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ORIGINAL ARTICLE

Self-sampling HPV test in women not undergoing Pap smear for more than 5 years and factors associated with under-screening in Taiwan

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KEYWORDS
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Background/Purpose: Under-utilization of Papanicolaou (Pap) smear causes a gap in the prevention of cervical neoplasms. A prospective population-based study was conducted investigating whether a self-sampling human papillomavirus (HPV) test was feasible for under-users of Pap smear and factors associated with under-screening in Taiwan.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Pap smear;
self-sampling;
screening rate

Methods: Women not having Pap smear screening for > 5 years were invited to participate in this study. Invitation letters and educational brochures were mailed to 4% of randomly selected eligible women from Taoyuan City, Taiwan, and responders received an HPV self-sampling kit. Those with HPV-positive results were recalled for a Pap smear and colposcopy.
Results: Between March 2010 and June 2012, 10,693 women were invited, 354 responded (3.3%), and 282 (2.6%) gave valid informed consent, answered the questionnaire, and submitted HPV samples. The median age of enrolled women was 48.1 years. Forty-seven women (16.7%) had a positive HPV test, and 14 women accepted further survey to find two CIN2+. Another two cases of CIN2+ were identified from a national registry database. The cost of direct mailing self-samplers was less than that done on request (from NT$434,866 to NT$164,229, response rate of 5% to 15%, respectively, versus NT$683,957 for detecting 1 CIN2+). Reasons for not attending screening included lack of time, embarrassment, assumed low risk, fear of positive results, and perceived potential pain. Among the responders, 90.8% found the method acceptable.
Conclusion: Our study indicated that different approaches (e.g., direct mailing self-samplers to under-users and/or various educational interventions) must be explored to improve coverage in populations with culture characteristics similar to Taiwan.

Introduction

Under-utilization of Papanicolaou (Pap) smear causes a gap in the prevention of cervical neoplasms in many countries. Around 30% of females aged > 30 years did not undergo a Pap smear in the past 5 years, which sets a caveat in the prevention of cervical cancer in Taiwan.[1] In the countries with long sustained Pap smear programs, most invasive cervical cancers (between 60% and 80%) are found in women who have not had a Pap test within the past 5 years.[2] Whether this under-screening rate has been due to sexual discrimination, social, cultural, or medical inconvenience has yet to be determined by population-based studies.

Human papillomavirus (HPV) is the etiology of high-grade cervical intraepithelial neoplasm (CIN) and cervical cancer.[3] Pap smear and HPV co-tests in women aged ≥ 30 years are recommended every 5 years as primary cervical screening in developed countries. A single "screen-and-treat" visual inspection with acetic acid might be reasonable in areas with very limited resources.[4,5] However, a report from The Netherlands showed that primary HPV screening was not cost-effective for young women (a combination of primary cytology screening for women < 33 years of age), while HPV screening for older women can be more cost-effective with primary HPV screening.[6]

HPV testing using self-sampling specimens for cervical screening have been studied by many investigators.[7–9] A recent meta-analysis also confirmed that sensitivity of self-sampling vaginal specimens is generally comparable to the physician-collected cervical samples by polymerase chain reaction (PCR)-based methods, although self-sampling specimens might be slightly inferior by signal-based methods.[9] A randomized study from The Netherlands of 2830 women not responding to regular national screening reminders revealed that they were more willing to do self-sampling HPV testing (34.2%) than to accept a recalled cytology (17.6%).[10] Another study from Sweden reported a 39.1% response rate for self-sampling HPV testing done at home for women not attending organized screening for ≥6 years.[11]

The current study aimed to investigate: (1) if a self-sampling vaginal swab for HPV testing would be acceptable to women without a Pap smear for > 5 years and (2) the cost of finding one CIN2 or a more severe CIN2+ in a population with low screening rates. The study results might answer whether a self-sampling HPV test could be implemented among under-users of Pap smear, and could provide a national policy reference for the strategy of promoting primary prevention of cervical cancer.

Methods

Eligibility criteria and patient recruitment

This prospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB 97-2300A3). A list of women residing in Taoyuan City, Taiwan, and not having Pap smear screening in the past 5 years (n = 259,162) was obtained from the Department of Public Health, Taoyuan City government. We planned to recruit 1500 participants and 1200 valid specimens. To achieve this, we mailed a study invitation, a copy of the informed consent, and a health brochure to 4% of randomly selected women from the list, and assumed that 15% of the receivers would mail back their letter of intent. The responders would receive a second letter enclosing an HPV self-sampling kit and a copy of a post-test questionnaire. Our HPV self-sampling kit included a self-sampling brush and a copy of instructions (Iron Will Biomedical Technology, New Taipei, Taiwan). They were instructed to perform self-sampling by inserting the swab into the vagina ~5–8 cm deep, rotating it 360°, putting it into the test tube containing preserving medium, and mailing it back to

us along with the informed consent using a pre-paid envelope.

Women issuing informed consent and answering the questionnaire were eligible for analysis of factors relating to under-utilization of Pap smear, while those having the former two, but absent vaginal samples, were excluded from further analysis. All participants gave written permission to obtain their 15-year health data regarding Pap smear frequency, cytological, and pathologic reports from the Taiwanese national registry database. Women with positive HPV results would be notified to come to Chang Gung Memorial Hospital for a colposcopy, Pap smear, and/or cervical biopsy.

DNA extraction and SPF1/GP6+ PCR

DNA was extracted according to the protocol for isolation of total DNA from cultured animal cells (Qiagen Inc., Valencia, CA, USA) and as described previously.[12–14] In all cases, 100 ng was used for each PCR,[14] and the SPF1/GP6+ consensus primers were used to amplify a fragment of approximately 184 bp in the L1 open reading frame, as previously described.[12–14]

HPV genotyping by Easychip HPV Blot and E6 type-specific PCR

Fifteen microliters of the resulting amplimers were hybridized with an Easychip HPV Blot (King Car, I-Lan, Taiwan) membrane. Thirty-eight types of HPV [6, 11, 16, 18, 26, 31, 32, 33, 35, 37, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71 (CP8061), 72, 74, 81 (CP8304), 82 (MM4), 83 (MM7), 84 (MM8), and L1AE5] were capable of detection. The hybridization and detection procedures have been reported previously.[12–14] The E6 type-specific PCRs were performed in order to validate the types of multiple infections.

HPV types were divided into two groups (low-risk and high-risk). The leading 14 HPV types (HPV-16, -18, -58, -33, -52, -39, -45, -31, -51, -70, -56, -59, -35, and -53) linked to cervical cancer in Taiwanese women[15] were grouped together in the high-risk group, while the remaining 24 HPV types were considered low-risk.

Data analysis

Descriptive analyses to assess the prevalence rate of HPV infection according to host characteristics (age, education, economic status, knowledge of cervical cancer/HPV, and attitude toward cervical screening). The cost analysis was based on finding CIN2+ over a 3-year period. Odds ratio (OR) of finding CIN2+ by HPV results with a 95% confidence interval (CI) was calculated using information from the national registry database obtained from the Health Promotion Administration, Taiwan. We calculated the utilization of cervical screening with 5-year intervals up to 15 years, and the occurrence of CIN2+ in participants or women receiving invitations as compared to those not invited. The cost calculation was based on actual direct cost (mail, sampling kits, HPV testing, Pap smears, colposcopy, and cervical conization). All calculations were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA) and STATA 9.0 (StataCorp LP, College Station, TX, USA).

Results

Between March 2010 and June 2012, a total of 10,693 women were invited. The original study design is represented in Figure 1. Of these, 354 (3.3%) responded and 352 submitted post-educational questionnaires and informed consent, but only 282 (2.6%) returned valid informed consent, a completed questionnaire, and HPV-test samples. Seventy women gave informed consent, but did not return HPV-test specimens. The median age of enrolled women was 48.1 years (range, 35.2–79.7 years). Among the 282 women with a valid HPV sample, 47 (16.7%) had positive results.

HPV, Pap, and colposcopy results

Fourteen of the 47 women with HPV-positive results (29.8%) came to the hospital for further investigation. All 14 received colposcopy, while nine also received a Pap smear. The overall abnormal cytological diagnosis [atypical squamous cells of undetermined significance or worse (ASCUS+)] rates in women receiving Pap were 33.3% (3/9). Of the 14 women who received a colposcopy, three cases with histology-proven CIN (1 with CIN 1 and 2 with CIN 2) were found. The findings/HPV types of these 14 women are provided in Table 1. Among the 47 women having positive HPV tests, 78.7% harbored a single type of infection, and 21.3% had multiple types, with the three most common types being HPV70, HPV52, and HPV71.

Analyses using the national registry database

Thirty-three of the 47 HPV-positive women were unavailable to attend our next step. According to the national registry database, 40 (57.1%) of the 70 women without HPV-test specimens, 23 (70.0%) of the 33 unavailable HPV-positive women, and 136 (57.9%) of the 235 HPV-negative women accepted Pap smear or cervical biopsy between August 2010 and December 2013. This study has clearly impacted these participating under-users, regardless of HPV results. Between March 2010 and December 2013, one CIN2+ occurred in each of the unavailable HPV-positive and HPV-negative groups, but none occurred in those without HPV. With a median follow-up of 31.4 months, the rates of finding CIN2+ by HPV-positivity calculated using national registry database were 6.4% (3/47) for HPV-positive (HPV16, HPV52, and HPV58) and 0.4% (1/235) for HPV-negative women. The OR of HPV-positive to HPV-negative was 15.96 (95% CI, 1.62–156.9; Fisher's exact test; $p = 0.015$).

Reasons of Pap smear under-utilization

For the responders ($n = 354$), there were no differences between women providing valid informed consent, completing the questionnaire, and providing HPV-sample specimens ($n = 282$) and those who did not ($n = 70$) in

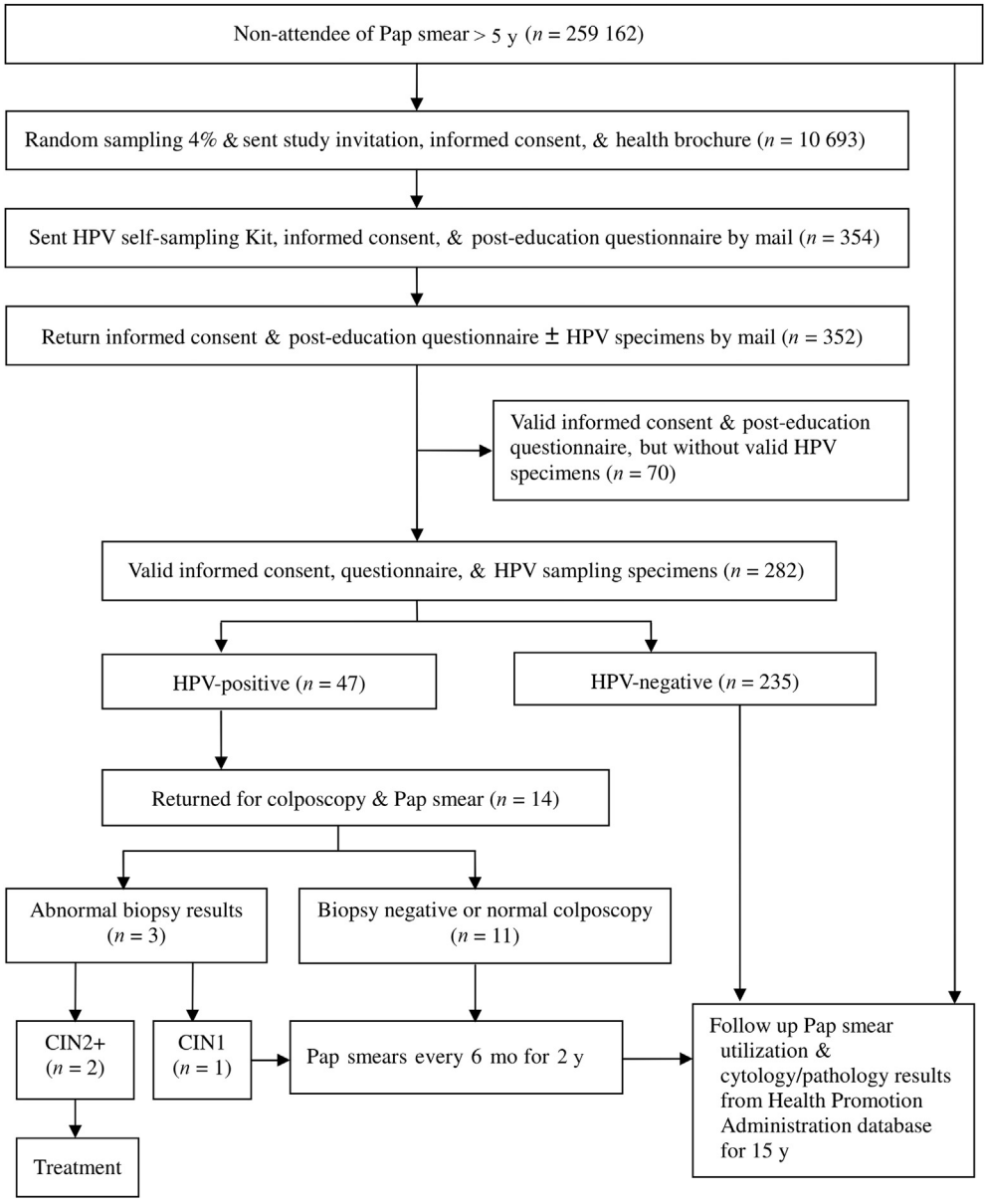

Figure 1 Flowchart describing this study. CIN 1 = cervical intraepithelial neoplasia Grade 1; CIN2+ = cervical intraepithelial neoplasia Grade 2 or worse.

age, marriage status, education, religion, occupation, income, or family economic status (Table S1). The reasons for their not attending screening included embarrassment (36.4%), lack of time (35.8%), forgetting (25.9%), assuming they were at low risk (24.4%), fear of a positive result (13.1%) and perceived potential pain (10.8%; Table 2).

Knowledge and beliefs about cervical cancer and HPV

Most of the responders (92.7%) knew that a Pap smear is a simple and convenient method used to screen cervical cancer, and that further evaluation is necessary if the Pap smear result is abnormal (98.0%). A majority of them (88.9%) knew that early HPV testing could help to screen for cervical neoplastic lesions. Menopausal women misunderstanding about not needing a Pap smear was not prevalent (12.8%). Among our responders, 33.5% did not know that most invasive cervical cancers developed from pre-invasive lesions, while 79.4% knew that HPV infection is a sexually transmitted disease (Table 3).

Sources of screening information and knowledge of cervical neoplasms

Our attendants learned about screening and gained knowledge of the disease from television (51.4%), newspapers and magazines (31.3%), and radio (18.5%), while only 14.5% of them learned from internet websites. They received medical information from hospital staff (57.4%), public-health nurses (49.1%), health education brochures (32.7%), and relatives and friends (16.5%; Table 4).

Table 1 Demographics, colposcopy, and cytology/pathology findings of HPV-positive women who received further investigations.

Case	Age (y)	Colposcopy	Pap smear	Pathology	HPV type
1	52	Unsatisfactory	NA	NA	HPV-71
2	63	CIN2/3	NA	CIN 3	HPV-58
3	57	CIN2/3	CIN 3	CIN 3	HPV-52
4	41	No dysplasia	ASCUS	NA	HPV-44
5	41	No dysplasia	Normal	NA	HPV-62
6	43	No dysplasia	Normal	NA	HPV-71
7	50	No dysplasia	Normal	NA	HPV-42
8	41	No dysplasia	Normal	NA	HPV-51
9	46	No dysplasia	Normal	NA	HPV-44
10	56	No dysplasia	NA	NA	HPV-70
11	49	No dysplasia	NA	NA	HPV-84
12	50	No dysplasia	NA	NA	HPV-70
13	56	No dysplasia	Inflammation	NA	HPV-70
14	46	No dysplasia	ASCUS	CIN 1	HPV-52

ASCUS = atypical squamous cell of undetermined significance; CIN 1 = cervical intraepithelial neoplasia Grade 1; CIN 2/3 = cervical intraepithelial neoplasia Grade 2 or 3; HPV = human papillomavirus; NA = not applicable.

Opinions about self-sampling HPV testing

Of all responders, 90.8% found self-obtained HPV testing convenient and acceptable, with 87.2% willing to choose the self-obtained method in the future, and 88.3% willing to recommend this test to other people. Post-sampling vaginal spotting, increased vaginal discharge, and lower-abdominal discomfort occurred in 10.3% of respondents, with no special complaint from 87.9%. A total of 65.2% of responders thought the HPV self-obtained test gave them resolution for the unwillingness to attend Pap smear screening (Table 5).

Cost analysis

The cost of the project, including mailing, HPV kits, HPV testing, Pap smear, colposcopy with/without biopsy, personnel, and consumables came to NT $2,518,921. If we count all four cases of CIN2+ from the responders (n = 354) as benefits of the study impact, the cost of detecting one CIN2+ case was approximately NT $683,957 (Table S2).

Table 2 Reasons for non-attendance of cervical screening (n = 352).

Reasons[a]	n	%
Lack of time	126	35.8
Transport	16	4.5
Fear of positive result	46	13.1
Embarrassed	128	36.4
Perceived potential pain	38	10.8
Feeling of low risk	86	24.4
Forgetting	91	25.9
Others	29	8.2

[a] More than one reason could be chosen.

Discussion

Previous studies suggested that the sensitivities of HPV testing were comparable between self-sampling and clinician-collected samples.[7–11] Therefore, we offered the self-sampling HPV-testing option, as well as health information on cervical cancer and HPV with educational brochures, to the under-users of Pap smear in the neighboring community in the same mailing. Unfortunately, only 3.3% of the 10,693 women responded. Forty-seven of the 282 (16.7%) women had positive HPV results, and 14 of the 47 (29.8%) received colposcopy/cytology. The HPV-positive rate tended to be higher among Pap under-users in other studies,[16–18] and in the current study as compared with our previous population-based study from Taoyuan County (now Taoyuan City), Taiwan, which found that the HPV prevalence rate was 11% among women aged 30–94.[19]

Our questionnaire revealed that the reasons for not attending screening included lack of time, embarrassment, feeling at low risk, fear of positive results, and perceived potential pain, which could be resolved by appropriate education and a convenient test. Our attendants learned about screening and gained knowledge of the disease from television (51.4%) and newspapers and magazines (31.3%), while only 14.5% of them learned from internet websites, which is a source of information that should be considered in promoting increased coverage rates. Of the full responders, 90.8% found self-obtained HPV testing convenient and acceptable, with 87.2% willing to choose the self-obtained method in the future, and 88.3% willing to recommend this test to other people.

Two CIN2+ women were detected among the 14 women who underwent further colposcopy/cytology. Another two were identified from the national registry database, making the rates of finding CIN2+ by HPV-positivity 6.4% (3/47) for HPV-positive and 0.4% (1/253) for HPV-negative women, with a median follow-up of 31.4 months. The OR was 15.96 for HPV-positive women (95% CI, 1.62–156.9; Fisher's exact test; p = 0.015). Except for detecting CIN lesions, the current study changed those under-users who responded, because 57.9–70% of responders accepted Pap smear or cervical biopsy in the following 9 months after enrolment, regardless of their HPV results.

Similar trials of inviting Pap-non-attendants to perform self-sampling HPV tests by mail obtained higher response rates as compared to standard recalls for cytology in England (10.2% vs. 4.5%) and in The Netherlands (30.8% vs. 6.5%).[16,17] In an Italian randomized trial, the response rate among those directly receiving self-sampling kits was better than those either receiving the self-sampling kit on request, or merely recalled to do a Pap smear (19.6% vs. 8.7% vs. 3.9%).[18] The cost of detecting one CIN2+ case in the current study was approximately NT $683,957, with mailing HPV kits on request (Table S2). If the alternative strategy of mailing HPV kits to all under-users could result in a response rate of 5–15%, and post-intervention follow-up behavior led to results similar to those observed in this study, the expected cost (15%, NT $164,229; 10%, NT

Table 3 Knowledge and beliefs about cervical cancer and human papillomavirus ($n = 352$).

Questions (standard answer)	Answers		
	n	Right (%)	Wrong or do not know (%)
The purpose of Pap smear is to find out early cancer & give therapy early to increase the cure rate of disease (True)	342	98.5	1.5
The further evaluation is necessary if the Pap smear result is abnormal (True)	345	98.0	2.0
Pap smear is a simple & convenient method to screen cervical cancer (True)	342	92.7	7.3
Pap smear plus HPV test could increase the detecting rate of cervical cancer or its precursors (True)	343	91.0	9.0
HPV test could help to early screen the cervical neoplastic lesions (True)	342	88.9	11.1
Women with more sexual partner are more easily getting cervical cancer (True)	343	87.8	12.2
All women have risk of HPV infection after sexual debut (True)	342	88.0	12.0
Cervical carcinogenesis is closely related to HPV (True)	341	87.4	12.6
Menopausal women no longer need Pap smear (False)	345	87.2	12.8
Genital HPV is mostly through sexual transmission (True)	340	79.4	20.6
The national insurance provides a yearly Pap smear for women aged 30 years or older (True)	344	78.2	21.8
Cervical cancer a family inherited disease (True)	340	69.4	30.6
Better to avoid intercourse the night before Pap smear (True)	345	69.3	30.7
Most of the invasive cervical cancers developed from pre-invasive lesions (True)	337	66.5	33.5
HPV testing can use self-collected specimens, but not for Pap smear (True)	341	56.0	44.0
Pap smear is the only way of screening for cervical cancer (False)	341	36.4	63.6

HPV = human papillomavirus.

$291,401; 5%, NT $434,866) for detecting one CIN2+ would be lower than that seen by undergoing the test on request (Tables S3—S5).

The American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology consensus guidelines recommended cervical cytology at 3-year intervals for women aged 21—29 years, and HPV and cytology co-testing every 5 years, or cytology alone every 3 years in women aged 30—65 years.[20] In a long-term community-based study of Taiwanese women aged 30—65 years ($n = 11,923$) with clinician sampled co-tests, the 16-year cumulative risk of cervical cancer in HPV-negative women was 0.26% as compared to 13.5% in HPV16-positive women, and 10.3% in HPV58-positive women at baseline.[21] A recently published pooled analysis of four randomized trials ($n = 176,464$) from European countries showed that HPV-based screening was better than cytology-based screening at preventing invasive cervical cancer, with benefits not significant at 2.5 years, but very significant at 5.5 years.[22] HPV-based testing for primary cervical screening from age 30 years at an interval of 5 years is the world trend.[5]

The nationwide coverage rate remains a key challenge to implementing any screening program. Self-collection of vaginal specimens for HPV testing has been shown to be more effective at detecting CIN2+ than cervical cytology in community-based randomized trials.[23] The Ministry of Health and Welfare in Taiwan began offering free self-sampling HPV testing to women aged > 36 years who had not received a Pap smear for 6 years, or handicaped women aged > 30 years, but the response rate was unsatisfactory by reminder letter (1.3% annually).[1] The low response rate was similar to our results, and we expected it to be higher by mailing self-sampling kits directly instead of after responding to our invitation letter. However, this expectation remains to be proven by a future field study.

Our previous study indicated that unawareness of the importance of Pap smear, busyness, and shyness were the

Table 4 Sources of information about screening and knowledge of cervical neoplasms ($n = 352$).

Source[a]	*n*	%
Hospital	202	57.4
Television	181	51.4
Public health nurse	173	49.1
Health educational brochure	115	32.7
Newspapers & magazines	110	31.3
Relatives & friends	58	16.5
Radio	65	18.5
Internet	51	14.5
Others	1	0.3

[a] More than one source could be chosen.

Table 5 Opinions about self-sampling HPV testing ($n = 282$).

Opinions	*n*	%
Simple & acceptable	256	90.8
No definite discomfort	248	87.9
Bleeding/lower abdominal pain/discharge	29	10.3
Willing to take the method again	246	87.2
Glad to recommend to other people	249	88.3
The method resolve the problem not attend Pap smear screening for years	184	65.2

HPV = human papillomavirus.

three leading causes of not undergoing Pap smears among women with newly diagnosed cervical cancer.[24] Resaei et al[25] reported that educational intervention for cervical cancer prevention by booklets, though not as substantial as lectures, was significantly more effective as compared to no manipulation.

Most respondent women found self-sampling HPV by mail acceptable (90.5%), and self-sampling with our kit not uncomfortable (87.2%), which ensure the feasibility of this method in the general population. The results from the knowledge questionnaire among Pap under-users in our study exceeded our expectations. Although it was similar to an open-book test, it impacted the knowledge and behavior of these women toward cervical screening. Although the response rate was unsatisfactory, the current study changed those under-users who responded, because 58.5—73% ultimately accepted Pap smear or cervical biopsy in the following 9 months after enrolment. The national health database will allow us to determine whether the current study also changed non-responders behavior toward greater motivation for cervical screening. Television, newspapers, and magazines are useful media methods for delivering educational interventions.

In conclusion, our study indicated that under-screened population are not easy to access, but that health brochures increased receiver knowledge on cervical cancer and HPV. Different approaches must be explored to improve the coverage rate in populations with similar cultural characteristics as Taiwan. Direct-mailed HPV kits to all under-users instead of mailing kits on request might be a reasonable alternative. A face-to-face educational intervention project through volunteer obstetricians and gynecologists serving as community cancer-prevention advocates is currently underway.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2015.10.014.

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