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IN PRACTICE

Comparison of non-invasive sampling methods for detection of HPV in rural African women

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Background: The prevalence of cervical cancer is extremely high in low income countries, primarily because of a lack of cytological screening. The link between human papillomavirus (HPV) and cervical cancer has long been recognised, and it has been suggested that isolated HPV testing in women who do not participate in existing screening programmes may be used to identify women at higher risk of developing cervical cancer. This community based study compares two self administered techniques for detecting HPV (tampons and self administered swabs) with a clinician directed technique, the cervical cytobrush.

Methods: 377 rural women were interviewed and of these 210 women had full gynaecological examination, and accepted all three sampling methods for HPV. HPV typing of DNA extracts was performed using polymerase chain reaction and enzyme linked immunosorbent assay techniques.

Results: Using the cervical cytobrush as the gold standard, self administered swabs (SAS) showed a sensitivity of 63.9%, and tampons showed a sensitivity of 72.4%. The acceptability of these two tests was 97.1% and 84.6% respectively. When combining acceptability with sensitivity, the SAS detected 61.9% and the tampons detected 60.9% of the true positives.

Conclusion: In a setting where women are at a considerable risk of developing cervical cancer, with no access to a formal screening programme, self directed HPV testing could be a useful screening tool in identifying those women at increased risk who may require further investigation.

Cervical cancer affects approximately 500 000 women each year¹; 80% of these cases occur in the developing world where it is by far the commonest cancer in women.² Here, morbidity and mortality are high because cytological screening is not readily available and women tend to present late with advanced stage disease when treatment options are limited.

The link between human papillomavirus (HPV) and cervical cancer has long been recognised^{1–4} and the detection of HPV has been used as an adjunct to cervical cytology to identify women who are at risk of developing cervical cancer.^{5–6} Although it is recognised that this is the best use of HPV testing, isolated HPV testing in women who do not participate in existing screening programmes may be useful.⁷

Now that HPV vaccines are being developed and tested, there is a need to test for HPV in low income countries, in both the field and clinic settings. The purpose of this study is to compare the acceptability and sensitivity of two different types of non-invasive techniques for detecting HPV (self administered swabs and tampons) with a clinician directed technique, the cervical cytobrush.

METHODS

Between February and June 2002, women who had previously been screened for HPV in a reproductive morbidity survey (RMS)⁸ were recruited from a rural area of the Gambia. All women from the RMS who had previously accepted a speculum examination were invited to participate in the present study. Those who were pregnant at the time of interview were excluded from the study.

Women were interviewed by a female gynaecologist, and were then verbally instructed to collect a vaginal sample using a sterile self administered Dacron swab (SAS) inserted high into the vagina and rotated five times, witnessed by the doctor. The sample was then placed in phosphate buffered saline and stored in a cool box until the end of the day when it was frozen and stored at -70°C . Cervical smears were taken, and HPV sampling was performed by inserting a cytobrush into the cervix and rotating it through 360° . This was placed immediately in 1 ml of phosphate buffered saline, kept in a cool box until the end of the day, then stored at -70°C . Finally, the participants were asked to insert a tampon into the vagina, which was removed 1 hour later and stored in a cool box until the end of the day when the contents of the tampon were then expelled into phosphate buffered saline and stored at -70°C . Women were examined and treated for reproductive tract infections in agreement with WHO syndromic management guidelines. Cervical smears were assessed at the Department of Pathology, Llandough Hospital, Cardiff, UK, and were classified by the Bethesda system. Those women with abnormal cytology were offered treatment.

DNA was extracted from samples using QIAmp DNA mini-kit (Quiagen Ltd, Crawley, UK) and HPV polymerase chain reaction (PCR) was performed as described previously.⁹ Specimens were HPV typed using enzyme linked immunosorbent assay (ELISA) and monospecific probes.

RESULTS

In all, 377 of the 946 eligible women attended for interview (39.9%). Table 1 shows the proportions of women accepting each test; 224 women accepted all three sampling methods (59.4%), and of these, 210 were β globin positive or HPV positive and can be used for comparison (55.7%).

χ^2 Tests showed that there was no significant difference in the proportions with DNA detected, or in the prevalence of HPV between the three sampling methods.

Of the 210 women for whom HPV results were available in all three samples, 36 were positive for HPV in the cervical cytobrush specimen. Using this as the gold standard, the tampons had a sensitivity of 72.2% (95% CI 57.6% to 86.8%) and a specificity of 92.5%, with a positive predictive value of 66.7% and a negative predictive value of 94%; the SAS had a

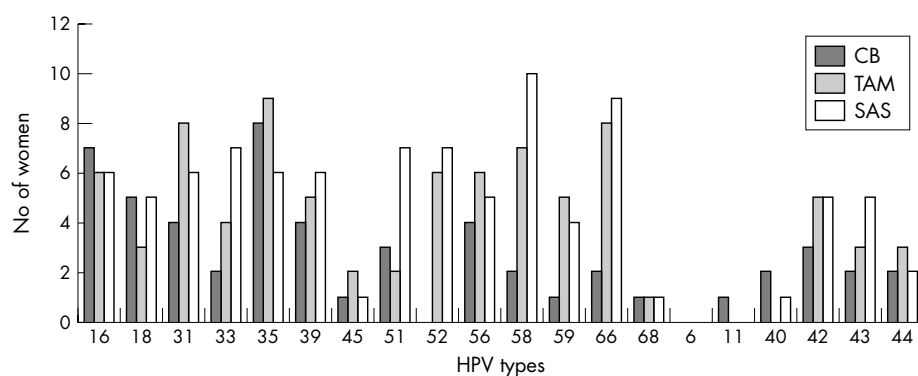
Abbreviations: ELISA, enzyme linked immunosorbent assay; HPV, human papillomavirus; PCR, polymerase chain reaction; RMS, reproductive morbidity survey; SAS, self administered swabs

Table 1 Acceptability of each test, efficiency at collecting DNA, and prevalence of HPV

Sampling method	% Accepting test (number accepting out of 377) (n*)	% with DNA (n*)	% with HPV (n*)	Sensitivity of test	% True positives detected adjusting for acceptability
Cervical brush	72.4% (273)	97.9 (273)	15.3 (268)	100	72.4
Tampon	84.4% (318)	97.4 (318)	17.4 (310)	72.2	60.9
Self administered swab	97.1% (366)	98.9 (366)	16.3 (362)	63.7	61.9
Tampon + self administered swab	82.5% (311)	96.1 (299)	22.8 (298)†	77.8	64.2

*Total number of women tested.

†HPV in either sample.

**Figure 1** HPV types in the three different sampling methods. CB, cytobrush; TAM, tampon; SAS, self administered swabs.

sensitivity of 63.9% (51.9% to 83.3%), and a specificity of 93.7%, with a positive predictive value of 67.6% and a negative predictive value of 92.6%.

When acceptability of the sampling method was combined with the sensitivity of the test, the self administered tampon and swab detected 60.9% and 61.9% of the true positives, respectively, compared with 72.4% by the cervical cytobrush method (table 1).

If the SAS and tampon tests are combined, such that the result is considered positive if either test is positive, then compared to SAS alone, the combined test shows a significant increase in sensitivity (with cervical brushes as the gold standard) of 14% (3% to 25%) and a significant decrease in specificity of 5% (3% to 9%). However, once acceptability has been taken into account, there is little gain in the proportion of true positives detected by combining the two tests (table 1).

For all three sampling methods, high risk HPV types were more prevalent in our sample, than low risk types. Figure 1 shows the distribution of HPV types in this population, using the three different sampling methods.

DISCUSSION

The study described in this paper is one of the very rare community studies in a selected population of women based in a country that is unable to offer a formal screening programme for cervical cancer. In such low income countries where health infrastructure is poor, HPV testing has the potential to be a valuable tool for the prevention of cervical cancer.

Previous studies have looked at the possibility of different methods of sampling cervical DNA in order to diagnose both cytological abnormalities and those women who are at higher risk of cervical cancer—those with persistent high risk HPV infection.¹⁰

Several studies have shown that clinician directed testing for HPV has a sensitivity for detection of high grade lesions or cervical cancer that is equivalent or superior to that of cytology. Ogilvie *et al* (Diagnostic accuracy of self obtained

HPV cervical-vaginal samples vs clinician obtained samples: a systematic review, 2003: unpublished) reviewed the diagnostic accuracy of self obtained HPV cervicovaginal samples verses clinician obtained samples. They found that in all studies reviewed, the sensitivity and specificity were diminished when patients collected their own samples. This was consistent with our findings. The sensitivity of the SAS in our population was 63.7%, which is slightly lower than in other similar studies; however, it is important to note that in previous studies women were often recruited from colposcopy or genitourinary medicine clinics, or have known cervical cancer. These women are likely to have a higher HPV viral load in their cervico-vaginal secretions, which is easier to detect in self collected samples.

Studies of SAS and tampons performed in industrialised countries takes place in a society where tampon use is common.¹¹ This is not the case in the Gambia, and little has been done to assess the acceptability of different types of sampling in sub-Saharan Africa. While less than half of the invited women took part in our study, SAS was highly acceptable among those who did. The acceptability of tampons was slightly lower, but still higher than for the clinician directed cervical cytobrush. Among participating women, each of the self directed methods detected approximately 60% of true positives. This would identify a substantial proportion of women who may be at higher risk of developing precancerous or cancerous change in the cervix. Further research is needed to explore how a screening programme based on HPV detection could operate within low income countries with poor health infrastructure. Further socioeconomic analysis is required to assess the effectiveness of self directed HPV testing as a screening strategy.

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CONTRIBUTORS

LB, GW, PS, LM, and BW were responsible for study design, and NL carried out field work, gynaecological examinations, laboratory analysis (including HPV testing and typing) and drafting of the paper; BW was also responsible for supervision of laboratory work; GE was involved in field work and was also one of the two gynaecologists on the study; DJ and LM performed the statistical analysis and, with PS, were responsible for interpretation of results; all authors were involved in reviewing drafts of the paper, and contributed to the final version.

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