ORIGINAL ARTICLE

Comparative study of the results from conventional cervico-vaginal oncotic cytology and liquid-based cytology

Estudo comparativo dos resultados obtidos pela citologia oncótica cérvico-vaginal convencional e pela citologia em meio líquido

Sueli Aparecida Batista Stabile[1], Dilson Henrique Ramos Evangelista[2], Valdely Helena Talamonte[3], Umberto Gazi Lippi[4], Reginaldo Guedes Coelho Lopes[4]

ABSTRACT

Objective: To compare two oncotic cervical cytology techniques, the conventional and the liquid-based cytology, in low risk patients for uterine cervical cancer. **Methods:** Comparative prospective study with 100 patients who came to their annual gynecological exam, and were submitted simultaneously to both techniques. We used the McNemar test, with a significance level of $p<0.05$ to compare the results obtained related to adequacy of the smear quality, descriptive diagnosis prevalence, guided biopsy confirmation and histology. **Results:** Adequacy of the smear was similar for both methods. The quality with squamocolumnar junction in 93% of conventional cytology and in 84% of the liquid-based cytology had statistical significance. As for the diagnosis of atypical cells they were detected in 3% of conventional cytology and in 10% of liquid-based cytology ($p=0.06$). Atypical squamous cells of undetermined significance were the most prevalent abnormality. The liquid-based cytology performance was better when compared with colposcopy (guided biopsy), presenting sensitivity of 66.7% and specificity of 100%. There was no cytological and histological concordance for the conventional cytology. **Conclusions:** Liquid-based cytology had a better performance to diagnose atypical cells and the cyto-histological concordance was higher than in the conventional cytology.

Keywords: Colposcopy; Cytological techniques; Vaginal smears; Cytodiagnosis; Uterine cervical neoplasms/prevention & control

RESUMO

Objetivo: Comparar duas técnicas de colpocitologia oncótica, a convencional e a em meio líquido, em pacientes de baixo risco para carcinoma de colo uterino. **Métodos:** Trata-se de estudo prospectivo e comparativo, em que foram avaliadas cem mulheres que compareceram à consulta médica de rotina e foram submetidas simultaneamente à coleta pelas duas técnicas de citologia. Os resultados obtidos em relação à adequabilidade, à qualidade dos esfregaços, à prevalência nos diagnósticos descritivos e à confirmação com biópsia dirigida e histologia foram comparados pelo teste de McNemar, com nível de significância de $p<0,05$. **Resultados:** A adequabilidade dos esfregaços mostrou-se semelhante. A qualidade, com presença de elementos da junção escamo-colunar em 93% das citologias convencionais e 84% das citologias em meio líquido, teve significância estatística. Nos diagnósticos de atipias, elas foram detectadas em 3% das citologias convencionais e em 10% das citologias em meio líquido ($p=0,06$), sendo as atipias em células escamosas de significado indeterminado a alteração mais prevalente. Quando comparadas à colposcopia com biópsia dirigida, o desempenho da citologia em meio líquido foi superior, com sensibilidade de 66,7% e especificidade de 100%, enquanto que, para a citologia convencional, não houve concordância cito-histológica. **Conclusão:** O desempenho em diagnosticar atipias e a concordância cito-histológica da citologia em meio líquido foram superiores ao da citologia convencional.

Descritores: Colposcopia; Técnicas citológicas; Esfregaço vaginal; Citodiagnóstico; Neoplasias do colo do útero/prevenção & controle

Study carried out Hospital Cândido Rondon – HCR, Ji-Paraná (RO), Brazil.

[1] Master's degree program, Instituto de Assistência Médica ao Servidor Público Estadual – IAMSPE, São Paulo (SP), Brazil; Hospital Cândido Rondon – HCR, Ji-Paraná (RO), Brazil.

[2] Mathematics and Statitics Department, Universidade Federal de Rondônia – UNIR, Ji-Paraná (RO), Brazil.

[3] Master's degree program, Instituto de Assistência Médica ao Servidor Público Estadual – IAMSPE, São Paulo (SP), Brazil; Hospital Cândido Rondon – HCR, Ji-Paraná (RO), Brazil.

[4] Gynecology and Obstetrics Service, Hospital do Servidor Público Estadual de São Paulo "Francisco Morato de Oliveira" – HSPE-FMO, São Paulo (SP), Brazil

Corresponding author: Sueli Aparecida Batista Stabile – Rua José Bezerra de Barros, 100 – Urupá – Zip code: 76900-222 – Ji-Paraná (RO), Brazil – Phone: (55 69) 3421-1556 – E-mail: suelistabile@hotmail.com

Received on: Aug 31, 2011 – Accepted on: Dez 9, 2011

Conflicts of interest: none.

INTRODUCTION

Cervical-vaginal cytology was introduced by George Papanicoulau and Aureli Babes in 1928[1,2]. In 1983 after the researches of Papanicolau and Traut[1] this technique became most effective to prevent and early diagnosis uterine cervical cancer.

Uterine cervical cancer causes death of approximately 18,430 women yearly in Brazil according to an estimation in 2010 made by the Instituto Nacional do Câncer (INCA)[3].

It is the most common cancer type in the northern region of Brazil after the non-melanoma skin cancer. In that region, uterine cervical cancer has a risk estimation of 22.82 per 100 thousand women. In Rondonia, a Brazilian state, this risk is 14.54. Each year 500 thousand new cases of this disease appear, causing 230 thousand deaths worldwide.

Conventional oncotic cytology (CC) is an easily performed test and that was responsible for the decrease in death from 44 to 8 cases per 100 thousand women between 1947 and 1973 in countries with high quality assistance program[1]. It is a screening test not for a definitive diagnosis, with relatively low sensibility to detect high degree lesions in a single examination (50%)[3], and which presents a false-negative rate varying from 20 to 40%[1].

Attempting to find higher sensibility for the method, which according to a meta-analysis[4] is 58% (varying from 11 to 99%) with specificity of 68% (varying from 14 to 97%), new techniques to collect and prepare the samples were developed so the liquid-based cytology (LBC) was introduced.

Although this method is widely used the limitations of cervical-vaginal cytology, which are related to its sensibility, have became evident: subjectivity, mistakes in collection and fixation[5], large number of unsatisfactory tests, small number of cells that remain in the slide (20%)[6] and false-negative results. Perhaps, the mistakes in collection are the most important factors because they precede all others steps in the process.

Among the false-positive results there are several causes, like inflammatory and atrophic processes, cauterizations, biopsies, surgeries, chemotherapy and radiotherapy.

The liquid-based cytology was approved in 1996 by the FDA in the United States to be used in gynecology and in other specialties[7]. It was developed in an attempt to reduce gaps in conventional cytology promoting the use of cleaner slides, no superpositions of cells or other obscuring elements. This is due to the filter system where only epithelial cells are retained resulting in a monolayer or a thin layer slide.

Limitations and gaps of conventional cytology are well known and some disadvantages of the LBC are the high costs of equipments and their maintenance, as well as staff training to interpret in new morphological cell aspect different from CC, which can generate a higher number of smears with atypia, particularly because atrophic and immature metaplastic cells can be misrecognized as atypical cells if not properly interpreted with this technique.

Some advantages of LBC are the presence of 100% of the collected sample a fixative liquid with the possibility to perform hystochemical tests, molecular biology test and new exams, if required, using the same sample. Besides, there are less false-negative results and unsatisfactory smears. Also, cell preservation with a sample of higher quality enables a better interpretation, and reduces the length of exams in 30%[8], therefore, increasing the productivity of laboratories[9].

OBJECTIVE

To compare two oncotic cervical cytology techniques, CC and LBC, considering the following criteria: prevalence of different atypical cells in both techniques, quality of collected smears, agreement between colposcopic and cytologic diagnosis; agreement between cytological and histological findings in cases when biopsy was used.

METHODS

This is a comparative prospective study with 100 women chosen from 400 patients who came to their routine annual gynecological exam. They had oncotic colpocytology collected at a private institution in the city of Ji-Parana, Brazil.

Cytologies were taken by a single professional, a gynecologist, in a single procedure (split sample). Firstly, a conventional slide cytology was taken, and then the same brush (cervex brush) was rinsed in the liquid medium DNA-Citoliq (Digene®, Brazil).

A single laboratory prepared and interpreted the smears – that is, the same cytopathologist team, who was not aware of the results of the other applied technique performed the analysis of the collected sample (the team changed for the analysis of the smears of the last 10 patients).

Regarding the descriptive findings in the results from CC and LBC cytologies, normal and inflammatory

cytologies were separated from atypic cytologies. We considered the following changes in squamous or glandular cells: atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells of undetermined significance not excluding high-grade lesion (ASC-H); glandular cells atypia (AGC); low-grade intraepithelial lesion (LSIL); high-grade intraepithelial lesion (HSIL); and invasive cancer.

The histological exam that confirms the cytological diagnosis is considered the gold-standard, which is performed using colposcopy-guided biopsy. All patients were submitted to this technique by the time of the collection before obtaining the results of the cytologies. We considered as abnormal colposcopy those with major o minor changes, and excluded the miscellaneous ones, which consisted in atrophic or inflammatory colpitis.

When changes were found in conventional and/or liquid-based cytology with normal or abnormal colposcopy that did not require a biopsy, an investigation by bacterioscopy or HPV DNA research was done and repeating the exam 4 months later.

All patients signed an informed consent form. This study was approved by the Ethical and Research Committee of the Instituto de Assistência Médica ao Servidor Público Estadual (IAMSPE) and registered as CEP/IAMSPE # 079/09.

Results obtained were organized in tables and submitted to the McNemar statistical test.

The following were considered as exclusion criteria: patients who did total hysterectomy, absence of uterine cervix, treatment with gynecologic creams in the last month before the exam, vaginal or uterine cervix affection that contraindicated the collection, presence of intrauterine device and unsatisfactory cytology in at least one of the two techniques.

RESULTS

To compare the criteria used in the study, we first analyzed adequability of the sample considering them either satisfactory or unsatisfactory.

Among the 100 CC smears, two were unsatisfactory by desiccation (2%), and among the 100 LBC smears one was unsatisfactory for erythrocytes excess (1%). There were no cases of unsatisfactory cytology in both techniques for the same patient. We excluded these three unsatisfactory citologies for parameter analysis.

Regarding the quality of the smears in the CC, the elements of squamocolumnar junction (SCJ) were observed in 90 of the 97 satisfactory CC (93%) and in 80 of the 97 LBC exams (84%). This difference was statistical significant (p=0.04).

In the descriptive diagnosis (Table 1), the prevalence of normal exam was 97% for CC and 90% for LBC, not presenting statistical significance.

ASC-US in LBC was the most frequent diagnosis (eight cases) and ASC-H in CC (two cases). One ASC-US case had this diagnosis in both techniques. The concordance between CC and LBC for atypia diagnosis by the Kappa index, according to Altman, was classified as poor (0,1).

In the colposcopy performed among all the satisfactory cytologies (97 cases) (Tables 2 and 3), there were five cases where SCJ could not be seen, characterizing unsatisfactory colposcopy. No abnormal cytology was found in these cases.

In normal cytologies among CC (94 cases) three cases presented abnormal colposcopy (two major and one minor); 11 cases being colpitis. Among normal LBC (87 cases), 2 had colposcopy with major (1 case) and minor (1 case) changes; 7 cases being colpitis.

Table 1. Descriptive diagnosis prevalence of cytological techniques in liquid medium

Diagnosis	Conventional	Liquid medium
	n (%)	n (%)
Normal/inflammatory	94 (97)	87 (90)
ACS-US	1 (1)	8 (8)
ASC-H	2 (2)	0 (0)
AGC	0 (0)	1 (1)
LSIL	0 (0)	1 (1)
HSIL	0 (0)	0 (0)
Invasive Cancer	0 (0)	0 (0)
Total	97 (100)	97 (100)

ASC-US: Atypical squamous cells of undetermined significance; ASC-H: Atypical squamous cells of undetermined significance cannot excluding high-grade lesion; AGC: glandular cells atypia; LSIL: low-grade intraepithelial lesion; HSIL: high-grade intraepithelial lesion.

Table 2. Colposcopy in patients with unsatisfactory cytology using the conventional technique

Colposcopy	Normal/ inflammatory	Cell atypias	Total
	n (%)	n (%)	
Normal	75 (77)	2 (2)	77
Unsatisfactory	5 (5)	0 (0)	5
Small changes	1 (1)	1 (1)	2
Large changes	2 (2)	0 (0)	2
Miscellaneous	11 (11)	0 (0)	11
Invasion	0 (0)	0 (0)	0
Total	94	3	97

Table 3. Colposcopy in patients with satisfactory cytology obtained by liquid medium technique

Colposcopy	Normal/ inflammatory	Cell atypias	Total
	n (%)	n (%)	
Normal	73 (75)	4 (4)	77
Unsatisfactory	5 (5)	0 (0)	5
Small changes	1 (1)	1 (1)	2
Large changes	1 (1)	1 (1)	2
Miscellaneous	7 (7)	4 (4)	11
Invasion	0 (0)	0 (0)	0
Total	87	10	97

Of the three cytologies that had atypias among the CC exam, one (ASC-H) had minor changes in colposcopy and two had normal colposcopy. Among LBC (10 cases of atypias), one had major changes and another minor changes, four colpitis and the remaining four had normal colposcopy.

Agreement between CC and colposcopy by the Kappa index, according to Altman, was poor (0.05) and, between LBC and colposcopy was reasonable (0,4).

The histology of the three CC diagnosed with atypias (Chart 1), showed two cases of ASC-H and one of the ASC-US, but only one of ASC-H cases had minor changes in the colposcopy with biopsy diagnosing endocervical polyp.

Among the normal CC three had colposcopy findings with indication for biopsy and in two of them, the LBC showed atypias (ASC-US). The biopsy of these three cases showed the following atypias: low-grade vaginal intraepithelial neoplasia (VAIN 1) high-grade cervical intraepithelial neoplasia (CIN 2) and high-grade vaginal intraepithelial neoplasia (VAIN 2).

There was no agreement between cytology and histology for CC, and the Kappa index for CC agreement with histology was classified as poor (-0,6). Because of the small number of positive cases it was not possible to state the sensibility and the specificity for the sample method.

Chart 1. Agreement between histological diagnosis and cytological diagnosis

Cytological findings	Biopsy	Conventional cytology	Liquid medium cytology
Cell atypias	+	0	2
	-	1	0
Normal cells	+	0	1
	-	3	1
Total		4	4

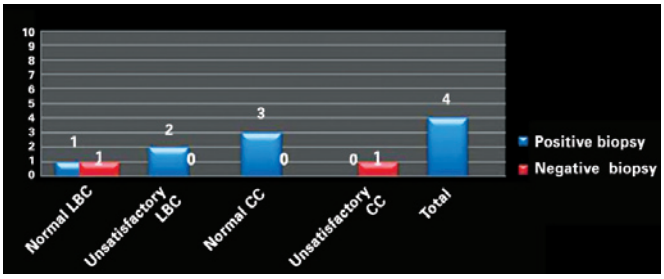
Among 87 normal LBC, two had changes in colposcopy and were submitted to biopsy. One of the cases with normal CC presented positive histological results (VAIN 1). In another case the CC showed atypias, however, in the biopsy, showed a normal result and was in accordance with the LBC.

Among the ten LBC cases that had atypias, in two cases the biopsy was indicated due to colposcopic changes. In other two, the histology confirmed atypias (VAIN 1 and CIN 2). The Kappa index, according to Altman, for the agreement between LBC and histology was considered moderate (0,5).

Accuracy of LBC to detect atypias was 75%. In four biopsied cases, three were true-positive and, one of them, the result of LBC was normal. The true-negative case was in concordance with LBC and discordant to CC, showing atypias. The sample sensibility was 66.7% and specificity 100%. The number of false-negative for LBC was 33% to true-positive and 0% to false-positive.

If considered all normal cytologies, including those not tested using the gold-standard (87 smears), just one case was positive and had LBC normal (1%).

Figure 1 shows the agreement between the histological diagnosis and the cytological one in four cases in which the biopsy was performed.



LBC: liquid-based cytology; CC: conventional oncotic cytology.

Figure 1. Agreement between histological diagnosis and cytological diagnosis of four biopsied cases

Patients clinically diagnosed with evident atrophy or inflammation were excluded of this study, the cases of abnormal cytology not in agreement with the colposcopy were investigated with bascterioscopy and hormonal assessment. All non-biopsied cases with abnormal cytology and that needed treatment were treated accordingly, and all presented normal cytological status in the follow-up.

DISCUSSION

Some studies comparing CC and LBC using a simultaneous collection (split sample) or other type

of collection in different patients of comparable population have controversial conclusion.

In collections done in the same patient LBC was put in disadvantage because it was done after CC. In collections done separately in epidemiologically equivalent populations it is not possible to state the resemblances in the collection time, its uniformity related to the experience and the care taken by those performing the collection, the real clinical similarity of the populations and laboratories, among other aspects. Besides, randomized studies with histological evidences for all cases are scarce.

In our study that evaluated a population with low risk for cervical uterine cancer, no case of high-grade lesion among cytologies was observed.

The total of unsatisfactory cytologies, which represents the adequacy of the smears, was similar for both techniques (1% for LBC and 2% for CC) which differs from most studies.

As for the smears quality endocervical and/or metaplastic cell were found more frequently in CC than in LBC with statistical significance. Perhaps this finding, consistent with other studies, is justified because smears were collected firstly using CC, so that this technique would provide more transfer of such cells to the slide.

Regarding the prevalence of abnormal diagnoses (3% to CC and 10% to LBC) the low number of biopsy findings causes trouble to analyze the performance of each technique, however, the finding of a high number of atypias in LBC, although not statistically significant, seems to be consistent with other studies.

We found, among biopsied cases: one CC case with abnormal colposcopy and normal LBC (the result was negative for cancer cells); two cases with normal LBC, abnormal colposcopy and normal CC (the result was high-grade lesion); and another case with normal CC and LBC, but it presented major abnormalities colposcopy (the result was low-grade lesion).

We emphasize that the low number of positive cases in the low risk population of this study obtained a greater accuracy to detect atypias using LBC. In only one case of low-grade lesion in the vaginal wall, LBC was normal, which is consistent with most studies.

We found in the literature just one study[10] that submitted all participants to colposcopy. In that study with 913 patients, and separated into 2 cohorts it was concluded that LBC was superior only in relation to the small number of unsatisfactory cytologies.

Some national studies, consisting in two cohorts with collection in two different times[11], showed small number of unsatisfactory smears and a great representativity of SCJ in LBC. In other studies[12,13], using simultaneous collection with or without histological diagnosis, both technique performances were similar. However, they emphasized that for high risk cancer patients, with abnormal colposcopy, in 55.4% with normal CC and in 31.2% with normal LBC high-grade lesions were detected by biopsy. Other studies[14,15] confirmed higher sensibility for LBC and higher specificity for CC.

Several studies with simultaneous collection performed in many countries[16-19] suggested that LBC as well as cytology had higher sensibility to detect low and high-grade lesions, with greater sample adequacy and presenting a small number of unsatisfactory smears. Regarding specificity not all studies agree with the LBC superiority.

Studies with the analysis of two cohorts involving more patients[20-25] most of the time showed higher accuracy of LBC to detect low and high-grade intraepithelial lesions. All of them agreed that LBC produced less unsatisfactory smears.

There are in the literature many systematic reviews cited by various authors. One review[26] analyzed 17 manuscripts and concluded that sensibility for LBC was 76% and for CC 67%, and for specificity no statistical significance was found. In addition, in that review, LBC detected 6,5% more cases of abnormalities, while CC presented negative results. Such numbers are from the USA where 45 millions of cytologies are collected yearly, in other words, 162 thousand more diagnoses of high-grade lesions and 3,000 more cases of invasive cancer were made. This review concluded that LBC had greatest sensibility.

A Cochrane systematic review[9] including 16 studies (split sample and two cohorts) with histological confirmation stated that sensibility for CC varied from 34.5 to 93.6% and for LBC from 53 to 95.7%. For low-risk population there was significant decrease in the number of false-negative, but for the high-risk population there was no significant difference between both techniques. When the two population were merged, the LBC sensibility was 12% greater than the CC.

Another review[27] including 56 studies concluded that both techniques did not show difference in their performance.

A large systematic review and meta-analysis in 2008[28], assessed 109 studies with several designs and concluded that LBC had lower unsatisfactory results. Regarding sensibility and specificity no significant differences were observed.

In general, most studies agree that there is a small number of unsatisfactory cytologies with LBC. In studies that involved high-quality services the difference was not significant. In most studies the sensibility of both techniques for high-grade lesions seem to be similar, however, for low-grade lesions LBC overcame CC. Considering that the prevalence of high-grade lesion is confirmed in women by histology with ASC-US, varying from 5 to 17%[29], this finding becomes a relevant factor.

The present study was in disagreement with most studies when it showed that the adequability of samples was almost the same for both techniques. However, when CC collection is made according to the established concepts to produce a good smear, the studies showed that both techniques were adequate.

Our results are consistent with other studies related to the smear quality. We found more SCJ elements in CC, and observed more accuracy in LBC to detect cell atypias with sensibility of 67%.

It is important to emphasize the role that colposcopy had in the detection of precursor cancer lesions of cervical uterine non-diagnosed only by oncotic cytology.

Because our study assessed a small sample and focused on a low-risk population for uterine cervical cancer, the results cannot be extrapolated to the general population.

CONCLUSION

When cytological diagnose was compared with colposcopy/histological diagnoses, no concordance was found cytologically/colposcopically/histologically for CC whilst such results showed better agreement for LBC regarding accuracy and specificity.

REFERENCES

1. Martins NV, Ribalta JC. Patologia do trato genital inferior. São Paulo: Roca; 2005.
2. Koss LG, Gompel C. Citopatologia ginecológica com correlações histológicas e clinicas. São Paulo: Roca; 2006.
3. Instituto Nacional do Câncer (INCA). Estimativa para 2012 do Câncer do colo uterino no Brasil e diferentes regiões [Internet]. [Acessado em 2012 abril 10; Disponível em: http://www.inca.gov.br/conteudo_view.asp?id=1793
4. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol. 1995;141(7):680-9.
5. Franco R, Amaral RG, Montemor EB, Montis DM, Morais SS, Zeferino LC. Fatores associados a resultados falso negativos de exames citopatológicos do colo uterino. Rev Bras Ginecol Obstet. 2006;28(8):479-85.
6. Guedes AC. Comparação do desempenho do esfregaço citológico cérvico-vaginal convencional com esfregaço colhido em meio líquido em mulheres com alto risco para neoplasia de colo uterino [tese]. Campinas: Universidade Estadual de Campinas; 2002.
7. Campagnoli EB, Sandrin R, Braosi AP, Lima AA, França BH, Machado MA. Citologia em base líquida - uma nova opção para o diagnóstico de lesões bucais. Rev Bras Patol Oral. 2005;4:119-27.
8. Guo M, Hu L, Martin L, Liu S, Baliga M, Hughson MD. Accuracy of liquid-based Pap tests: comparison of concurrent liquid-based tests and cervical biopsies on 782 women with previously abnormal Pap smears. Acta Cytol. 2005;49(2):132-8.
9. Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. Health Technol Assess. 2004;8(20):iii,1-78.
10. Sykes PH, Harker DY, Miller A, Whitehead M, Nea IH, Wells JE, et al. A randomised comparison of SurePath liquid-based cytology and conventional smear cytology in a colposcopy clinic setting. BJOG. 2008;115(11):1375-81.
11. Pereira SM, Utagawa ML, Pittoli JE, Aguiar LS, Maeda MY, Longatto Filho A, et al. Avaliação da celularidade citológica em preparados de base líquida. Rev Inst Adolfo Lutz. 2003;62(1):35-9.
12. Mattosinho de Castro Ferraz M da G, Nicolau SM, Stávale JN, Focchi J, Castelo A, Dôres GB, et al. Cervical biopsy-based comparison of a new liquid-based thin-layer preparation with conventional Pap smears. Diagn Cytopathol. 2004;30(4):220-6.
13. Alves VA, Castelo A, Longatto Filho A, Vianna MR, Taromaru E, Namiyama G, et al. Performance of the DNA-Citoliq liquid-based cytology system compared with conventional smears. Cytopathology. 2006;17(2):86-93.
14. Girianelli VR, Thuler LC, Szklo M, Donato A, Zardo LM, Lozana JA, et al. Comparação do desempenho do teste de captura híbrida II para HPV, citologia em meio líquido e citologia convencional na detecção precoce do câncer do colo do útero e de suas lesões precursoras no Rio de Janeiro, Brasil. Rev Bras Cancerol. 2004;50(3):225-6.
15. Longatto Filho A, Pereira SM, Di Loreto C, Utagawa ML, Makabe S, Maeda MY, et al. DCS liquid-based system is more effective than conventional smears to diagnosis of cervical lesions: Study in high-risk population with biopsy-based confirmation. Gynecol Oncol. 2005;97(2):497-500.
16. Davey E, d'Assunção J, Irwig L, Macaskill P, Chan SF, Richards A, et al. Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study. BMJ. 2007;335(7609):31.
17. Zhu J, Norman I, Elfgren K, Gaberi V, Hagmar B, Hjerpe A, et al. A comparison of liquid-based cytology and Pap smear as a screening method for cervical cancer. Oncol Rep. 2007;18(1):157-60.
18. Lerma E, Quintana MJ, Quilez M, Esteva E, Carreras A, Bonfill X, et al. Effectiveness of liquid-based cytology and papanicolaou tests in a low risk populations. Acta Cytol. 2007;51(3):339-406.
19. Rahimi S, Carnovale-Scalzo C, Marani C, Renzi C, Malvasi A, Votano S. Comparison of conventional Papanicolau smears and fluid-based, thin-layer cytology with colposcopic biopsy control in central Italy: a consecutive sampling study of 461 cases. Diagn Cythopathol. 2008;37(1):1-3.
20. Kirschner B, Simonsen K, Junge J. Comparison of conventional Papanicolaou smear and SurePath liquid-based cytology in the Copenhagen population screening programme for cervical cancer. Cytopathology. 2006;17(4):187-94.
21. Harrison WN, Teale AM, Jones SP, Mohammed MA. The impact of the introduction of liquid based cytology on the variation in the proportion of inadequate samples between GP practices. BMC Public Health. 2007;7:191.
22. Williams AR. Liquid-based cytology and conventional smears compared over two 12-month periods. Cytopathology. 2006;17(2):82-5.
23. Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomized controlled trial. BMJ. 2007;335(7609):28.
24. Strander B, Andersson-Ellström A, Milson I, Radberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program: a prospective randomized study. Cancer. 2007;111(5):285-91.
25. Beerman H, van Dorst EB, Kuenen-Boumeester VB, Hogendoorn PC. Superior

performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. Gynecol Oncol. 2009;112(3):572-6.

26. Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecol Oncol. 2003;90(1):137-44.
27. Davey E, Barratt A, Irwig L, Chan SF, Macaskill P, Mannes P, et al. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. Lancet. 2006;367(9505):122-32.
28. Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol. 2008;111(1):167-77.
29. Wright TC Jr. Cervical cancer screening in the 21st century: is it time to retire the Pap smear? Clin Obstet Gynecol. 2007;50(2):313-23.