Clinical Evaluation of A New Model of Self-Obtained Method for the Assessment of Genital Human Papilloma Virus Infection in an Underserved Population

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Background: We designed a self-sampling method to collect exfoliated genital cells for human papilloma virus (HPV) detection. The aim was to assess whether it was suitable as an assistant tool for the early detection of cervical pre-cancer and cancer in a special category of the women who are not frequently screened for cervical cancer.

Methods: We compared the results of HPV detection that were self-obtained and physician-obtained cervical swabs from the same patient that were analyzed using hybrid capture II assay. The diagnostic rate of cervical pre-cancer and cancer between self-obtained method and physician-obtained method were analyzed.

Results: A total of 1194 women were prospectively registered from September 1997 through September 1999. Among them, 144 (12.1%) of self-test samples and 155 (13%) of physician-obtained samples were oncogenetic associated-HPV positive. Statistically, no significant differences existed in the screening rate for cervical cancer using either the self-collected samples or the physician-obtained samples ($p > .05$). The sensitivity of cervical precancer or cancer detection using self-obtained HPV testing was higher (96.3%) as compared with the Pap smear (79.2%) ($p < .02$).

Conclusion: The detection correlation of the HPV test between the self-obtained method and physician-obtained method was 93%. Our results indicated that self-sampling was a reliable method for testing for HPV. The identification of HPV infection through the self-obtained method can be used in early identification of high-risk women with cervical precancer and cancer especially in underserved populations.

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Key words: cervical cancer, cervical intraepithelial neoplasia, Papanicolau smear, human papillomavirus, hybrid capture.
Worldwide, cervical carcinoma is the second leading cause of death from cancer in women. It has been well established that organized cytological screening programs can substantially reduce the morbidity and mortality rates from cervical cancer in developed countries. Despite the recommendations by the health care professionals, there are still segments of the general population that are not receiving these screening services as frequently as recommended. As a result, cervical cancer may be diagnosed at the late stage and the mortality rate may be increased. One critical issue of the reduced screening is the identification of subgroups that are underserved. The subgroups include women that tend to be older, uninsured, minority, poor, physically disabled, debilitated, and living in rural areas. There are at least four segments of the population who are not frequently screened namely, those with debilitating diseases (hemiplegics, cerebrovascular accidents), physically disabled (handicapped), elderly women, and those in rural populations. The speculum assisted cervical smear is rather uncomfortable and inconvenient that precludes those women from receiving regular smears for cancer prevention.

Disability is an important factor for reduced screening because of the rapidly increasing elderly population. While cervical cancer typically occurs during fifth and sixth decades of life, 27% of patients are > 65 years of age. On the other hand, delivering preventive care is often more difficult for rural than for urban primary care practices. On the other hand, medical practices are also different in rural areas. There are fewer physicians and the patients spend less time with their physicians. However, there are also important limitations to screening samples obtained during pelvic examination: such as examinations require a trained health professional working in a clinical setting. In addition there are often cultural inhibitions that render routine pelvic examination unacceptable to symptomatic women belonging to certain ethnic backgrounds, which limit the utilization of screening services. Epidemiological and basic molecular biological studies support the concept that certain genital Human Papilloma Virus (HPV) are the major risk factors for the development of cervical cancer and constitute 85-95% of human cervical carcinomas, suggesting that the parameter of HPV typing is important for identifying women at risk. Recently, the introduction of HPV testing in screening protocols has been a subject of active research and considerable public health relevance. The clinical usefulness of HPV testing using Hybrid Capture II has been evaluated in a number of studies and had shown that HPV test could be used as an assistant diagnostic biomarker for early detection of cervical pre-cancer or cancer.

In order to evaluate the screening value of high risk HPV infection in the diagnosis of cervical per cancer and cancer, we designed a self-sampling method to collect genital exfoliated cells using hybrid capture II assay. We particularly focused our study on women with limitations of activity, elderly women, and those residing in rural areas. The aim was to assess whether it was suitable as an assistant tool for the early detection of cervical pre-cancer and cancer in this special category of the women. The study was designed as a prospective, double blind trial performed in a population-based cohort. We compared the results of HPV detection in self-obtained and physician-obtained method using cervical swabs from the same patients analyzed them using hybrid capture II assay.

**METHODS**

The community based randomized trial was conducted in the communities in northwestern Taiwan, a region with the lowest doctor patient ratio in the country. From September 1997 through September 1999, 1194 women participated in the study. All of the patients included were either handicapped (hemiplegics, cerebrovascular accidents, physically disabled, etc), living in rural area, or elderly women. Exclusion criteria were pregnancy and virgin women. Women with history of abnormal vaginal smear and/or cervical intraepithelial neoplasia (CIN) or cancer were also excluded.

The study protocol was approved by the research committee of Chang Gung Memorial Hospital. Informed written consent was obtained from all of the participants. Patients enrolled in the study were sent a questionnaire form, collection tube, and instructions for sampling. A special telephone number, e-mail address and web site were set.
up for communication. We supplied a special nurse, if needed, to assist them in performing the smear. For those handicapped and debilitated women with hemiplegic, dementia or cerebrovascular accidents, vaginal swab specimens were taken by a family member or special nurse. After sampling, patients were asked to send the collection tube (sealed) to the hospital laboratory. The complete process followed a specific sequence: (1) self-obtained specimens for HPV DNA testing were collected from home; (2) within 3 days after self sampling, the women were called to the gynecology clinic for speculum assisted samples by a physician; (3) pap smear was obtained using a wooden spatula or cytobrush; and (4) colposcopic examination with 5% acetic acid.

Women were asked to swab the inside of the vagina by themselves using a standard 15 centimeter cotton swab. They were instructed to perform the test by inserting the sterile swab into the vagina as far as possible and then rotating the swab up and down and placing it in a transport container with specimen transport Media (Specimen transport media, DIGENE Corp). After the self-sampling was performed, a speculum-assisted speculum sample was obtained from the endocervix and ectocervix for HPV DNA testing. The cervical swabs were each immediately placed in plastic tubes filled with 0.5 ml specimen transport media.

All of the collection specimens were stored at 4°C and send to laboratory room for HPV testing. The presence of genital oncogenetic-associated HPV was assayed using the Hybrid Capture II method. Samples were discarded if the collecting tubes were broken during transportation, blood stained, dried, or contaminated. The results of both sets of samples were compared. During the collection of the speculum assisted sample, a cervical scrap was also obtained for Papanicolaou smear using a cytobrush or wooden spatula. The specimen was sent to the pathology department to be examined by a cytopathologist, who was not aware of the hybrid capture results. The Bethesda system for Pap smear was used. Women with identified genital oncogenetic-associated HPV infection or abnormal Pap smear, including Abnormal squamous cell of indeterminate significance (ASCUS), low-grade squamous epithelial lesions (LSIL), high-grade squamous epithelial lesions (HSIL), squamous cell carcinoma, and adenocarcinoma, were referred to the colposcopy clinic and biopsies were taken from colposcopically verified lesions.

**Laboratory methods**

**Hybrid capture assay**

The HPV DNA assay was performed using a commercially available Hybrid Capture System II (Digene Corporation, located in Gaithersburg, MD U.S.A.). Hybrid capture is a solution hybridization method in which ribonucleic acid (RNA) probes for HPV DNA are hybridized in solution with the sample DNA. The Digene Hybrid Capture II System is a sandwich capture molecular hybridization assay that employs chemi-luminescent detection. Specimens for HPV testing were processed according to the manufacturer’s instructions. Specimens were treated with alkali-denaturate solution at 65°C for 45 minutes, and hybridized under high stringency with a mixture of specific ribonucleic acid (RNA) probes, HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The resultant DNA-RNA hybrids were captured on the surface of the microtiter plate wells coated with an anti-DNA-RNA hybrid antibody. The immobilized hybrids reacted with an alkaline phosphatase-conjugated antihybrid monoclonal antibody. Light was then emitted and measured as relative light units (RLUs) on a luminometer. The intensity of the light unit emitted was proportional to the amount of target DNA in the specimen. A RLU measurement greater than or equal to the positive control cut off value (0.2 pg/ml HPV DNA) indicated the presence of HPV sequences in the patient’s specimen, whereas a RLU measurement less than the cut off value indicated the absence of HPV sequences.

**Statistical analysis**

Diagnostic performance index values such as sensitivity and specificity were calculated for each method. The crude percentage of agreement between sampling methods was the percentage of pair samples where HPV test results were identical. Comparisons of different characteristics between the groups were based on the Pearson chi-square test. The comparisons of correlation and discrepancy between groups were based on the McNemar’s chi-square test. A significant difference was considered
RESULTS

Among the 1194 patients who enrolled in the study, 151 women were handicapped, 353 were living in rural area, and 690 were elderly women. The median age of women was 51.3 years. Five hundreds and four patients (42.2%) were younger than 50 years and 690 patients (57.8%) were older than 50 years.

Of the 1194 women, 144 (12.1%) of the self-test samples and 155 (13%) of the physician-obtained samples were oncogenetic associated-HPV positive. Overall, the self-obtained method had a good correlation for the presence of HPV DNA with the physician-obtained sample group. The results of HPV tests in the self-obtained method and the physician-obtained method with the correlation are shown in Table 1. The correlation of the HPV positive detection results in the self-obtained group compared with physician group was 92.9%. There were 11 cases of discrepancy between the self-obtained and physician-obtained methods. All of them were HPV test negative in the self-obtained methods and positive in the physician-obtained methods. None of the samples was HPV test positive in the self-obtained method and negative in physician-obtained method. The discrepancy of the HPV positive detection results was 7.1%. The overall correlation of HPV test in the self-obtained group compared with the physician group was 99.1%. Statistically, no significant differences existed in the screening rate for cervical precancer or cancer diseases using either the self-collected samples or the physician-obtained samples ($p > .05$). However, it was seen that the detection rate between the two groups in the cervical low grade lesions was different while, it was exactly same in the high grade lesions (CIN II and CIN III) and cancer.

Regarding the Pap smear screening, the Pap smear distribution was as follows: normal in 1074, ASCUS in 68, LSIL in 32, HSIL in 15, and cancer in two women. After colposcopic examination and directed biopsy, the identified cervical precancer or cancer lesions was CIN I in 23, CIN II in 10, CIN III in 16, and cancer in two women based on HPV self-obtained screening. The results were CIN I in 25, CIN II in 10, CIN III in 16, and cancer in two women based on HPV physician-obtained method. Statistically, no significant differences existed in the screening rate for cervical precancer or cancer diseases using either the self-collected samples or the physician-obtained samples ($p > .05$). However, it was seen that the detection rate between the two groups in the cervical low grade lesions was different while, it was exactly same in the high grade lesions (CIN II and CIN III) and cancer.

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<table>
<thead>
<tr>
<th>Pathology</th>
<th>ASCUS or SIL (N = 117)</th>
<th>Self-test (N = 144)</th>
<th>Physician (N = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>75</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td>CIN I</td>
<td>20</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>CIN II</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CIN III</td>
<td>11</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. HPV Infection Rate-Based on Sampling Methods:

<table>
<thead>
<tr>
<th>Physician-obtained</th>
<th>Self-obtained</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV positive</td>
<td>HPV positive</td>
<td>144</td>
<td>11</td>
</tr>
<tr>
<td>HPV negative</td>
<td>HPV negative</td>
<td>0</td>
<td>1039</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>144</td>
<td>1050</td>
</tr>
</tbody>
</table>
The positive predictive value, false negative rate, and false positive rate using the self-obtained HPV test were 35.4%, 3.7%, and 64.6%, respectively. Statically, the false negative rate of the Pap smear was higher than the HPV test using the self-obtained method in the study ($p < .01$). According to age distribution, the specificity of the HPV test using the self-obtained methods in women younger than 50 years was particularly lower in 24.2% as compared with the Pap smear in 87.5%. The specificity of the HPV test using the self-obtained method in women older than 50 years was particularly lower in 62.2% as compared with the Pap smear in 80% (Table 5).

**Table 3.** Sensitivity and Specificity of the Detection Cervical Cancer and Pre-cancerous Lesion Using Pap Smear

<table>
<thead>
<tr>
<th>CIN (+)</th>
<th>CIN (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>53</td>
</tr>
<tr>
<td>Pap smear normal</td>
<td>11</td>
</tr>
<tr>
<td>Pap smear abnormal</td>
<td>42</td>
</tr>
</tbody>
</table>

Sensitivity 79.2%, Specificity 93.4%, Positive predictive value: 35.9%
False negative rate: 20.8%, False positive rate: 64.1%

**Table 4.** Sensitivity and Specificity of the Detection Cervical Cancer and Pre-cancerous Lesions Using Self-obtained HPV test

<table>
<thead>
<tr>
<th>CIN (+)</th>
<th>CIN (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>53</td>
</tr>
<tr>
<td>HPV test negative</td>
<td>2</td>
</tr>
<tr>
<td>HPV test positive</td>
<td>51</td>
</tr>
</tbody>
</table>

Sensitivity 96.3%, Specificity 91.8%, Positive predictive value: 35.4%
False negative rate: 3.7%, False positive rate: 64.6%

**Table 5.** Final Pathology in Correlation with Age Distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>CIN (N = 50)</th>
<th>Cancer (N = 2)</th>
<th>HPV specificity (self-test)</th>
<th>Pap smear specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0</td>
<td>0</td>
<td>0/15 (0%)</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>20-30</td>
<td>2</td>
<td>0</td>
<td>2/9 (22.2%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>30-40</td>
<td>9</td>
<td>0</td>
<td>9/33 (27.2%)</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td>40-50</td>
<td>12</td>
<td>1</td>
<td>13/42 (30.9%)</td>
<td>10/11 (90.9%)</td>
</tr>
<tr>
<td>50-60</td>
<td>17</td>
<td>1</td>
<td>18/26 (69.2%)</td>
<td>12/14 (85.7%)</td>
</tr>
<tr>
<td>60-70</td>
<td>7</td>
<td>0</td>
<td>7/15 (46.6%)</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>3</td>
<td>0</td>
<td>3/4 (75%)</td>
<td>2/3 (66.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>2</td>
<td>52/144 (36.1%)</td>
<td>41/49 (83.7%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Widespread use of cervical screening programs has led to a marked decline in the rate of incidence and death from invasive cervical cancer. Although, screening for cervical carcinoma has been widely accepted as beneficial, significant limitations continue to impair screening of large populations because of the limited availability of trained medical personnel, limited time, patients’ inconvenience or non-compliance, and inability to reach medically underserved population. The false negative rate of the Papanicolau smear also have pronounced been during recent years and the false negative results have ranged from 20 to 50%. To improve the Pap smear screening rate and decrease the false negative rate, several reports have demonstrated that the HPV test could be used as an assistant tool in the early diagnosis of cervical precancer and cancer, such as used in triage in ASCUS group and is concurrently used with the Papanicolau smear. Additionally, several researchers have reported that self-obtained methods can be used as an alternative to collect vagino-cervical specimens for the HPV test. In these studies,(11~13) the women included were either young or of the general population for screening of HPV DNA using self tests. In our study, we included women who were physically handicapped, elderly women or residing in rural areas, which did not regularly participated in conventional screening programs.

Biochemical assays for detecting HPV DNA have been developed which include PCR testing, insitus hybridization, and hybrid capture test II. PCR testing for HPV has high sensitivity for detecting HPV related lesions, but considerable inter-observer and inter-laboratory variations exist, which can increase the false negative rate. Hybrid capture II test has a well-validated analytic sensitivity and has been shown to be an accurate reproducible test. Although Hybrid capture is a sandwich detection method that detects either HPV types of high and intermediate oncogenic risk (i.e., HPV 16, 18, 31, 33, 35, 45, 51, 52, 56 and 58), and we can not get HPV subtype specific results. However, this test is capable of detecting lower concentrations of purified HPV DNA than the earlier dot-blot hybridization methods and includes probes for a wider spectrum of HPV types. In our study, we found 200-5000 cells
(data not shown) detected by microscope. Additionally, its capability to quantitate viral load in cervical specimens provides a means of possibly increasing test specificity for the disease, so we used this method for self testing even though the sampled tissue was small. In this study, we did not analyse the viral load through its semi-quantitative capability.

We compared the self-test method with the physician-obtained method for detecting cervical HPV infections. In our study, the self-collected sampling method had almost the same results as the physician-obtained method in detecting the cervical lesions (correlation of HPV detection rate: 93%). This finding is consistence with the results of a previous study, which demonstrated a correlation of 84%. Our results imply that the self-test method can be used as an alternative method to identify HPV prevalence in this special category of underserved women. However, the correlation was slightly lower in the women older than 50 years, although the results were not statistically different. The differences in correlation may be due to vaginal dryness or atrophic cervix with less exfoliative cells. Second, contamination is another concern in the self-test sampling method and can occur at any stage. We took all precautions to avoid the contamination. The women were advised to take extra precautions while performing the test without touching the swab and the transport media.

The prevalence of HPV infection (12% and 13%) was different from other community based studies, suggesting that there is considerable variation in the sensitivity for HPV testing, possibly because of the patient selection or study design. In general, the prevalence of HPV infection was highest in sexually active young women which was around 20-30% and its prevalence in older postmenopausal women was 5-10%. The women enrolled in the current study were mainly elderly and that may be the reason for the differences of HPV prevalence with the previous study performed by Wright et al. Additionally, HPV infection in younger women tends to be at a transient status and often spontaneously regress, whereas in older women the virus is more prone to persist. Persistence of HPV infection in women is associated with increased risk of persistence or progression of cervical lesions. In our study, we performed only a single test. Whether or not this single test is representative of the lesion present is an open question. The presence of genital oncogenetic associated HPV in elderly women implicates a higher risk predicting factors in comparison with young women. We propose that women with positive HPV DNA should be advised to attend gynecology clinic and undergo Pap smear and colposcopy even if the speculum assisted smear is difficult to perform. We plan to undertake a longitudinal study of HPV test to identify the persistence of HPV infection. For those women with negative genital HPV test, the screening interval of cervical smear can be prolonged from 3 to 5 years.

The current study revealed that women who are disabled, elderly, and residing in rural areas should be offered this method as a primary screening procedure. Thus, the technique of self-testing may find a place as an alternative low technology method for screening women do not regularly participate in screening programs. It may improve service utilization in the underserved population. Better screening in these subjects would facilitate early detection of pre-invasive cancers and could prove to be cost effective. Moreover, clinicians may want to use this instrument or modify it so that they may identify problems prevalent among a particular population. We believe that this package also meets the demands of primary care physicians who are being asked to care for an increasing number of elderly patients.

Although HPV DNA testing of self-collected vaginal samples has a number of advantages for selected populations, this approach is not without limitations. One limitation is that simply identifying women as being high risk for HPV does not guarantee that they will return for either colposcopic evaluation or treatment. In such cases, women should be motivated to undergo cytological screening. Another drawback of self-testing could be the avoidance of a pelvic examination, resulting in failure to detect other gynecological disorders.

In conclusion, our results indicate that self-sampling is a reliable method for testing HPV. This method may offer a great promise in clinical epidemiologic studies of HPV infection and cervical neoplasia and may be particularly useful in the evaluation of medically underserved populations. We plan to further evaluate the self-testing for further persistence of HPV infection at 6-month intervals in those with HPV positive test results.
Acknowledgment

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REFERENCES

人類乳突狀病毒感染自採檢體檢測方法的臨床評估

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背 景：子宮頸癌為罹患癌症婦女致死原因的第二位，在發達中國家已建立許多篩檢機制，以期降低子宮頸癌的罹患率及死亡率，並希望普及全婦女。如果子宮頸癌一直到末期才被診斷，則死亡率必大大增加，可是有四個族群常常不易接受子宮頸癌篩檢，像行動不便者、臥病在床，年老者，或住在偏遠農村的婦女、或是連續三年都不做子宮頸抹片檢查等；我們設計了一套自採檢體檢測的方法，目的是評估可否用於篩檢這四類族群的婦女，提早檢測出癌前期或癌，並比較由醫師取樣或病人自我取樣人類乳突狀病毒的結果作一分析。

方 法：本計畫採前瞻性研究執行，從1997年9月到1999年9月取樣年？20歲到80歲共1194位婦女，先在家自我收集檢體，並於3天內，將檢體送到婦產科門診並由醫師依一般程序，在陰道補助下，取再一次檢體作人類乳突狀病毒去氧核醣核酸檢測，並用木棒或刷子再作一次抹片檢查。若懷疑有不正常抹片，則先以5%醋酸塗抹，再以陰道鏡檢查，我們對病人自我採集的檢體和醫師採集的檢體，作人類乳突狀病毒感染去氧核醣核酸的檢測，並比較對子宮頸癌及癌前期的診斷作一分析。

結 果：在1194位婦女中，有144位自我取樣的婦女，佔全收集婦女的12.1%，及155位醫師取樣的婦女佔全收集婦女的13%。其人類乳突狀病毒去氧核醣核酸檢驗呈陽性反應，在統計比較上而言，醫師取樣和病人自我取樣並無明顯差異，而在自我取樣方面，人類乳突狀病毒去氧核醣核酸檢驗敏感度為96.3%，高於抹片檢查的79.2%，而偽陽率則是人類乳突狀病毒去氧核醣核酸檢驗的3.7%，(2/53)及抹片檢查的20.8% (11/53)。

藉由人類乳突狀病毒去氧核醣核酸檢驗自我檢測及診斷癌前期癌者，有23位為子宮頸上皮細胞變性第I期，10位為第II期，16位第III期，及子宮頸癌有2位。

結 論：本計畫結果顯示病人自採検体或医师採檢對人類乳突狀病毒檢測的可靠性相符，所以針對不易接受子宮頸癌篩檢的婦女，可由病人自我取樣再送人類乳突狀病毒檢驗，以期提早篩檢出子宮頸癌前期或癌，本方式對行動不便者、臥病在床、年老者，及住偏遠農村的婦女提供一方便的子宮頸高危險群篩檢的輔助方式。

(長庚醫誌 2002:25:664-71)

關鍵字：子宮頸癌，子宮頸上皮細胞變性，抹片檢查，人類乳突狀病毒，人類乳突狀病毒檢測法。

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