Jornal Brasileiro de Patologia e Medicina Laboratorial
ISSN: 1676-2444
jbpml@sbpc.org.br
Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial
Brasil

Mitteldorf, Cristina Aparecida T. S.
Cervical cancer screening: from Pap smear to future strategies
Jornal Brasileiro de Patologia e Medicina Laboratorial, vol. 52, núm. 4, agosto, 2016, pp. 238-245
Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial
Rio de Janeiro, Brasil

J Bras Patol Med Lab, v. 52, n. 4, p. 238-245, August 2016

10.5935/1676-2444.20160040

Cervical cancer screening: from Pap smear to future strategies

Triagem de câncer do colo uterino: do teste de Papanicolaou a estratégias futuras

Cristina Aparecida T. S. Mitteldorf

Hospital Sírio Libanês, São Paulo, Brazil.

ABSTRACT

Previously, the screening for detection of cervical cancer was performed by simple cervicovaginal sample collected by the physician whenever the patient attended the medical consultation, and soon it was established as the annual "Pap smear". Since then, an elementary test has evolved into a complex process with multiple algorithms for the identification of invasive disease. The detection of human papillomavirus (HPV) has become part of the new screening recommendations, resulting in major changes in the guidelines. This review intends to emphasize the most important topics that are part of cervical cancer screening, including cervical cytology and HPV detection, and to discuss particular aspects of cervical cancer in Brazil. Despite the great benefits achieved by the cervical cancer screening programs with cytology and HPV test, there are still important issues to be discussed and improved in defining future strategies, including simplicity and possible application in different socioeconomic contexts, definition of the best test or tests to be applied and recommended interval, minimizing possible harms. After the establishment of screening algorithms well defined by leading organizations, management protocols should be disseminated among physicians and patients by education programs.

Key words: cervical cancer; cervical cancer prevention; molecular diagnostic methods; vaginal smears; HPV DNA tests.

INTRODUCTION

Although the observation of cells was the first and original approach to the study of human diseases in the 19th century, the development of cytology as a diagnostic modality, as it is known today, followed the fundamental contribution of Dr. George Nicolas Papanicolaou, who first reported in 1928 that malignant cells from the cervix can be identified in vaginal smears. His work in collaboration with the gynecologist Herbet Traut provided a detailed description of the cytology of the female genital tract and the basis of the discovery of unsuspected occult cancer in asymptomatic patients, published many years later. Although initially their observations were received with skepticism by both pathologists and clinicians, many confirmed their findings subsequently, and cervical smears were embraced as a routine screening test for preinvasive lesions of the cervix, since then known as "Pap smear" or "Pap test"[1, 2].

The first cervical cancer screening clinics were established in the 1940s, when a number of women were screened for detection of early uterine cancer. In one year, it was found 54 cases of cancer in 639 women, 51 of them correctly diagnosed by cytology and six detected exclusively by Pap smear[3].

The implementation of a very simple and effective screening test was followed by a dramatic decrease in mortality rate related to cervical cancer in different populations[4-13].

Over the past 30 years, the widespread routine cervical cancer cytology screening has contributed to a 50% reduction in the incidence of cervical cancer in the United States. As demonstrated by the data, proper screening may effectively prevent cervical cancer, since 50% of women diagnosed with cervical cancer had never undergone cervical cytology testing and another 10% had not received screening in the five years preceding their diagnosis[14]. Cervical cancer is very rare among screened women[15].

Cervical cytology is reported according to the Bethesda system, which was introduced in 1988. The principles of the reports include clear, uniform, and reproducible terminology, reflecting the most current understanding of cervical neoplasia. It was revised in

First submission on 09/05/16; last submission on 10/07/16; accepted for publication on 11/07/16; published on 20/08/16

1999, 2001 and the last updated version occurred in 2014, which includes an assessment of the specimen adequacy, whether there is evidence of lesions and the severity of the lesions[16].

HUMAN PAPILLOMAVIRUS

Most cervical cancers develop from infected cells with high-risk human papillomavirus (hrHPV), originated from the squamocolumnar junction. The causal link was described by Dr. Harald zur Hausen, who won the Nobel prize in 2008 for isolating the human papilloma virus (HPV) types 16 and 18 from cervical cancer tissue[17].

HPV is among the most powerful human carcinogens and has been implicated not only to cervical cancer, but also to cancers at several sites. HPV infection is the most common sexually transmitted infection worldwide, mainly in low- and middle-income countries[18]. Apparently hrHPV is a necessary but not a sufficient condition for almost all cervical cancers. The risk of preinvasive lesions and invasive cancer of the cervix is strongly associated with persistent infection with hrHPV, especially type 16. Fortunately, most HPV infections in human are harmless, and cause no lesion. Due to the interaction between host and the pathogen, the majority of infected women will clear the virus and the precancerous lesions will regress. Only about 1% of low-grade lesions (CIN1) and 12% of high-grade lesions (CIN3) will progress and become invasive if left untreated[19].

Since the causal link between cervical cancer and hrHPV infection was established, much effort has been devoted to the study of prevention and identification of HPV infection. Currently vaccination against carcinogenic strains of HPV is commercially available, but even in some developed countries the vaccination uptake has been slow[19, 20].

PAPANICOLAOU TEST – "PAP SMEAR"

In use for more than 50 years, the Pap test in its original preparation, also called "conventional cervical smear (CS) method for cytology collection", is still acceptable for screening purposes[21]. It remains as an alternative for cervical cancer screening due to its simplicity and low cost.

The liquid based cytology (LBC) was approved by the US Food and Drug Administration (FDA) in 1996 as an alternative to conventional cervicovaginal smear. Although several studies showed an increased detection of low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) by LBC preparations, a systematic review did not confirm that LBC is more accurate than conventional smears, but has an equivalent performance. Even so, LBC is gradually replacing the conventional cytological preparations, because it presents many other clear advantages, including the possibility of aliquoting for the hrHPV test[22].

Cervicovaginal cytology is clearly far from being a perfect screening test. In a systematic review, it was shown to have a sensitivity of only 51% (ranging from 30% to 87%) and a specificity of 98% (ranging from 86% to 100%), although methodological quality and frequency of histological abnormalities varied greatly, and only 12 of the 94 studies with less biased estimates were analyzed[23].

Furthermore, there is a significant interobserver variability in the interpretation of cytology, contributing to variations in sensitivity and specificity rates. We must not forget that the interpretative variability is also significant for histological specimens, even among well-trained observers demonstrated in cervical biopsies, as well as many other sites and organs[24].

A meta-analysis found that about 29% of failures to avoid invasive cervical cancer can be attributed to false-negative cytology. The authors examined 42 studies from 1950 to 2007, and the most common failure of the process was history of poor screening: 54% of women had inadequate screening intervals and 42% had never been screened. It should be emphasized that the proportion of Pap smears originally reported as normal and that, after review, were classified as false-negatives, or those normal cases that were not reviewed, but simply assumed to be false-negative, varied greatly among studies. Sampling errors may have contributed to at least some of the cases not reviewed[25].

HPV TEST

The detection of HPV deoxyribonucleic acid (DNA) may be accomplished by several molecular methods, particularly including signal-amplification (Hybrid Capture® assay) and polymerase chain reaction (PCR) based methods. The Hybrid Capture® system is designed to detect HPV divided into high- and low-risk groups, without genotyping individual virus, demonstrating high sensitivity and specificity for hrHPV. The PCR-based techniques are highly sensitive and specific but, besides being a labor-intensive procedure, it also presents some drawbacks, such as false negative results. Real-time PCR assay is a rapid, reproducible and reliable diagnostic tool, which has the additional advantages of detecting very small viral concentrations and different targets simultaneously, as well as to determine the viral load[26].

Initially, the hrHPV test was recommended as a reflex testing of atypical squamous cells of undetermined significance (ASC-US) to screen patients to colposcopy. The sensitivity for detecting CIN3 or greater by hrHPV test was 96.3% compared to 44.1% of cytology by one repeat with a screening threshold of HSIL or greater[27].

In 2004, the National Institute of Health, the National Cancer Institute, the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Cancer Society (ACS) agreed to expand the use of hrHPV as a cotesting[28, 29].

The joint recommendation released in 2012 advocates HPV testing to be used in conjunction with routine cytology, as well as a reflex testing in women aged 30 to 65 years[14, 21]. A woman with a negative result for both hrHPV and cytology has a lower risk of developing CIN2 or CIN3 in the next four to six years[14]. The cotesting increases the detection of CIN2 or greater lesions at baseline and significantly decreases the detection rates of CIN2/CIN3 or greater lesions at subsequent screening compared to cytology alone[30].

The ATHENA trial demonstrated that 10% of women who tested positive for HPV 16 and/or 18 had high-grade cervical neoplasia (CIN2 or worse) that was not detected by cytology[31]. Many other studies have documented that HPV testing has a greater sensitivity and reproducibility with increased negative predictive values compared to cytology[32-38]. The data presented by these studies endorsed the idea of hrHPV test as a primary screening test, replacing cytology as screening women for colposcopy, advocated by many.

In 2014, the FDA approved the cobas® HPV test for primary screening of cervical cancer in women aged 25 or older, by detection of hrHPV genotypes, at intervals equal to or greater than three years[39].

Interim guidelines for primary hrHPV screening were developed by representatives from the Society of Gynecologic Oncology, the American Society of Cytopathology, and the College of American Pathologists, in addition to American Congress of Obstetricians and Gynecologists (ACOG), and all groups authoring the 2012 screening guidelines[40].

In the Quest Diagnostics Health Trend study, which enrolled more than 250,000 women, the HPV/Pap cotesting identified more women whose cervical biopsy result revealed a finding of CIN3 or greater than HPV-only testing (98.8% versus 94%). The data showed that up to 19% of women with cancer may be missed when they are screened using HPV testing only; HPV/Pap cotesting misses 5.5% of cancer cases, and Pap alone, 12.2%. The authors concluded that cotesting in women aged 30-65 is the most effective screening test for detecting cervical cancer[41].

Although the cobas® HPV test has been approved, it was stressed that it has limited sensitivity (27% for women equal to or older than 50 years, 36% for women equal to or older than 40 years, 53% for women equal to or older than 30 years, and 58% for women equal to or older than 25 years), which is much lower than that observed with the cotesting in women equal to or older than 30 years, perhaps because of suboptimal performance of cytology[21, 29, 42]. Negative HPV rates in patients with invasive cervical cancer varied among authors and seemed to increase with time before cancer diagnosis, perhaps due to the smaller size of lesions or lower viral titers during earlier periods[42]. Another arguable point is the use of CIN2 or/and CIN3 or worse as the right endpoint for evaluating cervical screening algorithm, since it does not reflect cancer risk accurately[16, 42].

SCREENING GUIDELINES

Screening recommendations proposed by several societies and private organizations have been published and are reviewed periodically when new evidence suggests that a change may be necessary. Previous established guidelines showed considerable variation prior to 2012.

The current American guidelines for cervical cancer screening were created in 2012 as a joint recommendation of the ACS, ASCCP and the American Society for Clinical Pathology (ASCP), which were accepted and promoted by the ACOG, in association with US Preventive Service Task Force (USPSTF). The benefit was defined as more detection of CIN3 or worse at baseline and reduction in CIN3 or worse detection at subsequent rounds of screening. The harm was defined as an increase in number of colposcopy[14, 21, 43].

Some reviews on cervical cancer screening guidelines present a summary from major organizations recommendations and the reader will find more detailed information[44]. The current main guidelines recommendations are the following:

- cervical cancer screening should begin at 21 years of age, regardless of age of coitarche or vaccination status, with cervical cytology tests exclusively until 30 years of age (either with conventional or liquid-based cytology), every three years;

- for women from 30 to 65 years of age, cotesting with cytology and HPV test every five years is preferred, although cytology screening every three years is acceptable;

- screening should be discontinued for women over 65 years of age at low risk, with no history of cervical intraepithelial neoplasia (CIN) grade 2 or greater, with negative results in prior screening;

• screening should be discontinued for women of any age who have total hysterectomy and have no history of cervical cancer or precancerous condition.

Adherence to guideline recommendations is quite variable. Many clinicians continued to suggest annual Paps, as recommended by ACOG, although current guidelines advocated against annual screening, since no advantage is observed in relation to Pap tests performed every two or three years. Physicians believe that patients were uncomfortable with less frequent testing and if they extend the screening intervals, patients would not return annually just for the clinical examination[45].

CERVICAL CANCER IN BRAZIL

According to the 2016/2017 estimates, Brazil will register next year 300,800 cases of cancer among women[46]. More than 16,000 new cases of cervical cancer are expected in 2016[47]. Cervical cancer remains as the third leading cause of cancer-related mortality among women for decades, without any improvement[48].

Currently, the Brazilian program to cervical cancer control is based on population screening and vaccination, used together as complementary actions and coordinated by the Brazilian National Cancer Institute (Instituto Nacional de Câncer José Alencar Gomes da Silva [Inca]), an agency of the Ministry of Health of Brazil facing national integrated actions for the control and prevention of cancer[49]. The screening method is the Pap test or Pap smear for women between 25 to 64 years old, or sexually active women; this test is provided annually (or once every three years after two normal tests) and it is followed by colposcopy for HSIL, carcinoma, or persistent LSIL or ASC-US.

LBC was also incorporated as the standard method of evaluating cervical samples in Brazil, largely replacing CS. Some Brazilian studies have demonstrated a better performance of LBC compared to CS, with lower rates of unsatisfactory specimens and higher sensitivity[50-52]. A more recent study critically analysed 218,594 cases collected in a public health service in the state of São Paulo and observed positivity of 5.7% versus 3%, respectively, in LBC and CS; unsatisfactory preparations were present in 0.3% and 3% of the cases, respectively[53]. However other groups have observed similar performances between the methods, finding no significant diferences[54, 55].

In 2012, a Quality Management Manual for Cytopathology Laboratory was published by Inca and the Ministry of Health of Brazil, in order to improve the quality and reliability of cytological test[56].

In 2014, the Ministry of Health of Brazil launched the National Immunization Program through a quadrivalent HPV vaccine (subtypes 6, 11, 16, and 18) for girls between 9-13 years old[57].

A recent study evaluated the cervical cancer screening program in Brazil from 2006 to 2013 using the Information System of Cervical Cancer Screening (Sistema de Informação do Câncer de Colo de Útero [SISCOLO]), created by the Department of Informatics of the Public Health System (Departamento de Informática do Sistema Único de Saúde [DATASUS]), which contains information on all Pap tests collected in the public health system, and was implemented for the management and monitoring of the cervical cancer screening program[58]. A decreasing trend in the rates of LSIL and HSIL was observed, as well as lower numbers of positive cytological diagnosis and an increased rate of rejected exams. The positivity rates and the frequency of unsatisfactory cases were lower than expected. The authors suggest that actions should be taken by the government to improve the effectiveness of cervical cancer control in Brazil, through more funding for internal quality control during both the pre-analytical and the analytical phase[59].

Albeit Brazil, like many other countries in Latin America, has a cytology-based screening program, they often have problems with quality and/or delays in follow-up care[60].

FUTURE STRATEGIES

The best screening algorithm remains a matter of debate.

Primary HPV screening is an attractive option to health service because the results are not subject to inter-observer variation. However, it requires equipments, reagents, personnel, training, quality control and accreditation. This scenario is far from the real world in different populations, even in developed countries, considering that many women will be screened or may never be screened at all.

We must remember the fact that the system for cervical cancer screening with both the Pap test and the HPV test is already working in many practices. There is no reason to disrupt such an operative scheme that is working successfully without adequate evidence of additional benefit of primary HPV screening. Further data are needed on the actual benefits and costs and the impact on the use of colposcopy and other diagnostic tests[61].

Supporters of primary HPV screening claim that this method not only finds more CIN3 or worse than cytology or cotesting does, but also find them earlier; moreover, the positive predictive value of the primary HPV screening algorithm was greater than that

one of cytology. In contrast, those who advocate cotesting believe this approach detects more disease than the HPV test alone and emphasize that the performance of this new algorithm has not been assessed in routine clinical use. The focus of the debate about the best screening algorithm to detect cervical cancer is much more complex, since it may involve reducing costs rather than maximizing protection, not only by decreasing the number of tests, but also by increasing the screening intervals[41].

In some practices, where access to cytological examination is limited, primary HPV testing may allow to provide screening for the patients, which had not been previously possible[61].

Several studies support that HPV testing is feasible in low-resource setting as a tool for cervical cancer screening. The incorporation of new technologies, adapted for low- and middle-income countries may be part of future programs for early diagnosis and control of the disease. Although the best screening strategy in this context is still a work in progress, perhaps HPV testing can be applied using a self-obtained vaginal samples that will allow first-line screening and triaging of HPV-positive women during a single visit, defining management and eventually treatment[62].

In summary, despite the great benefit that the cervical cancer screening programs achieved through the use of cytology and HPV testing, there are still important issues to be discussed and improved in defining future strategies, including simplification and possible application in different socioeconomic contexts, definition of the best test or tests to be applied and interval recommendation, minimizing harms. After well defined, screening algorithms were established by leading organizations; management protocols should be disclosed among physicians and patients through education programs, integrated into a multidisciplinary team, with the participation of all professionals involved in women's health, ensuring not only a more effective diagnosis, but also an appropriate treatment and monitoring, connecting the primary, secondary and tertiary levels of health. In Brazil, the new recommendations are being finalized and will soon be published by Inca, Ministry of Health of Brazil.

CONCLUSION

1) Cervical cytology, including conventional smear and liquid based cytology, is a successful method for cancer screening and is still recommended as the exclusive test for women 21 to 29 years of age; 2) since HPV was established as the main causative agent of cervical cancer, its detection improved screening sensitivity; 3) cotesting, hrHPV test used in association with cytology, is recommended for women 30 to 64 years of age, since it is the most effective screening method for detecting cervical cancer; 4) the sole routine clinical use of HPV testing, or primary HPV testing, is still a matter of debate, but, perhaps, it may prove to be an option for strategic screening in countries with limited resources, as new tests are becoming faster, automated and cost-effective.

RESUMO

Inicialmente, a triagem para detecção do câncer de colo uterino era feita por meio de uma simples amostra cervicovaginal colhida pelo médico, sempre que o paciente comparecia à consulta médica; logo se estabeleceu como "exame de Papanicolaou" anual. Desde então, um teste elementar evoluiu para um processo complexo, com múltiplos algoritmos para identificação de doença invasiva. A detecção do papilomavírus humano (HPV) tornou-se parte das novas recomendações de triagem, resultando em grandes mudanças nas diretrizes. Esta revisão pretende enfatizar os tópicos mais importantes que fazem parte do rastreamento do câncer de colo do útero, incluindo citologia cervical e detecção do HPV, bem como discutir aspectos particulares do câncer de colo do útero no Brasil. Apesar dos grandes benefícios alcançados pelos programas de rastreamento do câncer de colo uterino por meio do uso da citologia e do teste de HPV, existem ainda pontos importantes a serem discutidos e melhorados na definição de estratégias futuras, como simplicidade e possível aplicação em diferentes contextos socioeconômicos, definição do melhor teste ou testes a serem aplicados e intervalo recomendável, minimizando possíveis danos. Após o estabelecimento de algoritmos de rastreamento bem definidos pelas principais organizações, protocolos de manejo devem ser divulgados entre médicos e pacientes por programas de educação.

Unitermos: *neoplasias do colo do útero; prevenção de câncer de colo uterino; técnicas de diagnóstico molecular; esfregaço vaginal; testes de DNA para HPV.*

REFERENCES

1. Koss LG. Introduction. Historical overview. In: Koss LG, editor. Diagnostic cytology and its histopathologic bases. 4th ed. Philadelphia, Pennsylvania: JB Lippincott Company; 1992.

2. Naylor B. The century for cytopathology. Acta Cytol. 2000; 44(5): 709-25. PubMed PMID: 11015971.

3. McSweeney DJ, McKay DG. Uterine cancer: its early detection by simple screening methods. N Engl J Med. 1948; 238(25): 867-70. PubMed PMID: 18864481.

4. Cramer DW. The role of cervical cytology in the declining morbidity and mortality of cervical cancer. Cancer. 1974; 34(6): 2018-27. PubMed PMID: 4434331.

5. Miller AB, Lindsay J, Hill GB. Mortality from cancer of the uterus in Canada and its relationship to screening for cancer of the cervix. Int J Cancer. 1976; 17(5): 602-12. PubMed PMID: 1270176.

6. Christopherson WM, Scott MA. Trends in mortality from uterine cancer in relation to mass screening. Acta Cytol. 1977; 21(1): 5-9. PubMed PMID: 264759.

7. Macgregor JE, Teper S. Mortality from carcinoma of cervix uteri in Britain. Lancet. 1978; 2(8093): 774-6. PubMed PMID: 80695.

8. Clarke EA, Anderson TW. Does screening by "Pap" smears help prevent cervical cancer? A case-control study. Lancet. 1979; 2(8132): 1-4. PubMed PMID: 87887.

9. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. Lancet. 1987; 1(8544): 1247-9. PubMed PMID: 2884378.

10. Anderson GH, Boyes DA, Benedet JL, et al. Organisation and results of the cervical cytology screening programme in British Columbia, 1955-85. Br Med J (Clin Res Ed). 1988; 296(6627): 975-8. PubMed PMID: 3129115.

11. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999; 318(7188): 904-8. PubMed PMID: 10102852.

12. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. BMJ. 1999; 318(7193): 1244-5. PubMed PMID: 10231253.

13. Lynge E, Poll P. Incidence of cervical cancer following negative smear. A cohort study from Maribo County, Denmark. Am J Epidemiol. 1986; 124(3): 345-52. Erratum in: Am J Epidemiol. 2008; 143(7): 707. PubMed PMID: 3740035.

14. Committee on Practice Bulletins – Gynecology. ACOG practice bulletin number 131: screening for cervical cancer. Obstet Gynecol. 2012; 120(5): 1222-38. PubMed PMID: 23090560.

15. Nayar R, Wilbur DC. The Pap test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). Acta Cytol. 2015; 59(2): 121-32. PubMed PMID: 25997404.

16. Dinkenspiel H, Kinney W. State of the science: cervical cancer screening in transition. Gynecol Oncol. 2014; 133(3): 389-93. PubMed PMID: 24878390.

17. zur Hausen H. Condylomata acuminata and human genital cancer. Cancer Res. 1976; 36(2 pt 2): 794. PubMed PMID: 175942.

18. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet. 2013 Sep 7; 382(9895): 889-99. PubMed PMID: 23618600.

19. Tota JE, Chevarie-Davis M, Richardson LA, Devries M, Franco EI. Epidemiology and burden of HPV infection and related diseases: implications for prevention strategies. Prev Med. 2011; 53 (Suppl 1): S12-21. PubMed PMID: 21962466.

20. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 2007; 57(1): 7-28. PubMed PMID: 17237032.

21. Saslow D, Solomon D, Lawson HW, et al. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology. Screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012; 62(3): 147-72. PubMed PMID: 22422631.

22. Davey E, Barratt A, Irwig L, 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. PubMed PMID: 16413876.

23. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med. 2000; 132(10): 810-9. PubMed PMID: 10819705.

24. Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA. 2001; 285(11): 1500-5. PubMed PMID: 11255427.

25. Spence AR, Goggin P, Franco EL. Process of care failures in invasive cervical cancer: systematic review and meta-analysis. Prev Med. 2007; 45(2-3): 93-106. PubMed PMID: 17651792.

26. Abreu AL, Souza RP, Gimenes F, Consolaro ME. A review of methods for detect human Papillomavirus infection. Virol J. 2012 Nov 6; 9: 262. PubMed PMID: 23131123.

27. Solomon D, Schiffman M, Tarone R; ALTS Study group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. J Natl Cancer Inst. 2001; 93(4): 293-9. PubMed PMID: 11181776.

28. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol. 2004; 103(2): 304-9. PubMed PMID: 14754700.

29. Schiffman M, Herrero R, Hildesheim A, et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. JAMA. 2000 Jan 5; 283(1): 87-93. PubMed PMID: 10632285.

30. Bouchard-Fortier G, Hajifathalian K, McKnight MD, Zacharias DG, Gonzalez-Gonzalez LA. Co-testing for detection of high-grade cervical intraepithelial neoplasia and cancer compared with cytology alone: a meta-analysis of randomized controlled trials. J Public Health (Oxf). 2014; 36(1): 46-55. doi: 10.1093/pubmed/fdt057. PubMed PMID: 23735961.

31. Wright TC Jr, Stoler MH, Sharma A, Zhang G, Behrens C, Wright TL. ATHENA (Addressing THE Need for Advanced HPV Diagnostics) Study Group. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol. 2011; 136(4): 578-86. PubMed PMID: 21917680.

32. Kitchener HC, Gilham C, Sargent A, et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur J Cancer. 2011; 47(6): 864-71. PubMed PMID: 21334200.

33. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011; 12(7): 663-72. PubMed PMID: 21684207.

34. Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol. 2011; 12(9): 880-90. PubMed PMID: 21865084.

35. Cox JT, Castle PE, Behrens CM, Sharma A, Wright TC Jr, Cuzick J; Athena HPV Study Group. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. Am J Obstet Gynecol. 2013; 208(3): 184.e1-184.e11. PubMed PMID: 23174289.

36. Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 2+ and CIN 3+ among women with HPV-positive and HPV-negative LSIL Pap results. J Low Genit Tract Dis. 2013; 17(5 Suppl 1): S43-9. PubMed PMID: 23519304.

37. Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women who test Pap-negative but are HPV-positive. J Low Genit Tract Dis. 2013; 17(5 Suppl 1): S56-63. PubMed PMID: 23519306.

38. Ronco G, Dillner J, Elfström KM, et al. International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014; 383(9916): 524-32. PubMed PMID: 24192252.

39. Abraham J, Stenger M. Cobas HPV test for first-line screening for cervical cancer. J Community Support Oncol. 2014; 12(5): 156-7. PubMed PMID: 24971425.

40. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol. 2015; 125(2): 330-7. PubMed PMID: 25569009.

41. Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015; 123(5): 282-8. PubMed PMID: 25864682.

42. Stoler MH, Austin RM, Zhao C. Point-counterpoint: cervical cancer screening should be done by primary human papillomavirus testing with genotyping and reflex cytology for women over the age of 25 years. J Clin Microbiol. 2015; 53(9): 2798-804. PubMed PMID: 25948606.

43. Moyer VA; U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. preventive services task force recommendation statement. Ann Intern Med. 2012; 156(12): 880-91, W312. PubMed PMID: 22711081.

44. Davis M, Feldman S. Making sense of cervical cancer screening guidelines and recommendations. Curr Treat Options Oncol. 2015; 16(12): 55. doi:10.1007/s11864-015-0373-1. PubMed PMID: 26467929.

45. Perkins RB, Anderson BL, Gorin SS, Schulkin JA. Challenges in cervical cancer prevention: a survey of U.S. obstetrician-gynecologists. Am J Prev Med. 2013; 45(2): 175-81. doi: 10.1016/j.amepre.2013.03.019. PubMed PMID: 23867024.

46. Instituto Nacional de Câncer José Alencar Gomes da Silva (Inca) [Internet homepage]. Brasil. Estimativa 2016/2017: incidência de câncer no Brasil. Rio de Janeiro, January 2016. Available at: http://www.inca.gov.br/wcm/dncc/2015/estimativa-2016.asp.

47. Instituto Nacional de Câncer José Alencar Gomes da Silva (Inca) [Internet homepage]. Brasil. Estimativa 2016/2017: incidência de câncer de colo uterino no Brasil. Rio de Janeiro, January 2016. Available at: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/colo_utero/definico.

48. Ministério da Saúde [Internet homepage]. Brasil. Atlas on-line de mortalidade: taxas de mortalidade das 5 localizações primárias mais frequentes em 2013, ajustadas por idade, pela população mundial, por 100.000 mulheres, Brasil, entre 1979 e 2013. January, 2016. Available at: https://mortalidade.inca.gov.br/MortalidadeWeb/pages/Modelo04/consultar.xhtml#panelResultado.

49. Instituto Nacional de Câncer José Alencar Gomes da Silva (Inca) [Internet homepage]. Brasil. Programa nacional de controle do câncer de colo uterino. Available at: http://www2.inca.gov.br/wps/wcm/connect/acoes_programas/site/home/nobrasil/programa_nacional_controle_cancer_colo_utero/.

50. Pereira SMM, Utagawa ML, Pittoli JE, et al. Cellularity evaluation in liquid-based cytology preparations. Rev Inst Adolfo Lutz. 2003; 62(1): 35-9.

51. Longatto Filho A, Pereira SM, Di Loreto C, 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. PubMed PMID: 15863150.

52. Scapulatempo C, Fregnani JH, Campacci N, Possati-Resende JC, Longatto-Filho A; Rodeo Study Team. The significance of augmented high-grade squamous intraepithelial lesion detection on pap test examination: partial results from the RODEO study team. Acta Cytol. 2013; 57(5): 489-94. PubMed PMID: 24135251.

53. Longatto-Filho A, Levi JE, Martins TR, et al. Critical analyses of the introduction of liquid-based cytology in a public health service of the state of São Paulo, Brazil. Acta Cytol. 2015; 59(3): 273-7. PubMed PMID: 26279162.

54. Mattosinho de Castro Ferraz MG, Nicolau SM, Stávale JN. Cervical biopsy-based comparison of a new liquid-based thin-layer preparation with conventional Pap smears. Diagn Cytopathol. 2004; 30(4): 220-6. PubMed PMID: 15048954.

55. Alves VA, Castelo A, Filho AL, et al; DNA-Citoliq working Group, São Paulo, Brazil. Performance of the DNA-citoliq liquid-based cytology system compared with conventional smears. Cytopathology. 2006; 17(2): 86-93. PubMed PMID: 16548993.

56. Instituto Nacional de Câncer José Alencar Gomes da Silva (Inca) [Internet homepage]. Brasil. Manual de gestão da aualidade para

laboratórios de citopatologia. Rio de Janeiro: INCA; 2012. Available at: http://www1.inca.gov.br/inca/Arquivos/publicacoes/manual_gestao_qualidade_laboratorio_citopatologia.pdf.

57. Instituto Nacional de Câncer José Alencar Gomes da Silva (Inca) [Internet homepage]. Brasil. Prevenção primária do câncer de colo uterino – programa de vacinação. Available at: http://www2.inca.gov.br/wps/wcm/connect/acoes_programas/site/home/nobrasil/programa_nacional_controle_cancer_colo_utero/prevencao.

58. Ministério da Saúde [Internet homepage]. Brasil. Departamento de informática do Sistema Único de Saúde (DATASUS) – Sistema de informação do câncer do colo do útero (SISCOLO). Rio de Janeiro: INCA; 2011. Available at: http://www2.datasus.gov.br/DATASUS/index.php.

59. Costa RF, Longatto-Filho A, Pinheiro C, Zeferino LC, Fregnani JH. Historical analysis of the Brazilian cervical cancer screening program from 2006 to 2013: a time for reflection. PLoS One. 2015. 24; 10(9): e0138945. doi:10.1371/journal.pone.0138945. eCollection 2015. PubMed PMID: 26402737.

60. Bychkovsky BL, Ferreyra ME, Strasser-Weippl K, et al. Cervical cancer control in Latin America: a call to action. Cancer. 2015 Feb 15; 122(4): 502-14. doi: 10.1002/cncr.29813. Epub 2015 Dec 15. PubMed PMID: 26670695.

61. Feldman S. Human papillomavirus testing for primary cervical cancer screening: is it time to abandon Papanicolaou testing? JAMA Intern Med. 2014; 174(10): 1539-40. doi: 10.1001/jamainternmed.2014.4021. PubMed PMID: 25069413.

62. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: emerging technologies and policy choices. World J Clin Oncol. 2015 Dec 10; 6(6): 281-90. PubMed PMID: 26677441.

CORRESPONDING AUTHOR

Cristina Aparecida T. S. Mitteldorf
Rua Dona Adma Jafet, 91, 3º subsolo, bloco C; Bela Vista; CEP: 01308-050, São Paulo-SP, Brasil; e-mail: crismittel@terra.com.br.