Original Article

Roles of Self-Sampling for Human Papillomavirus in Developing Countries

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Objective: To evaluate whether or not self-sampling for human papilloma virus (HPV) infection in developing countries is acceptable and sensitive.

Materials and Methods: A sub-group analysis of a previous review published by Madzima et al. The primary outcome of the present study was either acceptability or sensitivity of HPV self-sampling compared with the Pap test.

Results: There were 43 relevant studies, four of which were conducted in developing countries. Three studies assessed the acceptability of the self-sampling method and one evaluated its sensitivity. There were 21,965 eligible participants. The acceptability rate of self-sampling was 82 to 98%, and its sensitivity was 4.2 times better than cytology in cases of invasive cervical cancer.

Conclusion: Self-sampling for HPV is highly acceptable and may be more sensitive than cervical cytology in developing countries.

Keywords: Acceptability, Human papilloma virus, Self-sampling test, Sensitivity

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Cervical cancer is a common genitourinary tract cancer, particularly in developing countries. According to 2012 global cancer statistics, the age-standardized rate (ASR) was almost double in less developed areas compared with more developed areas (9.9 vs. 15.7 per 10,000 population)[1]. In addition, the mortality rate of cervical cancer in less developed areas was almost triple that in developed areas (3.3 vs. 8.3 per 100,000 population). According to these data, cervical cancer is the second most common cancer and third most common cause of cancer deaths in developing countries. Cervical cancer has been shown to be the leading cause of mortality in African and Central American women[2].

Human papillomavirus (HPV) is a common genital infection. Approximately 75 to 80% of adults are infected by the HPV by age 50[3,4]. At least 15 HPV types are related to cancer, HPV16 and 18 are particularly strongly linked to cervical cancer. In a previous study, up to 99.7% of cervical cancer patients were found to have HPV. The persistence of HPV infection causes cervical neoplasia, followed by carcinoma development and membrane invasion[6]. Human papillomavirus infection has been shown to be related to both squamous cell carcinoma and adenocarcinoma[7]. Human papillomavirus 16 was found in 59% of patients with squamous cell carcinoma and 36% of patients with adenocarcinoma. In contrast to developing countries, the incidence and mortality rates of cervical cancer have decreased by 75% in developed countries[8,9]. Cervical cancer screening programs and HPV vaccination are the two main reasons for these reductions. The HPV vaccination may prevent cervical cancer and cervical cancer deaths by 34% and 18%, respectively[10].

The two effective methods for cervical cancer screening are the Papanicolaou (Pap) cytology test and HPV testing. The Pap test has been found to reduce risk of invasive cervical cancer by 65%, and HPV testing may be even 60 to 70% more effective than the Pap test[11,12]. The main disadvantage of Pap and HPV testing is that they require that the patient undergo a medical procedure as part of gynecological examination, resulting in embarrassment or discomfort. Self-sampling is an alternative option for HPV testing[13]. Soisson et al found that 771 out of 775 US women (99%) were able to provide adequate specimens for cytologic evaluation through self-sampling. A recent review also found that self-sampling for HPV testing is acceptable and valid[14]. However, most studies in the review were conducted in

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developed countries, where people tend to be more educated. The present study aimed to evaluate the acceptability and diagnostic properties of self-sampling in developing countries where cervical cancer is more common, people are less educated, and resources are limited[15].

Materials and Methods

The present study was a sub-group review of the previous published article: focused on studies conducted in developing countries[14]. The details of the literature search were described elsewhere[14]. The authors defined countries as "developing" in accordance with the definition laid out by the United Nations[16]. Articles were excluded if we were unable to access the full text, they were not in English, or they were conference papers. Data were extracted relating to the following aspects: study design, study location, inclusion criteria, exclusion criteria, numbers of participants, outcomes, and limitations.

The primary outcome of this review was either acceptability or sensitivity of self-sampling compared with the Pap test. Acceptability of self-sampling could be assessed using any methodology (such as interview or questionnaire). There were at least seven items that fell under the heading of acceptability including embarrassment, pain, anxiety, discomfort, complexity, relaxation, and confidence. The diagnostic properties of self-sampling were defined by a comparison of self-sampling for HPV testing versus standard HPV testing that was conducted by physicians or other equivalent test used for cervical cancer screening (i.e., the Pap test). The diagnostic properties included sensitivity, specificity, positive predictive value, and negative predictive value. Self-sampling must have been performed using US Food and Drug Administration (FDA)-approved HPV tests. Data were compared and discussed.

Results

There were 43 studies comparing HPV self-sampling with the Pap smear. Of those, five studies (11.63%) were conducted in developing countries. One study was excluded due to there being no full text available. In total, four studies were evaluated and reviewed[17-20]. There were a total of 21,965 eligible participants across these four studies. Three studies assessed the acceptability of self-sampling, and one evaluated its sensitivity. The three studies that evaluated the acceptability of self-sampling for HPV were conducted in Mexico, Thailand, and Cameroon in 2002, 2014, and 2015, respectively (Table 1).

The study from Mexico had the highest number of participants (1,069 women). All of the studies included women aged between 20 and 65 years with mean ages of 40.6 to 43 years. The eligible women in these studies came from various backgrounds. The studies conducted in Thailand and Mexico included women from all over the respective countries, but the study conducted in Cameroon only included women from a low-income area in Tiko. The women in the Thai and Mexican studies had experience with both self-sampling and the Pap smear, but some women from the Cameroon study had experience only with the Pap smear. The evaluation method used in the Thailand and Cameroon studies was a questionnaire, while the study from Mexico interviewed randomly sampled participants.

The acceptability rates of the studies conducted in Thailand, Cameroon, and Mexico were 82%, 95.6%, and 98%, respectively. The main reason for the high acceptability rate was privacy in the latter two studies, while less pain was the main reason in the study from Thailand. The other advantages of self-sampling were low cost (82% of participants in the Thai study), lack of anxiety (91.3% of participants in the Cameroon study), lack of pain (87.8% of participants in the Cameroon study), and comfort (85% of participants in the Cameroon study and 71.2% of participants in the Mexican study). In the Mexican study, 68% of women chose self-sampling over a Pap smear, but 34% of women in the Thai study were not sure if they had performed the self-sampling correctly. The study also commented on the need for a further large-scale study on the effectiveness of self-sampling for HPV screening in various Asian and/or developing countries.

There was only one study conducted to compare sensitivity of self-sampling with the Pap smear. This was a study from Mexico published in 2011. Women aged between 25 and 65 years were enrolled from rural areas in three Mexican states. There were 20,256 women who participated the study, 9,202 (45.43%) of whom were assigned self-sampling and 11,054 (54.57%) of whom were assigned a Pap smear. The HPV infection rate was found to be 9.61% (884 out of 9,202 women). The rates of positive cervical biopsy in women who conducted self-sampling and those that underwent the Pap test were 2.66% (245/9,202) and 0.38% (42/11,045), respectively.

Self-sampling for HPV had better sensitivity to detect all stages of cervical cancer according to protocol analysis and almost all stages of cervical cancer (except CIN3) according to intention (Table 2) compared with the Pap test. The sensitivity to detect cervical intraepithelial neoplasia 3 (CIN3) almost reached statistical significance (95% confidence interval of 1.0 to 4.1). The highest relative sensitivity was for CIN1 (41.1) according to protocol analysis. Self-sampling had a much lower positive predictive value to detect CIN2 in all three age groups. For example, the positive predictive value of self-sampling in women 25 to 65 years old was 12.2%, while the pap test had a positive predictive value of 90.5%.

Discussion

There were only three studies available that had been conducted in developing countries. Similar to studies conducted in developed countries[14], these studies showed that self-sampling was highly acceptable, with an average acceptability rate of 91.87% (Table 1). Of the seven aspects of acceptability that were examined, four had satisfaction rates over 80% including embarrassment, pain, anxiety, and discomfort (Table 1). However, although 68 to 82% of women in these three studies from developing countries preferred

Table 1. acceptability outcomes of self-sampling for human papilloma virus detection in developing countries

Factors	Study 1 [17]	Study 2 [18]	Study 3 [19]
Country	Thailand	Cameroon	Mexico
Year	2014	2015	2002
Numbers of participants	100 women	540 women	1,069 women
Inclusion criteria	- Age 30 to 65 y (Mean 40.6 y) - Intact cervix - Across Thailand - Various backgrounds -Every participant underwent both self-sampling and PAP.	- Age 30 to 65 y (Mean 43 y) - From city of Tiko and low -income neighborhood of Yaounde - Different background, education, knowledge, age, socio-professional class. - Some participants underwent PAP.	- Age 20 y and older under Mexican Institution of social security (IMSS) coverage - Different monthly household income. - Every participant underwent both self- sampling and PAP.
Test performed	- All participants performed self-sampling and underwent a Pap test. -Questionnaires were given to participants which consisted of questions regarding 1) Particpants' personal information and 2) Participants' acceptability	-Written and oral instruction about how to perform the test were delivered to the participants. -Questionnaires were given out. - Participants who underwent the Pap test were asked about their personal preferences.	- Women were randomly selected among participants from a larger study. - All participants performed self-sampling and underwent a Pap test. - Each woman was interviewed about her experiences and opinions.
Primary outcome (highest rate)	82% acceptability (felt less pain in comparison to the Pap test)	95.6% acceptability no embarrassment)	98% acceptability (Privacy advantage)
Other outcomes			
1.	82% would use a self-sampling kit if the price was less than 1,000 Thai baht (33.12 Thai baht = 1 USD).	91.3% No anxiety	68% chose self-sampling over the Pap test.
2.	34% of participants didn't believe in their ability to perform the test.	87.8% No pain	71.2% felt more comfortable with self-sampling than undergoing a Pap test.
3.		85% No discomfort	55.8% felt less embarrassed conducting self-sampling than undergoing a Pap test.
Other comments	The patients in this study may have different cultures, beliefs, and behavior from those in studies conducted in Western countries, leading to different acceptability results.	Further evaluation of the intervention in a larger sample and using a control group is recommended.	The authors believe it is necessary to develop strategies that go beyond screening promotion and can potentially change screening practices to convince women that early detection is effective.

self-sampling for HPV testing, 34% of women from the Thai study were not confident in their ability to collect the samples (Table 1 correctly)[17,19]. This limitation of self-sampling has also been found in developed countries and Muslim women[21,22].

Unlike in studies conducted in developed countries, there was no head to head comparison between self-sampling for HPV testing and sampling by clinicians in these studies[13]. In addition, there was only one study that compared self-sampling with an alternative method (the Pap test). Self-sampling for HPV had higher sensitivities to detect CIN and invasive cervical cancer than the Pap test (Table 2). However, it had a much lower positive predictive value (particularly for CIN2) leading to a higher proportion of patients undergoing colposcopy and greater costs[20]. Note that the predictive values may depend on the prevalence of cervical cancer. Likelihood ratios should be calculated to avoid the effects of prevalence.

The main limitation of this review was the small number of eligible studies, which means that the results may not be applicable in all developing countries. Secondly, cost-effectiveness was not examined. Further studies to evaluate

Table 2. sensitivity of self-sampling for human papilloma virus (HPV) detection compared with the Pap smear for cervical cancer detection in developing countries

Factors	Study 4 [20]
Country	Mexico
Year	2011
Number of participants	20,256 women
Inclusion criteria	-Age 25 to 65 y -From 540 medically underserved areas in Morelos, Guerrero, and State of Mexico
Study design	Randomized controlled trial
Methods	HPV test Mobile colposcopy Cervical biopsy
Comparator	Pap test
Gold standard	Cervical biopsy
Outcomes by protocol	Relative sensitivity of self-sampling over the Pap test
CIN 1	41.1 (15.2 to 111.2)
CIN 2	3.6 (2.2 to 6.0)
CIN 3	2.4 (1.1 to 5.1)
Invasive cervical cancer	4.2 (1.9 to 9.2)
CIN 2 or worse	3.4 (2.4 to 4.9)
CIN 3 or worse	3.2 (1.9 to 5.5)
Outcomes by intention	Relative sensitivity of self-sampling over the Pap test
CIN 1	35.4 (13.1 to 95.6)
CIN 2	3.1 (1.9 to 5.0)
CIN 3	2.0 (1.0 to 4.1)
Invasive cervical cancer	3.6 (1.6 to 7.9)
CIN 2 or worse	2.9 (2.0 to 4.1)
CIN 3 or worse	2.7 (1.6 to 4.5)
Outcomes by age group	PPV of self-method vs pap test for CIN 2 or worse
25 to 65 years	12.2 vs. 90.5
30 to 65 years	14.5 vs. 17.4
35 to 65 years	16.6 vs. 92.0
Other comments	High false positive HPV test No confirmation test for negative women

this issue are needed to facilitate the use of self-sampling for HPV testing. In addition, Pubmed and Embase were the only databases used in the present study. There may be other studies available in other databases. Lastly, only the sensitivity and positive predictive value of self-sampling were shown and compared with those of the Pap test. The specificity, negative predictive value, and likelihood ratios were not evaluated.

Conclusion

Self-sampling for HPV is highly acceptable and may be more sensitive than cervical cytology in developing countries.

What is already known on this topic?

Self-sampling for HPV is highly acceptable and may be more sensitive than cervical cytology in developed countries.

What this study adds?

Self-sampling for HPV is highly acceptable and may be more sensitive than cervical cytology in developing countries.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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บทบาทของการตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองในประเทศกำลังพัฒนา

ศรมน ชัยชาญ, กิตติศักดิ์ สวรรยาวิสุทธิ์, ปณิตา ลิมปะวัฒนะ, ปิยกาญจน์ วัชเรนทร์วงศ์, จาริญญ์ จินดาประเสริฐ, วีรจิตต์ โชติมงคล, กรรณิการ์ คงบุญเกียรติ, ไพบูรณ์ จัตกุล, ยุวเรศมคธ์ สิทธิชาญบัญชา, สิทธิชัย คำใสย์

วัตถุประสงค์: เพื่อประเมินว่าการตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองในประเทศกำลังพัฒนาเป็นที่ยอมรับและมีความไวหรือไม่

วัสดุและวิธีการ: เป็นการวิเคราะห์กลุ่มย่อยของงานวิจัยที่ได้ตีพิมพ์แล้วโดย Madzima และคณะ ผลลัพธ์หลักของการศึกษานี้คือ การยอมรับและความไวของการตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองเปรียบเทียบกับการตรวจ Pap

ผลการศึกษา: มีการศึกษาจำนวน 43 การศึกษาที่มีความสัมพันธ์กับหัวข้อการศึกษา มี 4 การศึกษาที่ดำเนินการวิจัยในประเทศกำลังพัฒนาโดย 3 การศึกษาประเมินความยอมรับได้ของการตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองและมี 1 การศึกษาที่ประเมินความไวของการตรวจ มีผู้เข้าร่วมการศึกษาทั้งหมด 21,965 คน อัตราการยอมรับได้ของการตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองคือ ร้อยละ 82 ถึง 98 และมีความไว 4.2 เท่าเมื่อเทียบกับการตรวจทางเซลล์วิทยาในกรณีของมะเร็งปากมดลูกชนิด invasive

สรุป: การตรวจหาเชื้อไวรัส Human Papillomavirus ด้วยตนเองเป็นที่ยอมรับเป็นอย่างดีและมีความไวมากกว่าการตรวจทางเซลล์วิทยาของปากมดลูกในประเทศกำลังพัฒนา