Prevention of cervical cancer in women with ASCUS in the Brazilian Unified National Health System: cost-effectiveness of the molecular biology method for HPV detection

Prevenção de câncer de colo uterino em pacientes com ASCUS no Sistema Único de Saúde: custo-efetividade de método de biologia molecular para HPV

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Abstract

This study aimed to assess the performance of PCR as a means of detecting HPV 16/18 compared to the single probe-based PCR for detecting high-risk HPV, and evaluate these methods for detecting cervical intraepithelial neoplasia (CIN) in follow-ups for ASCUS testing. It also compares the costs of cytology, PCR methods, colposcopy and biopsy in the Brazilian Unified National Health System. Of the 81 patients with ASCUS, 41 (50.6%) tested positive for HPV 16/18 in PCR testing and 47 (58.02%) tested positive for high-risk HPV with single probe-based PCR testing. The negative predictive value was 93.75% for HPV 16/18 PCR and 100% for single probe-based PCR in cases that progressed to high-grade CIN. The annual costs of patient referral were the following: R$2,144.52 for referral of patients with ASCUS cytology for colposcopy; R$6,307.44 for referral of patients with ASCUS cytology and PCR positive for HPV 16/18 or colposcopy; R$3,691.80 for referral of patients with ASCUS cytology with single probe-based PCR positive for high-risk HPV. Therefore, cost per user can be reduced by performing single probe-based PCR for high-risk HPV on patients with ASCUS.

Papillomavirus Infections; Cervical Intraepithelial Neoplasia; Polymerase Chain Reaction

Introduction

Cervical cancer is the second most common cancer in women worldwide. More than 500,000 new cases are diagnosed each year [1], most of which occur in developing countries. Human papillomavirus (HPV) is the main risk factor for cervical carcinogenesis [2], and it is one of the most prevalent sexually transmitted infections. The risk factors for HPV infection include being a young woman, early onset of sexual activity, smoking, having multiple sexual partners, and immunosuppression. The frequency of HPV infection decreases with increasing age in women with normal cytological findings. Patients with cytological alterations due to HPV show a regression rate of approximately 85% [3,4].

Over the last century, there has been a worldwide reduction in the incidence of cervical cancer and mortality from this disease. This reduction is attributed to the accumulation of knowledge about the etiology of cervical cancer and the implementation of health education programs. In Latin America, although developing countries have benefited less than the most developed countries, the rates of incidence and mortality have shown larger reductions than expected [5,6]. The coverage of such programs has been described as precarious in Brazil [7].

The method of screening for cervical cancer and its precursor lesions is the Pap smear. The Brazilian Ministry of Health has made the

following recommendations for screening: the three-year time interval between examinations after two negative annual tests; screening should begin at 25 years of age for women who are sexually active. In the case of atypical squamous cells of undetermined significance (ASCUS), the Pap smear should be repeated at six-month intervals, preceded, where necessary, with vulvovaginitis treatment. If two subsequent Pap smears test negative, then the patient should return to routine three-yearly cytological screening. If abnormal results persist or become more serious in follow-up cytological screening, the patient should be referred for colposcopy. In the case of ASC-H, the patient should be referred for colposcopy. In the case of low-grade squamous intraepithelial lesion (LSIL), patients should repeat the Pap smear within six months and vulvovaginitis must be treated. If the repeat cytology tests negative in two consecutive tests, the patient should return to routine three-yearly cytological screening. In the case of a positive subsequent cytology, the patient should be referred for colposcopy. All patients who present cytology suggestive of high-grade lesions should be referred for colposcopy [8].

Despite the impact of the Pap smear in screening programs for cervical cancer, this method has a number of limitations including: a high rate of false negatives, subjective nature of the test, the need for frequent repetition of the test, and wide variations in sensitivity and specificity between laboratories [9]. Errors in diagnosing cervical neoplasia and precursory lesions using cytological methods can be due to the lack of defined morphological criteria for microinvasion, absence of sampling of the squamous-columnar junction, and lack of neoplastic cells in the sample [10]. Although an histological examination of a colposcopically-guided biopsy is still considered the gold standard for evaluating cervical lesions, this method is limited due to the interpretation of morphology and provides little or no information regarding risk of persistence, progression, or regression, of lesions. Furthermore, analysis is subject to interobserver variability. The most widely used and investigated biomarker for cervical disease is HPV testing. There are several techniques used for HPV testing, including hybrid capture, which was the first test licensed by the U.S. Food and Drug Administration (FDA), and polymerase chain reaction (PCR).

The diagnosis of ASCUS is inconclusive and does not always warrant treatment, leading to a dilemma regarding the clinical management of this disease. In an attempt to shed light on this situation, the U.S. National Cancer Institute conducted the ASCUS-LSIL Triage study (ALTS) [11], a large randomized, multicenter study that compared management strategies for women with ASCUS or LSIL cytology [12]. These strategies included immediate colposcopy, repeat cytology and HPV detection of cervical intraepithelial neoplasia (CIN) 3 [12]. Among participants with ASCUS, the sensitivity of biomolecular testing for HPV in detecting CIN 3 lesions or more serious lesions associated with cancer was 96% with 56% of women referred for colposcopy. Cuzick et al. [13] reported that the HPV in Addition to Routine Testing (HART) study showed that positive HPV testing in women with normal or borderline cytology could be managed with repeat testing after twelve months. This strategy could potentially improve detection rates of CIN 2 or worse conditions without increasing rates of referral for colposcopy [13].

In 2007, our research group published a study [14] on the use of molecular biology methods in the Brazilian Unified National Health System (SUS, acronym in Portuguese) for treating patients with ASCUS and LSIL cytology for cervical-vaginal, cervical, and uterine cancer prevention. Our results indicated that one must consider the cost per use of wide-scale prevention programs, and PCR screening should be the choice method because it is cheaper and more sensitive than other screening methods. Moreover, PCR screening has a high negative predictive value.

This study has several objectives. Firstly, it aims to evaluate the performance of PCR for detecting HPV 16 and 18 in comparison to the single-probe based PCR for detecting high-risk HPV. Secondly, it aims to check the agreement between these molecular biology methods for the diagnosis of HPV. Thirdly, this study aims to evaluate the performance of single-probe based PCR for high-risk HPV and PCR for HPV 16 and 18 for detecting cervical intraepithelial lesions at a 12-month follow-up in patients with ASCUS. Finally, this study aims to evaluate and compare the costs of the Pap smear, single-probe based PCR for high-risk HPV, PCR for HPV 16 and 18, colposcopy and biopsy to the SUS.

Material and methods

A prospective study was conducted at the Federal University of Triângulo Mineiro (Universidade Federal do Triângulo Mineiro – UFTM, acronym in Portuguese) between 2009 and July 2011. The study consisted of women diagnosed with ASCUS aged between 17 and 60 years (N = 81) undergoing routine pelvic examinations at the general gynecology department of the UFTM. This study was approved by the Ethics Research Committee

of the UFTM and written informed consent was obtained from all patients enrolled in the study.

The inclusion criteria were women between 15 and 60 years with ASCUS. The exclusion criteria were immunosuppression, pregnancy and previous cytological changes. Subjects were interviewed to obtain information on age, lifestyle habits (smoking), contraception, and parity. After the interview, PCR testing for HPV 16 and 18 and single probe-based PCR testing for high-risk HPV subtypes were carried out on all women.

Cytological smears were taken to provide samples of the ectocervix and endocervical cells. Slides were stained using the Papanicolaou method and evaluated based on the Bethesda System. Cytological results were classified into the following categories: (1) inflammatory changes; (2) pre-invasive squamous lesions, including ASCUS; (3) low-grade squamous intraepithelial lesions (CIN 1 and HPV); (4) high-grade squamous intraepithelial injuries (CIN 2 and 3); (5) atypical glandular cells of undetermined origin (AGUS) and adenocarcinoma *in situ*; and (6) squamous carcinoma or adenocarcinoma. Cytological smears were evaluated according to the following morphological criteria: amphophilia, perinuclear halo, dyskeratosis, anisocytosis, nuclear criteria (binucleation or multinucleation), increased nucleus/cytoplasm ratio, anisokaryosis, hyperchromasia, nuclear atypia, and karyorrhexis. In addition, a Pap smear was performed. Patients with cytological smears showing ASCUS/LSIL observed as a result of any of the above methods (morphological criteria or Pap smear) were included in this study.

All patients with ASCUS underwent colposcopy. The Barcelona classification, proposed in 2002, was used to divide the findings into two categories: normal colposcopic findings (original squamous epithelium, columnar epithelium and normal transformation zone) and abnormal colposcopic findings (acetowhite, stippled, and mosaic-pattern epithelium; leukoplasia; iodine negative zone; and atypical vessels) [15]. These categories were then subdivided into greater or lesser alterations, depending on the degree of tissue compromising. Patients with a greater level of alterations underwent a directed biopsy using Gaylor forceps.

Material collected from PCR testing was stored in Trizol (Invitrogen, Carlsbad, USA) at -20° C and defrosted immediately prior to DNA extraction, at which time 200µL of chloroform was added for every 1.0mL of Trizol collected. The DNA was added to an amplification solution according to the protocol suggested by the manufacturer (Invitrogen, Carlsbad, USA). The primer oligonucleotide sequences used to amplify specific DNA fragments are shown in Table 1. The primers for the single probe-based PCR for detecting high-risk HPV subtypes 16, 18, 31, 33 and 35 are also shown. After performing the PCR, the amplification products were subjected to electrophoresis in 14% polyacrylamide gels and stained using silver. The Trackit (Invitrogen, Carlsbad, USA) 1kB DNA ladder (Invitrogen, Carlsbad, USA) was utilized as a positive control. The amplified sample (10.0µL) was homogenized with 3.0µL of buffer and placed in each well of the 14% polyacrylamide gel. The gel was run at 90 volts for approximately one hour and then placed in a fixing solution for 15 minutes. This solution was discarded, and the silver solution was added for 15 minutes. This process was then followed by washing in Milli-Q H_2O and incubation in a developing solution for approximately 15 minutes. The gel was then returned to the fixing solution for 15 minutes, after which time the bands were observed.

Table 1

PCR: oligonucleotides and sequence.

Oligonucleotide	Sequence
HPV 18 F	CGACAGGAACGACTCCAACGA
HPV 18 R	GCTGGTAAATGTTGATGATTAACT
HPV 16 F	CCCAGCTGTAATCATGCATGGAGA
HPV 16 R	GTGTGCCCATTAACAGGTCTTCCA
HPV high risk F	TTTGTTACTGTGGTAGATACTAC
HPV high risk R	GAAAAATAAACTGTAAATCATATTC

The results were analyzed statistically to evaluate the performance of the colposcopy, PCR for high-risk oncogenic HPV, and PCR for HPV 16 and 18 in detecting HPV and cervical lesions. The following performance tests for CIN were calculated as the gold standard for colposcopy and cytology with or without biopsy. The performance tests included the calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), with a 95% confidence interval (95%CI).

In Brazil, the SUS spends the following amounts on each diagnostic method for HPV and uterine cervical lesions: gynecological consultation, R$10.00; cervicovaginal cytological tests, R$6.64; colposcopy, R$3.38; collection of biopsy, R$18.33; and biopsy, R$43.21 (information obtained from the SUS price table; http://

sigtap.datasus.gov.br/tabela-unificada/app/sec/procedimento/, accessed on 31/Oct/2011). The costs of PCR for HPV 16 and 18 and single probe-based PCR for high-risk HPV (including the total cost of materials used in the examination) are R$65.00 and R$32.00, respectively (exchange rate on March 20, 2012 US$1.00 = R$1.83). The costs of gynecological, cervicovaginal cytology, colposcopy, and biopsy are shown in a table published by the SUS [12], and the costs of PCR and hybrid capture were calculated according to the sum of the cost of reagents and materials for patients after standardization of methods.

When calculating PCR performance in detecting CIN, the negative diagnoses included women with negative colposcopy results (and therefore not subject to biopsy) and those with biopsies showing squamous metaplasia, cervicitis or simply changes suggestive of HPV infection. The positive diagnoses included women diagnosed with CIN using colposcopy or cytology with or without biopsy.

We calculated the correlation between the two types of PCR using the following classification: kappa < 0.4: slight agreement, 0.4 ≤ kappa < 0.8: moderate agreement, 0.8 ≤ kappa < 1: strong agreement, and kappa > 1: perfect agreement.

Results

A total of 81 patients were evaluated by this study. The mean age of the patients was 36 ± 12.9 years (range 17-60 years). Of the patients, 20 (24.7%) were smokers. Hormonal contraception was used by 32 (39.5%) women, but no postmenopausal hormone therapy was used systemically. The average parity was 1.95 ± 1.83 (range 0-10).

PCR for HPV 16 and/or 18 tested positive in 41 (50.6%) patients of which 27 (65.8%) tested positive only for HPV 16, four (9.8%) were positive only for HPV 18, and 10 (24.4%) tested positive for both HPV types. The single probe-based PCR for high-risk HPV tested positive in 47 (58.02%) patients.

Of the 81 patients with altered cytology results, the colposcopy results were normal in 41 (50.6%) patients, unsatisfactory in 15 (18.5%), and altered in 25 (30.9%). Biopsies were performed in six patients. Of these, two (33.3%) tested negative for HPV, three (50%) showed changes consistent with HPV, and one (16.7%) showed suspicious changes, but these were not conclusive for HPV. None of the patients in the initial sample had CIN.

Table 2 shows the analysis of PCR results for diagnosing HPV 16 and 18 compared to the single probe-based PCR results for diagnosing high-risk HPV. Of the 81 cases, 31 (38.3%) were true positives and 24 (29.6%) were true negatives. The sensitivity of PCR for HPV 16 and 18 compared to single probe-based PCR for high-risk HPV was 0.6596 (95%CI: 0.5064-0.7912,), specificity was 0.7059 (95%CI: 0.5252-0.8488,), the PPV was 0.7561 (95%CI: 0.5970-0.8964) and NPV was 0.6000 (95%CI: 0.4331-0.7513). The efficiency (accuracy) was 67.9%. Patients were not diagnosed for HPV 16 and 18, 16 using PCR, suggesting the presence of an additional high-risk HPV subtype. Kappa was 0.36, which is considered weak agreement.

Table 3 shows the results of the 81 cases at the 12-month follow-up. The PCR results for HPV 16 and 18 were compared to the diagnosis of CIN at the 12-month follow-up. The patients lost to follow-up were excluded from the analysis. We observed that 6 (9.1%) cases were true positives and 23 (34.8%) were true negatives. The sensitivity of PCR for HPV 16 and 18 for detecting CIN at the 12-month follow-up was 0.4615 (95%CI: 0.1922-0.7488,), specificity was 0.4853 (95%CI: 0.3623-0.6093,), the PPV was 0.1463 (95%CI: 0.05572-0.2916) and the NPV was 0.8250 (95%CI: 0.6722-0.9266).

The single probe-based PCR results for high-risk HPV in the 81 cases were compared to the diagnosis of CIN at the 12-month follow-up. In the analysis, we observed that seven (10.6%) cases were true positives and 22 (33.3%) were true negatives. The sensitivity of PCR probes for

Table 2

Results of HPV diagnosis using PCR for HPV 16 and 18 compared to PCR single probe for high-risk HPV.

	Positive PCR high-risk HPV	Negative PCR high-risk HPV	Total
Positive PCR 16/18	31	10	41
Negative PCR 16/18	16	24	40
Total	47	34	81

Table 3

Cytologic findings in the development of squamous intraepithelial lesion (SIL) at 12-month follow-up.

Cytology	n	%
LSIL	11	13.6
HSIL	2	2.5

HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion.

detecting single CIN at the 12-month follow-up was 0.5385 (95%CI: 0.2512-0.8078,), specificity was 0.4151 (95%CI: 0.2816-0.5588), the PPV was 0.1842 (95%CI: 0.07746-0.3435) and the NPV was 0.7857 (95%CI: 0.5900-0.9171). These results are shown in Table 4.

The PCR results for HPV 16 and 18 in the 81 cases were compared with the diagnosis of high-grade CIN at the 12-month follow-up. In the analysis, we observed that the NPV was 93.75% (95%CI: 0.7918-0.9923). When comparing the results of the single probe-based PCR for high-risk HPV with the diagnosis of high-grade CIN at the 12-month follow-up for all 81 cases we observed that the NPV was 100% (95%CI: 0.8766-1.0000).

Figures 1, 2 and 3 show the annual cost of these 81 patients for immediate colposcopy with ASCUS cytology and if, hypothetically, were arried out PCR for HPV 16 and 18, or PCR single probe for high-risk HPV for these patients with abnormal cytology and only if positive, referred for colposcopy.

Discussion

Most HPV infections are transient, and HPV is eliminated by the immune system of the patient within a few months, leaving no damage. This process is defined as clearance of HPV. In younger patients, in general women under the age of 35, the rate of spontaneous remission is high; however, the persistence of the virus may increase with increasing age [16,17,18]. Therefore, in patients with LSIL, it is necessary to perform follow-up cytology and colposcopy examinations every six months. In our sample there was a high frequency of high-risk HPV.

Our study showed that 65.8% of patients tested positive for HPV 16, and 24.4% of patients were positive for subtypes 16 and 18. The persistence of HPV infection is an important factor for progression to cervical cancer. Positive testing for HPV subtype 16 is related to viral persistence and may also lead to an increased risk of progression of lesions in patients with high-grade cytological ASCUS [19]. The sensitivity of the PCR for HPV 16 and 18 in relation to the single probe-based PCR for high-risk HPV was 65.96%. The negative cases could be due to the presence of other HPV subtypes in high-risk patients with oncogenic ASCUS.

Our study showed that 50.6% of patients showed normal colposcopy results. In a previous study, Solomon et al. [12] evaluated 1,149 women with ASCUS and LSIL using colposcopy and found that 25.4% had normal colposcopy results, 46.9% had normal colposcopy-directed biopsies,

Table 4

Performance of PCR for HPV 16/18 and PCR single probe for high-risk HPV in diagnosing cervical intraepithelial neoplasia (CIN) at 12-month follow-up.

	Sensitivity %	Specificity %	PPV %	NPV %
PRC 16/18	46.15	48.53	14.63	82.50
PCR single probe	53.85	41.51	18.42	78.57

NPV: negative predictive value; PPV: positive predictive value.

14.5% had CIN 1, 6.3% had CIN 2, and 5.3% had CIN 3 or more severe lesions.

In our study, 50.6% of the patients with ASCUS tested positive for HPV 16/18 according to the PCR technique, and 58.02% were positive using single probe-based PCR for high-risk HPV. Possible management alternatives for a cytological diagnosis of ASCUS include: colposcopy, repeat cytology in four to six months, or molecular testing for HPV. Each method has its advantages and disadvantages. Although repeat cytology is commonly used in the management of women with ASCUS, the sensitivity of this simple test for detecting recurrent CIN 2 and 3 is relatively low; thus, many guidelines have recommended repeating the test at specific intervals until a patient shows multiple consecutive negative results for squamous intraepithelial lesion or malignancy before returning to routine screening. Repeat cytology may delay the diagnosis of CIN 2, CIN 3 or cervical cancer, and multiple follow-up visits may hinder patient adherence.

The advantage of colposcopy is that it immediately identifies the presence or absence of significant disease. Disadvantages include: it is an uncomfortable procedure for many women;

Figure 1

Annual cost to the Brazilian Unified National Health System (SUS) for the 81 patients, following referral of patients with ASCUS for colposcopy.

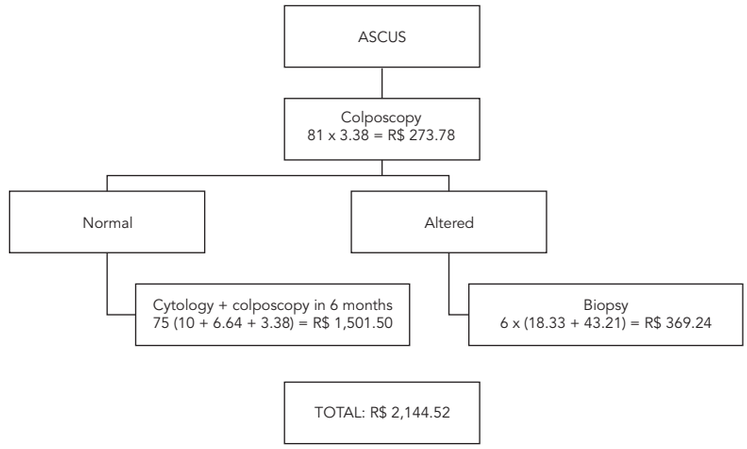


Figure 2

Annual hypothetical costs to the Brazilian Unified National Health System (SUS) of the 81 patients following the protocol of referring for colposcopy only the patients with ASCUS cytology and PCR positive for HPV 16 and/or 18.

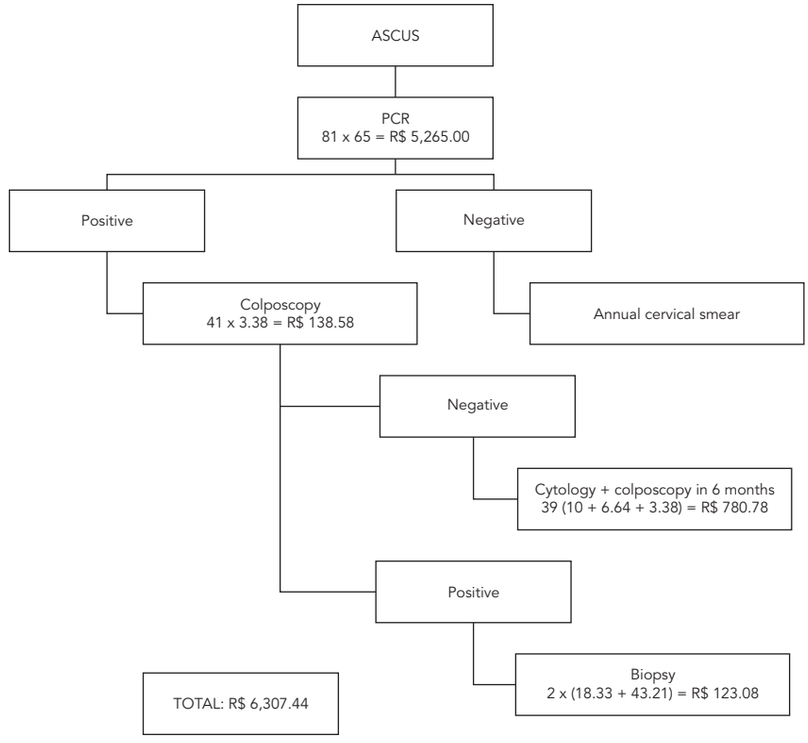
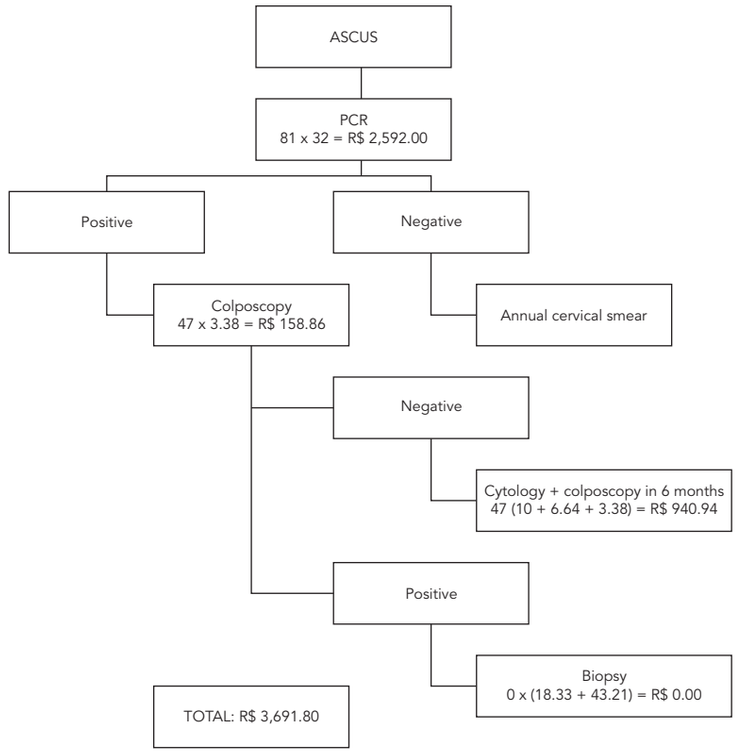


Figure 3

Annual hypothetical costs to the Brazilian Unified National Health System (SUS) of the 81 patients following the protocol of referring for colposcopy only the patients with ASCUS and positive PCR single probe for high-risk HPV.



it may raise concerns about cervical disease; it is expensive; and there are potential problems with overdiagnosis and overtreatment. With regards to HPV testing, sensitivity for detecting CIN 2 and 3 as confirmed by biopsies in women with ASCUS was 0.83 to 1.0, which is greater than the sensitivity of simply repeating a cytological test. The NPV for high-risk HPV is usually 0.98 or greater. In the case of persisting discomfort after the test the patient is required to return to the doctor. An alternative would be to collect samples at the initial screening visit and conduct the test only if the patient tests positive for ASCUS [20].

At the 12-month follow-up, 13.6% of the patients had CIN 1 and 2.5% had CIN 3. Despite the low specificity of the molecular test for HPV, which results in positive testing for a large number of women that have no cytological or histological evidence of the disease, women with negative cytological and positive HPV test results have been reported to evolve abnormal cytology at a frequency of 15% at a 5-year follow-up [21]. Women with normal cytological and positive HPV test results have an increased risk of developing high-grade lesions [22] and therefore a strict follow-up is necessary in these patients.

In the diagnosis of high-grade CIN at the 12-month follow-up it was observed that the NPV was 93.75% for PCR for HPV 16/18 and 100% for single probe-based PCR for high-risk HPV. Studies report a NPV for detecting high-grade lesions of greater than 95% and in some studies this value reaches 100%. Most studies report a NPV for detecting high-grade lesions ranging from 97 to 100% [12,14,18,23,24,25,26]. This high NPV means that the possibility of finding a high-grade lesion in patients with ASCUS is extremely low when the patient is PCR-negative for HPV with a high oncogenic risk. Thus, if this type of HPV testing was introduced in the SUS, only patients with ASCUS and positive PCR results for high-risk HPV would be referred for colposcopic examinations.

The presence of transient infections in patients under 35 years of age may lead to reduced test specificity for high-grade lesions. However, a negative HPV test in women with ASCUS would

decrease the number of referrals for colposcopy and unnecessary biopsies [14]. The application of cytology in addition to HPV testing would increase the detection rate of high-grade CIN and would detect more cancer than the use of cytology alone. Several guidelines propose the use of the hybrid capture assay in patients with ASCUS. New studies show the value of the PCR for HPV types 16 and 18 [14] and the single probe-based PCR for high-risk HPV in the management of these cytological abnormalities [27].

Positive HPV testing does not mean that the patient has CIN or cancer, but that the patient has a risk of developing these diseases. An overall assessment of the role of new technologies in the prevention of cervical cancer is needed in the context of the health care system in Brazil. Combining screening tests increases sensitivity but leads to a decrease in specificity and increased costs. Unfortunately, studies that demonstrate the best combination of screening tests are still lacking. The ideal screening method should be inexpensive, simple and acceptable to the target population and health professionals, provide immediate results and have high sensitivity and specificity [14].

The use of currently available methods in the SUS should be promoted and encouraged. However, it is important to remember that there is a need to introduce new methods to improve prevention and screening of cervical cancer. The cost of the HPV PCR test is currently higher than the cost of cytology, colposcopy and biopsy, as demonstrated by our study. However, the widespread use of HPV PCR could reduce the cost of this method, especially if the use of this method leads to an increase in screening intervals.

Savings also occur when considering the amount spent on treatment of patients with more advanced lesions. Savings occur not only in the cost of treatment, including surgery and hospitalization and other adjuvant treatments, but also for the social security system. High-grade lesions and invasive cervical cancer result in lost work days mainly during the active phase of a woman's life. The use of HPV PCR would therefore lead to overall savings for the health and social security systems and a better quality of life for women [14].

Another point addressed by this study is the question surrounding the HPV vaccine. Assessing sensitivity of PCR probes for HPV 16 and 18 showed a loss of cases, probably due to other high-risk HPV subtypes. More interestingly, the two cases that progressed to high-grade lesions tested as negative with PCR for HPV 16/18 and positive with single probe-based PCR for high-risk HPV. These results raise doubts regarding the validity of including the HPV vaccination in the SUS. Chironna et al. [28] also found that there was not only a high incidence of HPV 16, but also of HPV 53 in patients with ASCUS, which reinforces this idea. Furthermore, no greater benefits of the vaccine were observed in women between 30 and 50 years of age [29]. In addition to this concern, the eradication of the HPV 16 and 18 subtypes could lead to an imbalance between the subtypes and increase other high-risk HPV subtypes [30]. The prevalence of HPV subtypes may vary in different populations and therefore the economic and epidemiological impact of the vaccine is questionable.

Conclusion

The single probe-based PCR for high-risk HPV detects a larger number of high-risk HPV types compared to PCR for HPV 16 and 18, has a high NPV for CIN and an even higher NPV when evaluating high-grade lesions. Molecular biology methods could be used on patients with ASCUS for the prevention of cervical cancer and the wide-scale use of this technique leads to a reduction in cost per user and improvements in patient comfort due to an increase in the follow-up interval to 12 months. In addition, the single probe-based PCR for high-risk HPV is cheaper, more sensitive and has a high NPV for detecting high-grade lesions, making this technique a possible method of choice for the detection of this disease.

Resumo

Os objetivos deste estudo foram avaliar o desempenho do PCR para detecção de HPV 16/18 versus *PCR sonda única para a detecção de HPV de alto risco, avaliar estes métodos na detecção de neoplasia intraepitelial cervical (NIC) no seguimento de ASCUS, e comparar os custos de citologia, métodos de PCR, colposcopia e biópsia no Sistema Único de Saúde. Das 81 pacientes com ASCUS, 41 (50,6%) foram positivas para o HPV 16/18 PCR, e 47 (58,02%) foram positivas para PCR sonda única para HPV de alto risco. O valor preditivo negativo foi de 93,75% para HPV 16/18 PCR e 100% para PCR sonda única em casos que evoluíram para NIC de alto grau. Os custos anuais encaminhando todas as pacientes com ASCUS para a colposcopia, encaminhando à colposcopia as pacientes com ASCUS e PCR positivo para HPV 16/18 e encaminhando à colposcopia aquelas pacientes com ASCUS e PCR sonda única para HPV de alto risco positivo foram de R$2.144,52, R$6.307,44 e R$3.691,80, respectivamente. Considerando eventual redução dos custos para utilização em grandes quantidades, este método poderia ser realizado em ASCUS.*

Infecções por Papillomavirus; Neoplasia Intra-Epitelial Cervical; Reação em Cadeia da Polimerase

Contributors

R. S. Nomelini contributed to study design, data analysis and interpretation, writing and review of intellectual content. P. D. N. Guimarães contributed to obtaining the colposcopy, PCR and costs data, colposcopy and costs data analysis and interpretation and writing of the paper. P. A. Candido and A. C. C. Campos contributed to obtaining and interpreting PCR data and writing the paper, especially the content regarding the molecular biology method. M. A. Michelin contributed to PCR data analysis and interpretation and coordinated the implementation of the molecular biology method. E. F. C. Murta contributed to study design and review of intellectual content. All authors approved the final version of this article.

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