.

Is common recognized that cervical cancer could not be well controlled without a screening coverage of more than 70% [4]. It has been evidenced that low screening coverage is related to the poor availability of medical resources, because the technology adopted in the past screening, cytology and HPV testing was based on provider-collected samples and therefore relied on medical resources [5]. On the other hands, cytology-based primary screening needs regular repeats to affect cervical cancer control, which does not only rely on medical resources but also the quality control system. Since high sensitivity of the high-risk human papillomavirus (hr-HPV) could maximize the screening effectiveness and its satisfied negative prediction value enables a 5-10 year of the screening interval [6]. As HPV testing is playing more and more important roles in cervical cancer screening in the world, HPV genotype-based algorithms for positive triage and for "screening-see-and -treatment" programs have been reported as the solution for cervical cancer prevention in the medically underserved area with no qualified cytology and pathology serviced [7-10].

Self-sampling for HPV testing has been studied for more than twenty years. Multiple studies have demonstrated that vaginal samples collected by the screening women themselves could work as same as the provider collected endocervical samples in detection of high grade cervical intraepithelial neoplasia (CIN 2/3) when tested with PCR-based assay HPV assays [11-14]. Those findings suggested that using self HPV testing as the primary screening will be able to highly expand the screening coverage in both downtown city and the rural area as it is less relied on medical resources. Several preliminary research projects in China [15-17] has verified that self-sampling offers possibility to make cervical cancer screening reach under or non-screened women, [11-12, 14].

Publications indicated that majority of cervical cancers occur in women who could not be regularly screened and properly treated due to less opportunity for qualified screening program, which is highly related to poor education, low income, and rural residence [3, 5, 13-14, 18-19]. It is commonly recognized that women living in low-and-middle-income countries (LMIC) should be the target population for expanding screening coverage. Recently, WHO launched a global initiative to scale up preventive, screening, and treatment interventions to eliminate cervical cancer as a public health problem during the 21st century, [20] which bring in a global challenge for how to increase screening coverage in LMICs including China. Undoubtedly, self-collected HPV testing will play the key role in achieving the 2030 objectives setup by WHO for globally elimination of cervical cancers. However, further studies are needed to give answer for whether self- sampling will be effective to greatly expand the screening coverage and what are the key determinants for programing and implementation of a self-HPV testing-based screening program.

We therefore design and implement a study to investigate 1) the key elements impacting the acceptance of the women to self-sampling when applied it to women under different background and living in variety of communities, 2) the key determinants for programing a self-HPV testing-based cervical cancer screening project, and 3) the effectiveness of self-sampling in terms of motivating project participation and expanding the screening coverage. In addition, since internet has become part of the citizen's life, we were also to verify the role of internet in the screening program.

Methods

Study populations

2.1.1 The study was programmed and organized by Peking University People's Hospital and Peking University Shenzhen Hospital and applied from September 2018 to July 2020, 20,136 women aged 30~59 years with vaginal self-sampling HPV testing as primary screening on internet-based was performed in selected sites in 13 provinces, municipalities and autonomous regions in China, including Beijing, Liaoning Province, Jilin Province, Shaanxi Province, Qinghai Province, Zhejiang Province, Guangdong Province, Jiangxi Province, Guizhou Province, Yunnan Province, Inner Mongolia Autonomous Region and Guangxi Autonomous Region in China. Women were eligible for participation in the cervical cancer screening for free if they were 1) 30 to 59 years of age, 2) sexually exposed, 3) no cervical surgical history as CKC and LEEP, 4) no history of hysterectomy or pelvic radiotherapy, 5) unpregnant, (6) having no acute or recurrent genital and urinary tract infections, and 7) consented for participation. This project was approved by the Ethics Committee of Peking University People's Hospital (2018PHB056-01) and registered on the Chinese Clinical Trial Website (https://www.chictr.org.cn, ChiCTR2000032331).

2.1.2 Eligible participants were recruited via public notification on website (mcarey.com) and friend-circles on Wechat, and private notification via phone-call, oral or written notice. Participant recruitments were conducted by the medical staff from the community medical centers, maternal and child health system, local hospital, women's federation, and sub-district office. Women registered for participation on-site by visiting the website (http://47.106.227.241/) via personal computer or cell phone by themselves or with assistance from the staff. A informed consent form would be given after successful registration. Women consent for participation by signing the informed consent form were given a personal information form for filling, which included the educational background, occupation, screening history, etc.. Subsequently, given to each eligible participant was a sampling kit with an unique barcode pasted on for sampling and result inquiry. Then, participant would collect vaginal samples for herself using the sampling kit and in reference to the sampling graphic instruction or, if needed, the interpretation of the staff. Women can chose sampling in a private room on site or at home according to their willingness. A questionnaires would be given to each participant after sampling. The working flow is shown on Figure 1**.**

Questionnaires on acceptability of self-sampling

The Questionnaires were given to women who were willing to give answers. Women have right to refuse the questionnaires with no impact on their further services in this study as well as in the future medical cares.

Self-collection of the Vaginal samples

Eligible women were instructed to collect vaginal samples for themselves using a sampling kit containing a graphic sampling instruction, a cone-size brush, a sample processing card (FTA based card, BGI-Shenzhen, China) that could change color to indicate the sample application, or a vial containing preserve solution (Bioperfectus, Taizhou, China). Barcode was priorly pasted on each card or vial, which is not only the sample identification code but also the patients study id. Women were informed to avoid sex, vaginal flushing, and vaginal medication a day before sampling and sampling would be postponed to 3 days after period if anyone was in menstruation.

After getting sampling kits, women were instructed for sampling by having them read the "sampling instruction printed on the kit package or watch the video instruction on sit. Explanation and interpretation would be given to anyone who need further help. No assistance would be provided for self-sampling operation. To women who used liquid media for their sampling, an on-site nurse would check each vial to conform that the brush-head was in the vial and no liquid was leaked.

When sampling, woman took a squat or a standing position with one feet on a bench to open the legs, then, hold the handle of the sampling brush and insert the head of the brush into vagina aligning its axis and gently push the brush in with gentle sway back and forth until she feel resistance, followed by rotating the brush up to 5 circles before moving the brush out of vagina. Women armed to use card to process sample would apply the sampled brush-head on the sample application are of the card until they saw color changes; while women armed to us vial would put the sampled brush-head into the vial, break it off the handle to keep it in the vial, and cover the vial by screwing the cap of the vial tightly.

Provider collection of endo-cervical samples

In order to compare the concordance of self- and provider-collected samples on HPV testing and provide the participant a change to directly feel the two sampling ways, we selected several sites in Mentougou district in Beijing and Sandu Aqua Autonomous County in Guizhou to have the women sampled by the trained providers after self-sampling.. The provider-collected sample were tested for hr-HPV and for liquid-based cytology (TCT, Hologic, USA) and cytological $p16^{INK4A}$ detection. The cyto-results and the relevant pathology diagnosis for the abnormalities will be analyzed in other manuscript and were included in this analysis.

HR- HPV DNA test

Self-collected were tested for hr-HPV on SeqHPV assay if they were applied on TA cards, or on BMRT if they were in liquid vials. (1) SeqHPV is a sequencing-based HPV DNA testing assay developed by BGI Genomics, Shenzhen, China. It reports 14 hr-HPV genotypes (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68) identified using new generation of sequencing (NGS) technology. It had been validated in multiple trials to work well with both self- and provider-collected samples processed in liquid media and FTA card [21]. (2) BMRT is a quantitative real-time PCR assay for hr-HPV testing. It detects HPV genotypes using a fluorescence-based HPV genotyping technology. The DNA extraction kit and the fluorescence-based HPV genotyping were manufactured by Bioperfectus Technologies Co., Ltd, Jiangsu, China. This assay reports 21 HPV genotypes including 14 hr-HPV (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68) and 4 probable hr-genotypes (HPV-26, -82, and -73) and 3 low-risk HPV genotypes (HPV -6, -11 and -81) [22]. In our study, on the 14 hr-HPV types were referred as hr-HPV positive.

Colposcopy and multiple biopsies

Women who positive of any of the 14 hr-HPV types for self-and/or provider-collected samples (the positives) were referred for colposcopy and biopsy within 3 months after result reporting. Multiple biopsies were taken on the suspicious sites and endocervical curettage (ECC) were performed for all the patients. Histological diagnosis were reported HSIL, LSIL, and cervical mucositis, which served as the gold standard for evaluation of the screening effects. Women who were negative of HR-HPV but abnormal of cytology ≥ASCUS and/or positive of cytological $p16^{INK4A}$ were also retuned for colpo/biopsy following the same protocol, but the results were not included in this analysis.

Statistical analysis

Statistical analysis was carried out using the SPSS statistics program (version 20.0) for Windows (SPSS, Inc., USA) and Excel (version 2013) to calculate sensitivity, specificity, positive and negative predictive values, and ROC curve. In analysis of the data regarding to socio-demographic and women's attitudes to self-sampling, participants were grouped according to ages, educational background, marriage, Incomes, service accessibility, and screening history. The count data were subjected to chi-square test. P-values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 20,136 women were recruited for cervical cancer screening. After delete 10 (0.05%, 10/20,136) cases for label error and 23 (0.11%, 23/20,136) cases for unqualified samples, 20,103(99.89%) women were tested for HPV DNA (the screened women), among them, 2,787 (13.9%) were tested positive of HPV and 17,316 (86.1%) were negative of HPV. Of the women who positive of HPV, 73.38% (2,045/2,787) returned for colpo-biopsies and had pathological outcomes**.**

Two thousands and thirty one (2,031) from Mentougou district in Beijing (2,736) and Sandu Aqua Autonomous County in Guizhou province (1874) had their cervical exfoliative cell sampled collected by specially trained doctors on-site after their self-sampling, and had results for liquid-based cytology (TCT) and cytological $p16^{INK4A}$ detection. Of those patients, 143 who were abnormal of cytology (≥ASCUS) and /or positive of cytological $p16^{INK4A}$ returned for colpo/biopsy and had pathological diagnosis. However, those patients were not included in the analysis in this manuscript.

Socio-demographic characteristics

The mean age of the screened women was 44.31±7.70 years ranging from 30 to 59 years, Thirty-five point eighty-one percent (35.81%, 7198/20103) of the screened were from remote areas which refers to rural communities that were 37.28% (6017/16,139) more than 10 kilometers away from hospitals capable of providing cervical cancer prevention services (CPCS-hospitals), while 43.54% (7027/16,139) were living in towns which

refers to in-town/city communities that were less than 5 kilometers away from the CPCS-hospitals, and 19.18% (3095/16,139) were from suburban communities which refers to communities that were 5-10 kilometers away from the CPCS-hospitals.

Among all the 20103 women, 19,873 completely or partially filled the socio-demographic information form. Of the 16,155 women who had given information of screening history, 37.69% (6,089/16,155) of them checked for never-screened, 59.96% (9,686/16,155) checked for under-screened that refers to once being screened but no screening for a long time, and only 2.35% (380/16,155) checked for "regularly screened". Of the women 16,137 women who filled in the educational background, 18.54%(2,992/16137) of them checked "primary school education or below", 38.20%, (6165/16,137) of them checked "middle and high-schools education(including high-school). Monthly family income of less than 10,000RMB were reported by 89.48% (14,376) of the 16,066 participants who gave answers by checking the income selectable boxes. Details of the participants' socio-demographic features were shown in Table 1. The overall prevalence of HR-HPV infection was 13.86% (2787/20103). The top five most common HR-HPV subtypes were HPV-52 (3.42%), HPV-58 (2.29%), HPV-16 (2.17%), HPV-39 (1.35%), and HPV-51 (1.30%).

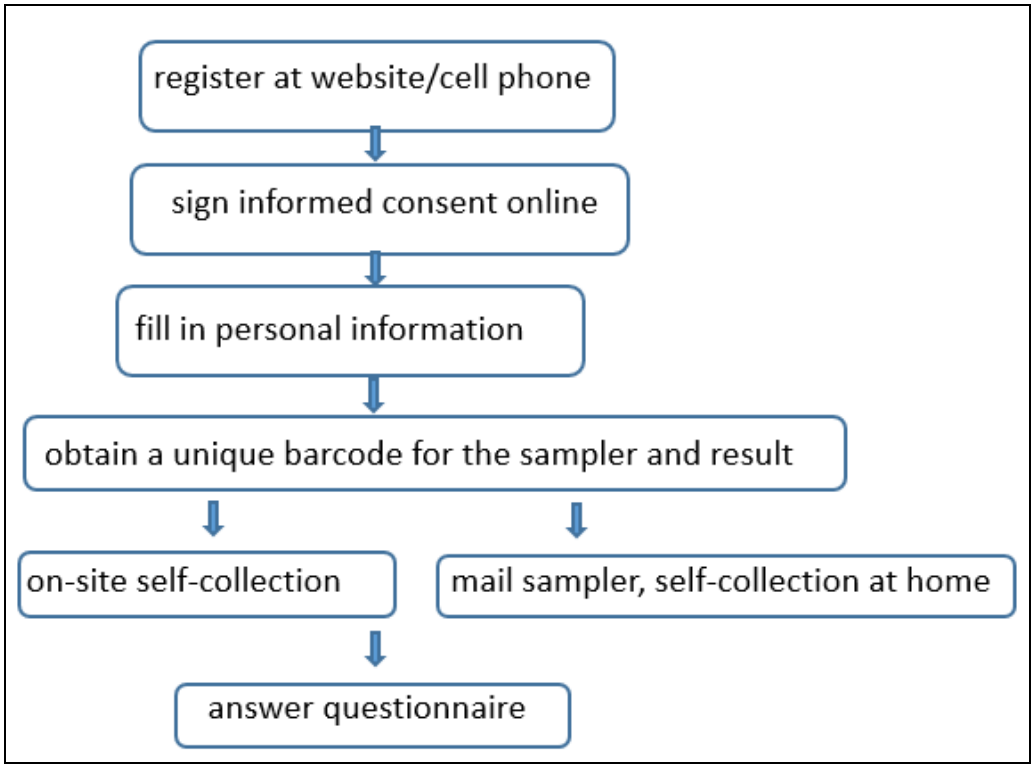

Fig 1: Working Flow Chart for sampling

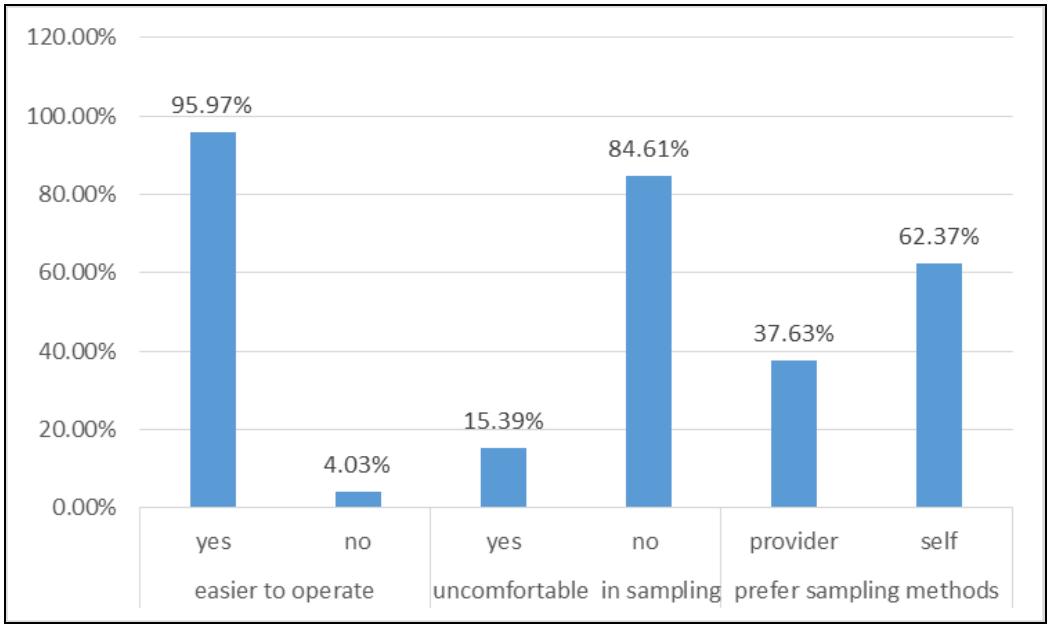

Fig 2: Results from survey on the participant's acceptance and tendency for self-sampling

Table 1: The demographic and behavioral features

Item	cases	%		Item	cases	%
Age (year)	19873					
30~34	2610	13.13		<5,000	9352	58.21
35~39	3448	17.35		Gravidity and parity	16106	
40~44	3814	19.19		0	351	2.18
45~49	4322	21.45		1~2	11603	72.04
50~54	3485	17.54		3 times and above	4152	25.78
55~60	2194	11.04		Screening history	16155	
Education-	16137			never screened	6089	37.69
college and above	6980	43.25		under screened	9686	59.96
middle school	6165	38.20		regularly screened	380	2.35
primary school and below	2992	18.54		Past screening methods	9827	
Occupation	16126			Base-HPV	3222	32.79
civil servant /public institution personnel	4202	26.06		Base-Cyto	6605	67.21
company white-collar	1617	10.03		Start of sex	16095	
migrant labor	2877	17.84		≤20	2396	14.89
peasant	2035	12.62		21~25	10003	62.15
inoccupation	1711	10.61		above 25	3696	22.96
Other	3682	22.83		Number of sexual partners	16084	
monthly family income（RMB）	16066			1	15391	95.69
> 30,000	346	2.15		2~3	357	2.22
10,000~30,000	1344	8.37		4 and above	32	0.20
5,000~<10,000	5024	31.27		Unwilling to answer	304	1.89

Table 2: The participants' recognized reasons for attitude to provide sampling

Participants' recognized reasons for attitude to provide sampling	N	%
1. more accurate for testing	2,032	42.03
2. more reliable results	1,621	33.53
3. other problems detectable while sampling	900	18.61
4. traditionally sample should be collected by provider	213	4.41
5. others	69	1.43
Total	4,835	100.00

Table 3

Participants' recognized reasons for attitude to self-sampling	N	%
1. More private	1,771	21.84
2. More convenient	2,647	32.65
3. Easier to operate	1,405	7.33
4. Less cost	427	5.82
5. less painful	1,717	21.18
6. others	142	1.74
Total	8,108	100.00

Table 4: Participant stated reasons for choosing self-sampling

	N (%)
Site for self-sampling	
at home	2237 (38.30)
in hospital	3017 (51.65)
community site of clinic nearby	303 (5.19)
Reliability of the results from self-sampling	
0~20	136 (1.87)
21~40	656 (9.03)
41~60	1094 (15.05)
61~80	3228 (44.42)
81~100	2153 (29.63)
Amount willing to pay for self-sampling base screening (RMB)	
<50	4367 (54.55)

50-100	1931 (24.12)
101-150	997 (12.45)
151-200	536 (6.70)
>200	174 (2.17)
Wished for financial resources for self-sampling-based screening	
government	5282 (63.40)
Social Insurance	2145 (25.75)
Medical services	666 (8.00)
At one's own expense	156 (1.87)
Others	82 (0.98)
If willing to introduce self-sampling to friends and relatives	
Willing	7430（92.53）
Unwilling	262 (3.26)
Not sure	338 (4.21)
What is the most concerned about application for screening via internet and self-sampling at home	
Reliability of internet services	2131 (20.54)
Reliability of testing result	3086 (29.75)
Potential deterioration of contamination on samples during transportation	2983 (28.76)
In-time result reporting	1917 (18.48)
others	256（2.47）

Table 5: Multivariate analysis of the factors influencing self-sampling tendency (Binary logistic analysis)

B			**S.E.**	**Wald**	**p**	**Exp (B)（OR）**		**95%CI**
Intercept		-3.672	1.434	6.561	0.010			
Reliability of self-sampling	0-20	0.275	0.175	2.466	0.116	1.317	0.934	1.856
	21-40	0.578	0.195	8.831	0.003	1.783	1.218	2.611
	41-60	0.350	0.159	4.844	0.028	1.419	1.039	1.937
	61-80	-0.407	0.124	10.825	0.001	0.666	0.522	0.848
	81-100	0[b]	.	.	.	.	.	.
Age groups	30-34	0.231	0.197	1.372	0.241	1.260	0.856	1.855
	35-39	-0.251	0.179	1.968	0.161	0.778	0.548	1.105
	40-44	-0.037	0.179	0.042	0.838	0.964	0.678	1.370
	45-49	-0.251	0.173	2.095	0.148	0.778	0.554	1.093
	50-54	-0.238	0.175	1.842	0.175	0.788	0.559	1.111
	55-59	0[b]	.	.	.	.	.	.
Social insurance	Yes	0.049	0.633	0.006	0.938	1.051	0.304	3.629
	No	-0.046	0.604	0.006	0.939	0.955	0.292	3.120
	In-petient	0[b]	.	.	.	.	.	.
Easiness/hardness of self-sampling	Easy	4.946	1.014	23.818	0.000	140.657	19.296	1025.327
	hard	0[b]	.	.	.	.	.	.
Age for sex exposure	≤20	0.260	0.175	2.204	0.138	1.297	0.920	1.828
	21-25	0.031	0.124	0.064	0.801	1.032	0.809	1.316
	≥26岁	0[b]	.	.	.	.	.	.
Education	Primary and lower	0.059	0.274	0.046	0.831	1.060	0.620	1.813
	Middle	0.077	0.246	0.097	0.755	1.080	0.667	1.748
	University	0-.063	0.218	0.082	0.774	0.939	0.612	1.441
	master and above	0[b]	.	.	.	.	.	.
Occupation	Unemplored	0.204	0.270	0.572	0.450	1.227	0.722	2.083
	Farmer	0.337	0.204	2.734	0.098	1.401	0.939	2.089
	Workers	0.066	0.170	0.151	0.698	1.068	0.766	1.489
	Office Lady-industrial	0.174	0.197	0.774	0.379	1.190	0.808	1.752
	Civil Servant or clerk	0.075	0.154	0.237	0.626	1.078	0.797	1.458
	Students	0.072	0.295	0.059	0.807	1.075	0.603	1.914
	Others	0[b]	.	.	.	.	.	.

Note: In each indicator, the data in the first row is used as the standard, and the other indicators are compared with the indicators in the first row.

Table 6: Analysis of the elements influencing the choices for self-or provider-sampling

	self-sampling preferable (n=3551)	**Provider-collection preferable (n=1891)**	**X^2**	**P**
Easiness of sample collection				
Feel easy	3309 (93.4)	1878 (99.7)	117.337	＜0.001
Feel hard	234 (6.6)	5(0.3)		
education				
primary school and below	557 (18.6)	290 (19.0)	23.189	＜0.001
middle school	1271 (42.5)	628 (41.1)		
collage and above	1160 (38.8)	609 (39.9)		
marriage				
married	2926 (97.6)	1501 (97.9)	4.900	0.180
unmarried	15 (0.5)	13 (0.8)		
divorced	47 (1.6)	15 (1.0)		
widowed	11 (0.4)	4 (0.3)		
occupation				
no occupation	343(11.4)	141 (9.2)	109.665	＜0.001
Farmers	424(14.2)	151(9.9)		
migrant worker	373(12.5)	362(23.8)		
Office ladies	292(9.8)	124(8.1)		
civil servant /public institution personnel	784 (26.2)	413 (27.1)		
Other	771 (25.8)	333 (21.9)		
census register				
yes	2664 (88.6)	1352 (87.6)	1.08	0.582
residence	321 (10.7)	178 (11.5)		
Temporary residence	21 (0.7)	13 (0.8)		
medical insurance				
yes	2834 (94.5)	1392 (90.6)	31.054	＜0.001
no	135 (4.5)	132 (8.6)		
for inpatient only	30 (1.0)	12 (0.8)		
Number of Births				
1~2	2129 (71.3)	1153 (75.7)	10.389	0.006
≥3	813 (27.2)	356 (23.4)		
none	42 (1.4)	14 (0.9)		
contraception				
tools	750 (25.2)	375 (24.7)	4.198	0.28
IUD	630 (21.2)	314 (20.7)		
oral contraceptive	152 (5.1)	91 (6.0)		
no	770 (75.9)	421 (27.7)		
Other	674 (22.6)	319 (21.0)		
history of screening				
never	911(30.5)	487 (31.7)	5.328	0.07
under-screening	1995(66.7)	1024 (66.6)		
regular screening	85(2.8)	27 (1.8)		
Age of sexual starting (y)				
≤20	411 (13.7)	273 (17.8)	13.642	0.001
21~25	1973 (65.9)	950 (62.1)		
≥26	610 (20.4)	308 (20.1)		
Reliability scale for self-sampling				
0-20	384 (10.9)	225 (12.3)	71.556	＜0.001
21-40	236 (6.7)	190 (10.4)		
41-60	408 (11.6)	300 (16.4)		
61-80	1519 (43.2)	613 (33.4)		
81-100	966 (27.5)	505 (27.6)		

Acceptability of self-sampling

Eight thousand one hundred and thirty-six (8,136) women among the enrolled participants responded the questionnaires on sampling means, but not all of them given full answers to all the questions. Most of the 8110

women who responded to question 1. (95.97%, 7783/8110) felt self-collection easy to do; 84.61% (6832/8075) among those responding to question 2. Reported no discomfort when using self-sampling brush; and 62.37% (4,997/8,012) of the women who responding to question 3. Expressed preference to self-sampling for cervical cancer screening in the future. The percentage and number of women choosing each specific reason for their attitude to provider-sampling among the total who choose provider-collection and gave answer to the questions are listed in table 2.

It is clear that a big portion of respondents to reasons for the above question 1) and 2) shows the public bias in understanding cervical cancer prevention, that for question 3) shows the public anticipation to medical service, and that to question 4) represents the public concept to cancer prevention. None of the public understanding is related to the real mean of provider-sampling, which indicates that no objective obstacle is existing to replace provider-sampling with self-sampling in primary screening and public education on cervical cancer prevention is still needed to increase the coverage.

The percentage and number of women choosing each specific reason for their attitude to self-sampling among the total who choose the same and gave answers to the questions are listed in table 2.

There were 5,841(71.80%,5841/8136)women choose self-sampling and responded the questions on preferable place to take self-sampling, of whom, 51.65% (3,017/5,841) choose hospital, 38.30% (2,237/5,841) choose home, and 5.19% (303/5,841) choose nearby community healthcare centers or clinic. However, 92.53% (7,430) of the 8,030 women who gave answers to question 7 expressed their willingness to introduce self-HPV testing to others by checking the selectable answers for YES. Participants' acceptance and perception after self-sampling were shown in Figure 2 and Table 3. Those data reflect the strong trusts of the public to medical facilities and the well acceptance to self-sampling and again evidence that public education is urgently needed to increase the screening coverage via adopting self-sampling.

Multivariate analysis showed that the reliability of self-sampling and its easiness were the independent influencing factors for self-sampling tendency ($p<0.05$), while no statistical significance was found in different age, education, occupation, gravidity, medical insurance, age of sexual initiation ($p>0.05$) (table 4).

Single-variant analysis to the elements that influence participants' preference to self-sampling or provider-sampling showed that self-sampling preference was related to the education level, occupation, age of sex-exposure, whether having social insurance, and the realized harness and reliability of self-sampling (table 5).

It is obvious that, among the women in this study, the number of women who felt self-sampling easy to do is significantly higher than that of women who feel hard for self-sampling and who felt easier for provider-collection ($P<0.001$). Independent element analysis showed that self-sampling was significantly preferred by women at all education levels ($P<0.001$) and all kinds of occupations ($P<0.001$), no matter what kind of social medical insurance they had ($P<0.001$), no matter birthed of not and how many births ($P=0.006$), no matter what sex exposure age ($P=0.001$), and no matter what scale was given to self-sampling ($P<0.001$); however, no deference in sampling preference was observed regarding to marriage statuses ($P=0.18$), residence categories ($p=0.0582$), contraception taken ($P=0.28$), as well as screening histories ($P=0.07$). Those facts suggest that self-sampling in not only widely acceptable, but much preferable than provider-sampling to women at any social status (Table 5).

Discussion

Practices of high-income countries on cervical cancer control have demonstrated that cervical cancer screening with high uptake have hastened the declines the incidence of cervical cancers upon implementation, especially when the coverage rate of cervical cancer screening reaches more than 80% in a country or a region [4, 23]. Strong evidence has proofed the validity of self-sampling for HPV testing [11-12, 18-19].

Self-sampling has been accepted by many countries and regions as the sampling technology for primary HPV testing in government sponsored cervical cancer screening programs as a way to increase screening coverage [2, 23-27].

Central government strategized cervical cancer screening has been implemented for more than 12 years in China, with majority of the screening program were based on provider-sampling and conducted in medical facilities.

However, the average screening coverage in China was about 30%~40% in most parts of China [3]. It was reported that there were many factors impacting the lower coverage of China cervical cancer screening, which included the demographic features, poor screening awareness, primary screening technologies, screening service models, and shortage of medical resources etc [3-4, 28].

However, the key elements that determinately impacts screening coverage and can be improved feasibly are the technologies taken for primary screening tests, the way to delivery screening services, and the roles of medical providers.

Self-sampling bases community screening with internet facilitation can provide convenient access for cervical cancer screening to the women living medically underserved country/regions and may potentially the solution for making cervical cancer screening to cover majority of women over the country.

Design of the questionnaires to investigate participant's attitude to Internet facilitated self-HPV screening

The questionnaires for investigation of the attitude of the participants to internet facilitated cervical cancer screening based on self-sampling included 10 questions followed by 50 selectable choices (single or multiple?). The questionnaires were designed to concern 3 aspects as 1) self-sense to self-sampling; 2) tendency to sampling

methods, and 3) self-realization to self-sampling. The questionnaires were distributed to the participants for their responses after self-sampling.

Feasibility and acceptance for self-sampling

Internet service has been covered to most area of China including the mast rural regions and is becoming a necessary part of the civil life, which is the basis for adoption of internet to facilitate cervical cancer screening. It has been well recognized that information transformation through internet services is the most effective way that enables worldwide coverage without space-time, educational, and geographic limits. It is no doubt that public education for cervical cancer prevention through internet can reach most of the women with access to internet service. In our study, 35.81% of the responders who accept self-sampling were living in marginal communities, 18.54% were with primary of lower education background, and 89.48% were from low-income families, suggesting that internet facilitated self-sampling screening is completely feasible and applicable in marginal regions and to poorly educated and low-income women. [2, 14, 29] Self-sampling provides opportunity to women who do not have access to provider-sampling base cervical cancer screening and, therefore, expands the coverage of the screening. In our study, 37.69% of the participants had never been screened, and the prevalence of ≥CIN2+ among this group was 0.81%（810/100000）, significantly higher than that of the participants who had screened regularly. The higher precancer prevalence tells us that the women who have never been screened should be the population that the screening program should concern about; the high-rate participation of the never-screened women in our project indicates that self-sampling-based screening project can reach the never-screened women if they can be applied at sited nearby those women.

Many studies have demonstrated that self-sampling was with high acceptability among all kinds of women. It was reported that self-sampling was attractive for its convenience for sampling at home, less discomfort, lower-cost, privacy, and less embarrassment, pain, anxiety. [30-33] In our study, the post-sampling questionnaire survey shown that percentages of the respondents who responded that self-sampling was easy to do, non-discomfortable, convenient, less painful, and more privacy protective are 95.97%, 84.61%, 32.65%, 21.18%, and 21.84%, respectively, demonstrating well acceptance for self-sampling after experiencing it. In addition, 78.67% of the questionnaire respondents expressing their acceptance for paying less than $16 (equaling RMB 100) of payments for self-sampling HPV test, which indicated that self-sampling-based screening programs may potentially be able to reach the WHO recommended coverage (70%) if the price can be controlled under 15 dollars per screening case.

Since self-sampling is easy to learn and be mastered by general women, [16, 30-31] it creates a possibility to organize screening project via internet services. With internet service, women can participate cervical cancer screening at home or any facilities nearby without need to travel a distance to visit medical services and take time to wait for just sampling, which, together with the no-need for doctor's involvement in the sampling, are obviously cost-effective. Cervical cancer screening based on self-collected HPV testing can increase the participation of the women and therefore increase the careening coverage. In addition, privacy protection and the convenience from self-sampling will also encourage office ladies to participate screening program. In our study, 43.25% of the participants were educational backgrounded with university and above, 36.09% were office ladies and public servants who usually had chance to be screened in hospitals, and multi-variant analysis showed that no significant influence on the acceptance for self-sampling in terms of different occasions, education levels, ages, availability for medical insurance, and the sex-exposure ages. Those facts are well supportive to conclude that self-sampling is suitable to most of the women regardless background and demographic difference. Another fact is that 64.11% of the 6,703 questionnaire respondents expressed willingness to introduce self-sampling to their relatives and friends for cervical cancer screening, suggested a fine possibility for popularization of self-sampling.

Self-sampling does have barriers for its application. Based on our study, those barriers are mostly cognitive. Multi-variant analysis showed that the top independent reason for not chose self-sampling was "not trust the testing result" (29.75%), followed by "worrying about specimen contamination during shipment" (28.76%), both were cognitive from information asymmetry but not evidence based conclusion. The second top independent reason, self-sampling was "hard to do", was given by some respondents. However, we currently cannot confirm it is an experience-based answer because we have no evidence for how many respondents who gave that answer were never been screened with provider-sampling. Other reasons given for not choose self-sampling were all cognitive, which were another study has been shown that educational interventions on HPV-related knowledge and perceptions of cervical cancer and self-sampling were associated with high confidence and acceptability. [32] Although we still need more evidence to demonstrate the real barriers for self-sampling, if they really exist, it is undoubted that make public well-known about self-sampling through public education will clear the top cognition related barriers for self-sampling.

The fact for self-sampling is that it is equal to provider sampling in detecting hr-HPV on PCR-based assays. [12, 34] Our study showed the testing failure with self-collected samples were 0.11%, and 18.54% of the women completed self-sampling were educationally backgrounded with primary-school or below, showing that self-sampling is qualified enough for HPV testing, and it can be applied regardless participants' education background. Careful referring the graphic or video sampling guidance could help women at any age, on all occasions, and at most education levels to complete self-sampling.

Self-sampling can make cervical cancer screening be applied in medically underserved regions and to medically underserved population with affordable cost [23, 35]. However, self-sampling-based screening program need the participants, the community, and the medical provider to play different roles in primary screening, positive triage, and precancer treatment. Internet service could be the most effective platform to link all the parts to pay their roles. Internet service can also play important roles for public education and participation motivation.

Positive management in internet-based self-screening project and the influent elements

Positive management is determinant to the success of the screening program. With the facilitation of the website, we provided the women who were abnormal of primary screening with the guidance for further examination and treatment through the website, which, together with the off-line contacts, made 73.38% of positives returned for colposcopy. Triage of the positives will be reported in another paper.

In conclusion, the Internet-facilitated self-HPV-testing screening and management model for cervical cancer prevention with large sample study is feasible and effective and can be used as a supplement to the traditional Chinese screening, especially in marginal areas with few medical resources, finally the coverage of cervical cancer screening will be significantly improved.

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Declarations of interest

None.

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