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The Role of Self-Collection by Vaginal Lavage for the Detection of HPV and High-Grade Intraepithelial Neoplasia

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Keywords
Secondary prevention · Papillomavirus infections · Cervical neoplasms · Molecular diagnostic techniques · Self-collection

Abstract
Objective: To compare the results of cervical cytology and high-risk HPV tests using samples obtained using two different collection modalities in a population of Brazilian women: self-collection (vaginal lavage) and cervical Pap testing. ***Methods:*** We enrolled 204 women who were aged 18–64 years and had previously obtained abnormal cervical cytology test results; 83.8% of them agreed to participate. The sample was divided into two aliquots: one for the cytological study and one for the molecular analysis of high-risk HPV. ***Results:*** Fifty-eight percent of the participants preferred to utilize self-collection as an alternative screening method. However, we noticed that the HPV positivity rate was significantly lower in self-collected samples when compared to those obtained using the conventional collection method ($p = 0.035$). The cytology tests of the samples obtained via self-collection were sensitive and had a positive predictive value and an area under the curve (AUC) that were significantly lower than those of the Pap test. However, the specificity and negative predictive value of these tests were similar. When compared with the HPV test, the self-collected samples demonstrated lower accuracy in predicting high-grade cervical intraepithelial neoplasia or worse, with a significantly lower sensitivity, positive predictive value, and AUC than the cervical Pap test samples. ***Conclusion:*** Self-collection by vaginal lavage is simple and well accepted by women. Due to its limitations, however, self-collection by lavage should be utilized with caution.

Introduction

Cervical cancer is a major public health problem, being the third leading cancer in women worldwide, following only breast and colorectal cancer. Approximately 500,000

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new cases and 280,000 deaths occur due to cervical cancer annually worldwide [1, 2].

High-risk HPV DNA testing is more sensitive than cytology in detecting precancerous lesions, as one of the main advantages of its use is the prolonged tracking period, even if this requires organized screening programs with strict protocols, monitoring, and tracing [3]. Self-collection should be offered as an option to women, especially those facing barriers to screening. Self-collection of cervicovaginal material via lavage may serve as a good tool to facilitate women's participation in cervical cancer screening programs [4].

In Brazil, cervical cancer remains a major public health issue, causing significant morbidity and mortality among women [5]. In spite of the government's efforts to reduce the rates of cervical cancer incidence and mortality in Brazil, the results of the screening program, which was based on cervical cytology, remain disappointing. Novel mechanisms by which to explore cervical cancer screening are necessary for a more effective control of this disease in the Brazilian setting.

The goal of this study was to compare the results of cervical cytology and high-risk HPV testing on samples obtained using two different collection methods in a population of Brazilian women: self-collection (vaginal lavage) and conventional collection (Pap test) by a doctor.

Subjects and Methods

The study included women aged 18–64 years who were referred to the Colposcopy Ambulatory of the Prevention Department at Barretos Cancer Hospital (Brazil) due to abnormal (atypical squamous cells of uncertain significance or worse) cervical cytology test results (Pap smear) from April 2013 to March 2014.

Once adequately informed about the study, the women received a syringe containing 20 mL of 0.9% sodium chloride solution that was attached to a urethral catheter No. 18. The women were instructed to lie comfortably on a stretcher and gently introduce the urethral probe approximately 10 cm or as deep as possible into the vagina and inject all of the saline solution (self-collection). Immediately after infusion of the saline solution, the women aspirated the fluid into the syringe. The recovered fluid (average volume 10 mL) was then transferred to an ethanol-based liquid medium for preservation and transport (SurePath; Becton, Dickinson and Company, Research Triangle Park, NC, USA). Figure 1 shows the materials used to perform the lavage.

When this step was completed, the women underwent gynecologic and colposcopy examinations (in the same room), which were performed by the attending physician. Prior to colposcopy, the medical doctor collected cervical material from the cervix (standard collection), sampled the ecto- and endocervix with a specific brush indicated for this purpose (Rovers; Rovers Medical Devices, Oss, The Netherlands), and transferred the material to a second flask containing an ethanol-based liquid medium (SurePath). When the collection was completed, colposcopy and biopsy of the cervix were performed whenever indicated.

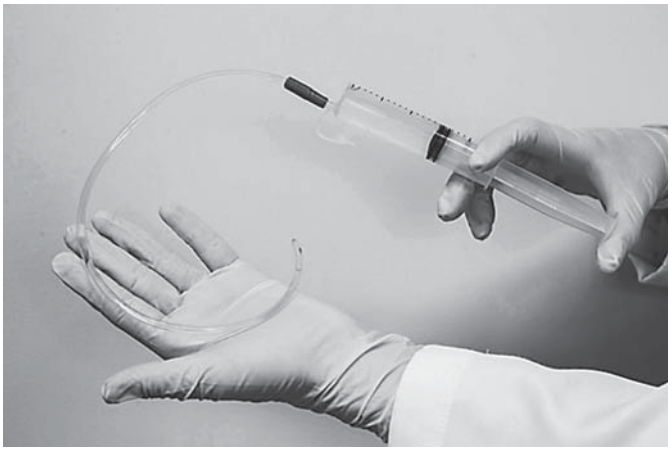

Fig. 1. The materials used to carry out the lavage: a syringe filled with 20 mL of 0.9% saline solution and a urethral probe.

When the colposcopy examination was completed, the women replied to a questionnaire about their acceptance of the self-collection procedure (vaginal lavage). Illiterate women were interviewed by two study coordinators trained and experienced in the administration of medical surveys. The researcher wrote down the results of the colposcopy examinations, cytological examination, hybrid capture, and histopathology (when the biopsy was considered necessary) for each woman on dedicated forms.

Figure 2 summarizes the distribution of the cases according to the collected material and tests performed. Overall, 204 women were recruited into this study, of whom 171 (83.8%) agreed to participate and signed the informed consent form. The main reasons for refusal were as follows: the procedure was considered difficult (27%); pain (21%); they preferred that the physician did the procedure (9%); fear/anxiety (6%); shame/embarrassment (3%); and other (34%). Of the participants, 30 were unable to perform the self-collection.

The samples were forwarded to the Pathological Anatomy Laboratory at Barretos Cancer Hospital for proper processing and reading. They were divided into two aliquots: one for the cytological study and another for the molecular analysis of high-risk HPV. The preparation of slides for cytology, as well as coloring, was completed in an automated fashion with the PrepMate™/PrepStain™ system (Becton, Dickinson and Company) according to the protocols of the hospital's pathology department and the manufacturer's recommendations. Reading of the slides was performed manually by a single blinded cytotechnologist employed at the pathology department and experienced in such readings who did not have knowledge of the type of collection being carried out. Ten percent of the negatives and all positives were reviewed by a single expert pathologist (C.S.-N.).

High-risk HPV testing was carried out using the Hybrid Capture 2™ test (Qiagen, Hilden, Germany). The test was performed according to the manufacturer's guidelines.

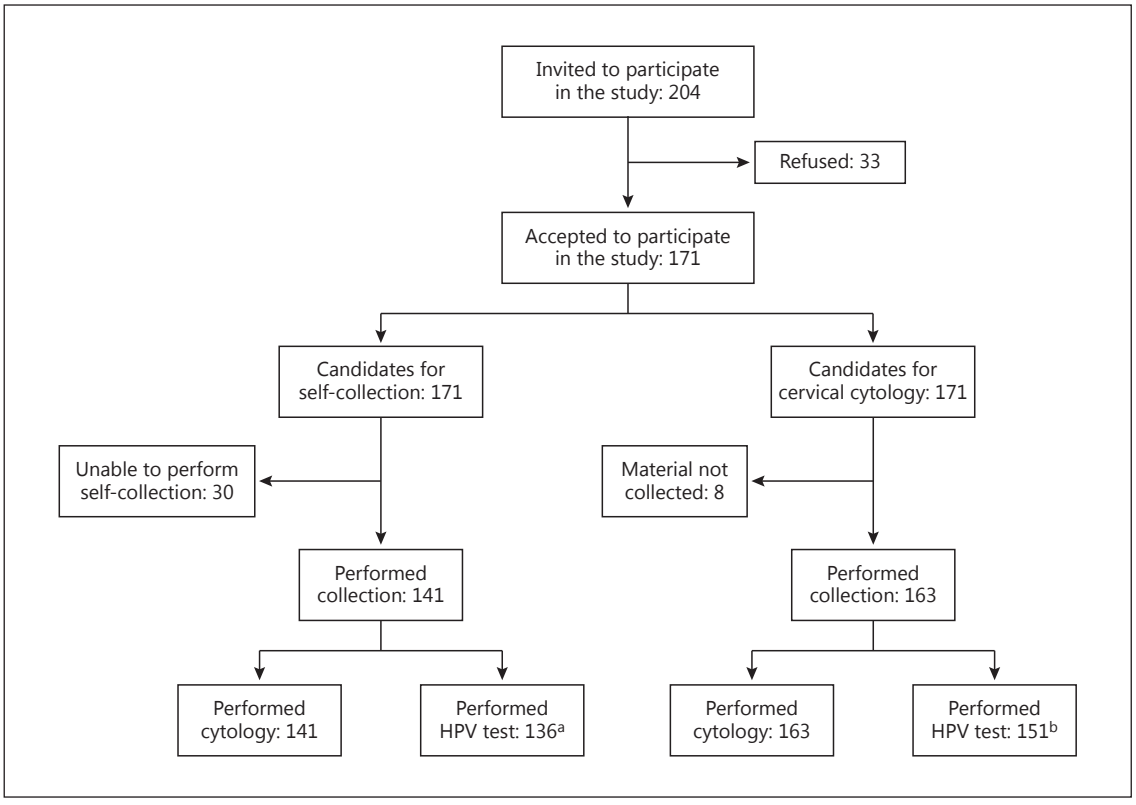

Fig. 2. Distribution of cases according to collected material and tests performed. [a] Five tests were not performed due to insufficient material. [b] Twelve tests were not performed due to insufficient material.

Table 1. Characteristics of the study population according to sociodemographic factors, sexual habits, reproductive history, and colposcopy and cervical biopsy results (n = 163)

Variable	Category	Subjects, n (%)	Average (SD)
Age	<25 years	19 (11.7)	
	25–45 years	83 (50.9)	
	46–64 years	61 (37.4)	
Educational level	No schooling (illiterate)	6 (3.7)	
	Elementary school	78 (47.9)	
	High school	62 (38.0)	
	Higher education	17 (10.4)	
Age at first intercourse, years	–	–	17.3 (3.2)
Number of sex partners (n = 159)	–	–	3.5 (4.5)
Number of children	–	–	2.3 (1.6)
Cervical biopsy	No lesion	35 (36.5)	
	CIN 1	27 (28.1)	
	CIN 2/3	25 (26.0)	
	Adenocarcinoma in situ	1 (1.0)	
	Invasive carcinoma	2 (2.1)	
	Insufficient material	3 (3.1)	
	Other	3 (3.1)	

Table 2. Numbers and percentages of cases according to their responses to the acceptance questionnaire assessing sample collection via vaginal lavage

Question	Answer	*n* (%)
Did you have trouble understanding how to carry out the exam?	No	143 (89.4)
	A little	13 (8.1)
	Moderately/a lot	4 (2.6)
Was it difficult to carry out the procedure lying down on the stretcher?	No	136 (85.0)
	A little	15 (9.4)
	Moderately/a lot	9 (5.7)
Were there any difficulties when inserting the probe into the vagina?	No	138 (86.3)
	A little	13 (8.1)
	Moderately/a lot	9 (5.7)
Was there any difficulty when injecting the liquid into the vagina?	No	143 (86.3)
	A little	13 (8.1)
	Moderately/a lot	4 (5.7)
Was there any discomfort when aspirating the liquid injected into the vagina?	No	90 (56.3)
	A little	39 (24.4)
	Moderately/a lot	31 (19.4)
Did the liquid you injected trickle out of the vagina?	No	23 (14.4)
	A little	46 (28.8)
	Moderately/a lot	90 (56.4)
Was it easy to use this method of collection?	Easy	112 (70.0)
	A little difficult	22 (13.8)
	Moderately/very difficult	26 (16.3)
Do you think this collection method caused any embarrassment or shame?	No	149 (93.7)
	A little	7 (4.4)
	Moderately/a lot	3 (1.9)
Did you find that this collection method was uncomfortable?	No	142 (88.8)
	A little	15 (9.4)
	Moderately/a lot	3 (1.9)
Which collection method do you prefer?	Self-collection	94 (58.8)
	Health professional	46 (28.8)
	It doesn't matter	19 (11.9)
	I don't know	1 (0.6)

Statistical Analysis

The results of the tests were examined using descriptive statistics. The McNemar test was used to compare percentages between paired groups. Concordance between the cytology results and the HPV test results was evaluated by the kappa statistic. The efficacy of both collection mechanisms in predicting the presence of precursor/invasive lesions of the cervix was measured by determining their sensitivity, specificity, and predictive values (negative and positive).

For these calculations, cervical biopsy or conization products were considered as the gold standard for examinations. Cases with cervical biopsies that indicated the presence of high-grade cervical intraepithelial neoplasia or worse (CIN 2+) were considered positive. Cases with adequate colposcopy and an absence of findings that warranted biopsy of the cervix were classified as negative. The respective accuracy indicators and their corresponding 95% confidence intervals (sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve [AUC]) as well as the concordance value were calculated so that the collection methods could be compared. For sample size calculation, the following assumptions were made: (1) a sensitivity of 65% and a specificity of 85% for cervical cytology examinations performed using water; (2) an accuracy of 0.15; (3) an α error of 5%; (4) an estimated prevalence of cervical disease of 30% in an outpatient high-risk population (colposcopy ambulatory); and (5) a loss of 1.0% (poor or missing material). Thus, the estimated sample size was approximately 150 women.

Results

Table 1 summarizes the characteristics of the study population. Most women were older than 25 years, were married or cohabiting with a partner, were white, had a low level of education, and had a low family income (less than BRL 1,000 a month [approx. USD 300]; data on marital status, race, and family income are not shown in Table 1). On average, the women became sexually active at the age of 17 years, had 2 children, and had a history of 3 sexual partners over their lifetime. All women underwent colposcopy, and in 23.3% of the cases, the squamocolumnar junction was not fully visible (n = 38). Colposcopic abnormalities were found in 74 of 125 women (59.2%) in whom the squamocolumnar junction was fully visible.

Table 2 shows the numbers and percentages of women providing affirmative answers to the questions on acceptance regarding the self-collection method. The responses to the first 4 questions showed that most participants had no problem with understanding and performing the procedure, and that they managed to insert the probe and inject the liquid. Most participants thought the method was easy to perform and not uncomfortable or embarrassing. Fifty-eight percent of the participants reported preferring to use self-collection as an alternative screening method.

Table 3 describes the results of the cervical cytology examination, the glandular representation, and the result of the HPV test (hybrid capture) according to the method of collection utilized.

Table 4 shows the comparison between the results of cervical cytology and HPV testing according to the method of collection used. The glandular representation rate was significantly higher when the standard collection method was used than with the self-collection method ($p < 0.001$). High-grade squamous intraepithelial lesions were diagnosed more frequently when the conventional collection method was used. We also observed that the

Table 3. Distribution of cases according to the results of their cervical cytology examination and HPV testing and the type of collection used

Variable	Category	Self-collection (n = 141), n (%)	Conventional collection (n = 163), n (%)
Result of the cytology examination	No change	97 (68.8)	107 (65.6)
	ASC-US	14 (9.9)	12 (7.4)
	ASC-H	2 (1.4)	3 (1.8)
	LSIL	14 (9.9)	18 (11.0)
	HSIL	1 (0.7)	15 (9.2)
	Invasive	1 (0.7)	1 (0.6)
	Adenocarcinoma in situ	0 (0.0)	1 (0.6)
	Unsatisfactory	12 (8.5)	6 (3.7)
Glandular representation	No	116 (82.3)	27 (16.6)
	Yes	12 (8.5)	129 (79.1)
	Unsatisfactory	13 (9.2)	7 (4.3)
HPV test (hybrid capture)	Negative	95 (69.9)	94 (62.3)
	Positive	41 (30.1)	57 (37.7)

ASC-US, atypical squamous cells of uncertain significance; ASC-H, atypical squamous cells not excluding high-grade lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

Table 4. Comparison of results of the cytological examination and HPV testing according to the type of collection used

Examination result	Category	Self-collection, n (%)	Conventional collection, n (%)	p value[1]
Unsatisfactory cytology	No	129 (91.5)	136 (96.5)	0.118
	Yes	12 (8.5)	5 (3.5)	
Glandular representation	No	129 (91.5)	29 (20.6)	**<0.001**
	Yes	12 (8.5)	112 (79.4)	
ASC-US+	No	94 (75.2)	86 (68.8)	0.291
	Yes	31 (24.8)	39 (31.2)	
ASC-H+	No	108 (86.4)	96 (76.8)	**0.036**
	Yes	17 (13.6)	29 (23.2)	
LSIL+	No	110 (88.0)	98 (78.4)	**0.029**
	Yes	15 (12.0)	27 (21.6)	
HSIL+	No	123 (98.4)	115 (92.0)	**0.008**
	Yes	2 (1.6)	10 (8.0)	
HPV test (hybrid capture)	Negative	90 (70.9)	77 (75.5)	**0.035**
	Positive	37 (29.1)	50 (39.4)	

Bold type denotes significance. ASC-US, atypical squamous cells of uncertain significance; ASC-H, atypical squamous cells not excluding high-grade lesions; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion. [1] McNemar test.

Table 5. Analysis of the accuracy of diagnosing ASC-US+ according to cytology and HPV testing results

Collection method	Statistic	Statistical criterion used for the diagnosis of CIN 2+	
		cytology (ASC-H+)	HPV (+)
Self-collection	Sensitivity, %	33.3 (13.3–59.0)	50.0 (27.2–72.8)
	Specificity, %	87.6 (79.0–93.7)	71.7 (61.4–80.6)
	Positive predictive value, %	35.3 (13.7–62.5)	27.8 (14.2–45.2)
	Negative predictive value, %	86.7 (77.9–92.9)	86.8 (77.1–93.5)
	AUC	0.61 (0.45–0.76)	0.61 (0.47–0.75)
Conventional collection (standard)	Sensitivity, %	71.4 (51.3–86.8)	81.5 (61.2–93.7)
	Specificity, %	86.9 (78.6–92.8)	71.3 (61.0–80.1)
	Positive predictive value, %	60.6 (41.8–77.3)	44.9 (30.7–59.8)
	Negative predictive value, %	91.5 (83.9–96.3)	93.1 (84.5–97.7)
	AUC	0.79 (0.69–0.90)	0.76 (0.66–0.87)

Values in parentheses denote 95% CI. AUC, area under the curve; ASC-US, atypical squamous cells of uncertain significance; ASC-H, atypical squamous cells not excluding high-grade lesions; CIN 2+, high-grade cervical intraepithelial neoplasia or worse.

rate of HPV positivity was significantly lower in self-collected samples than in samples collected conventionally (p = 0.035). We observed a low reproducibility in the HPV tests of the self-collected samples (κ = 0.43; 95% CI: 0.27–0.59).

Table 5 provides the results for the analysis of the accuracy in predicting CIN 2+ according to different diagnostic criteria. Cytology obtained by self-collection demonstrated a sensitivity, positive predictive value, and AUC that were significantly lower than those of standard collection. However, the specificity and negative predictive value were similar for both tests. In comparison with the HPV test, self-collected samples showed lower accuracy in predicting CIN 2+, with a significantly lower sensitivity, positive predictive value, and AUC than with standard collection.

Discussion

According to data from the Brazilian National Household Sample Survey (PNAD), the Pap smear examination coverage rate in Brazil should be greater than 80% [6]. However, when performing a historical analysis of the nearly 81 million Pap tests collected in Brazil from 2006 to 2013, Costa et al. [7] concluded that, in fact, the Pap test coverage was much lower than that reported by the PNAD, especially in the public system that accounted for a large proportion of Pap tests performed on women of the population targeted for screening (between 25 and 64 years old); considering that many women in the target screening population underwent Pap tests and that women usually underwent Pap tests twice a year, one can presume that 80% is unrealistic [7]. This shows the need to innovate and design new screening programs for cervical cancer in Brazil in order to improve Pap test coverage rates.

In the Brazilian setting, self-collection could be an attractive alternative for populations having poor access to health facilities, such as riverine communities in the Amazon region or remote rural areas. Many women who currently do not have Pap tests done at health care facilities due to embarrassment or because of being distant from the collection sites would be included in the national screening program if they were able to self-collect cervicovaginal material. However, a limitation of self-collection is that the cytology examination is poor and not applicable to screening. All analyses of this material should be done via molecular testing. Hence, the Brazilian public health system would need to be ready to perform molecular tests for large-scale HPV DNA detection if a self-collection approach were adopted. Nevertheless, according to the Brazilian Guidelines for Screening of Cervical Cancer, published by the Health Ministry in 2011, HPV testing is not yet recommended as a screening tool in Brazil [5].

Several studies have shown that self-collection is well accepted by most women, being an attractive alternative strategy for cervical cancer screening, especially in hard-to-reach and remote areas [8–15]. In Brazil, a limited

number of publications have evaluated self-collection as an alternative method [16–18]. A study conducted by Lorenzi et al. [19] included 2,000 randomly selected female candidates for screening of cervical cancer and divided them into two groups: one group carried out self-collection using a tapered brush inserted into the vagina, the other group underwent conventional collection performed by a health professional, using a brush and spatula. Using a modified hybrid capture test, careHPV (Qiagen Inc., Gaithersburg, MD, USA), the prevalence of high-risk HPV infection was evaluated in both groups. The positivity rates were similar: a rate of 13.5% was identified in the self-collection group, and a rate of 11.0% was identified in the group that underwent conventional collection (11.0%) [19]. In another study conducted in northeastern Brazil, Holanda et al. [17] compared the HPV positivity rate (hybrid capture) in a group comprising 878 women who underwent collection in two stages. In the first stage, women self-collected vaginal material using a brush in their own homes. One week later, another sample was obtained, and the collection was now performed by a gynecologist using a brush and spatula. Surprisingly, the high-risk HPV positivity rate was higher in the samples collected by the women themselves (33.9 vs. 28.6%) [17]. Although studies on self-collection for screening of cervical cancer are scarce in Brazil, one can still say that the technique seems to be very promising in a real-life context, in which many women may not even have access to the health care system for Pap testing.

Unlike other studies that have adopted specific devices to perform self-collection, we chose to use materials that would be easily found in public health facilities or even in pharmacies, such as a syringe, a urethral probe, and saline. The initial proposal was to offer women – and even potentially make available to health services – a simple and inexpensive alternative to self-collection that is not dependent on commercial devices specifically designed for that purpose, such as brushes or irrigators. This, in theory, could improve the outreach to women who do not participate in cervical cancer screening for fear or embarrassment, since performing self-collection with material that is inexpensive and readily available in the community is feasible.

The results obtained in this study show that self-collection is well accepted among women, with self-collection involving inserting a syringe filled with saline and a urethral tube deeply into the vagina. Most women did not report having any problem with understanding or carrying out the self-collection procedure; most of them reported that it was actually an easy method to perform. Data from the literature corroborate these findings. Jones et al. [20], who conducted a study on 197 women using a device for vaginal lavage for self-collection, found wide acceptance of the method, since the majority of the women (96%) reported that the collection process was comfortable. However, our results may be biased, since all the women, at least theoretically, did not have any problem with conventional collection. Therefore, it has to be expected to have been highly acceptable among them.

Nevertheless, one should note the limitations of the self-collection method employed in this study. The liquid injected into the vagina often flowed out of the vagina, causing some discomfort. In a few cases, there was total or partial loss of the cervical material, rendering it unusable even for laboratory analysis. Another important limitation is the fact that the vial used for storage of the material (SurePath) contained products that are harmful to health, such as ethanol, isopropanol, and, in very small amounts, methanol and formaldehyde. Household use of the vial could be risky and may cause health issues to women in the event of accidental or intentional ingestion of the conservation fluid, leading to severe poisoning, especially due to the intake of methanol and isopropanol. Thus, a hurdle that needs to be overcome is the provision of a vial containing a preservative solution free from products that are harmful to health, thus posing no risk if used in a domestic environment.

When the cytological results were evaluated, self-collection was expectedly in poor concordance with the results from the cytological examination of the samples obtained by conventional collection. Moreover, the representation of the transformation zone was higher in the cervical samples. These results are not surprising, given that the number of cells present in the lavage fluid was much lower than that present in the sample collected by smear, which contains more cells derived from the vagina. Similar data are to be found in the literature. Nobbenhuis et al. [4] studied 71 women who were submitted to vaginal self-collection by irrigation (syringe and catheter) followed by collection of cervical material using a brush by a gynecologist. The concordance of the cytological results obtained using the two forms of collection was poor, with an absolute concordance of 41% and a κ coefficient of 0.14, values that are very close to those identified in this study. The current study also found a poor representation of squamocolumnar junction cells and endocervical cells when collection was carried out by lavage, which did not come as a surprise, for the reasons previously mentioned. In conclusion, our results support those of previous studies which suggest that vaginal self-collection through ir-

rigation is no applicable or useful strategy for the screening of cervical cancer by way of cytology examination.

Regarding the analysis of accuracy for the detection of CIN 2+, the method that achieved the best performance was using the high-risk HPV test on cervical samples, a finding which should encourage public health authorities to not postpone the introduction of the test into the Unified Health System. In our study, following that procedure, a cytological examination was conducted on samples also derived from the cervix. Examinations of self-collected material showed a poorer diagnostic performance than those of material derived directly from the cervix. We observed that the molecular test conducted on samples obtained by self-collection underperformed that of conventional cervical cytology. Wang et al. [21] evaluated 396 women aged 25–65 years who performed self-collection with the aid of a device (Conical Cervical Sampler; Qiagen Inc.). The authors observed that the HPV test (careHPV) obtained by self-collection of samples presented a sensitivity of 75.0% overall and 66.7% when cells were preserved in liquid medium and on an FTA card, respectively. Nevertheless, the sensitivity rates were significantly lower when compared with tests performed on cervical specimens collected by a physician (83.3%, for both cells preserved in liquid medium and those on FTA cards). In another study, Labani and Asthana [22] demonstrated that samples obtained by self-collection contained much lower viral loads than those obtained by conventional collection. That finding would explain the results we found in our study, where the HPV test performed on samples obtained by self-collection had a worse diagnostic performance in detecting CIN 2+ than the test conducted on samples obtained directly from the cervix.

Valdez et al. [23] conducted a study involving more than 7,500 women in rural China and observed much higher sensitivity rates than those achieved in the current study using HPV testing for the diagnosis of cervical precursor lesions. According to that study, the careHPV test sensitivity rates for CIN 2+ detection were 82.6 and 95.8% when samples were collected by the women themselves and by the doctor, respectively. Regarding hybrid capture, the rates were 91.7 and 95.8% when samples were obtained by the women and by the doctor, respectively. Although their rates were much higher than those found in our study, Valdez et al. [23] also observed that the sensitivity of the HPV test was lower in samples obtained by self-collection.

In summary, self-collection performed by vaginal lavage with a syringe and urethral probe is a method that is simple and well accepted by women. Still, this study shows that cervical cytology performed on material obtained by self-collection should not be used for screening, given the dismal cellular sampling of endocervical cells and the transformation zone. Regarding HPV testing as a screening tool, the sensitivity of this method for detecting CIN 2+ in samples collected by the women themselves was poorer in quality when compared with the samples obtained directly from the cervix. Due to such limitations, self-collection by lavage should be utilized with caution, and its role in the screening of cervical cancer in Brazil needs to be better defined.

Acknowledgments

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Statement of Ethics

This study was approved by the Ethics in Research Committee at Barretos Cancer Hospital (CAAE: 13285013.6.0000.5437). The women who agreed to participate in the study signed an informed consent form. All information regarding the research participants was kept confidential.

Disclosure Statement

The authors declare that there are no connections or financing agreements between the authors and companies that may have an interest in the topic addressed in the article or with the products/items mentioned.

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