



Maximizing Screening for Cervical Cancer

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Abstract

Since the introduction of cytology or Pap test (Pap) in 1943, the cervicovaginal Pap has been used as the standard screening test for cervical cancer and its dissemination contributed to the reduction of incidence and mortality for cervical cancer worldwide, the incidence of cervical cancer has steadily declined, cases of deaths related to cervical cancer, are reported every year due to false negative results. Therefore, new detection methods have been proposed. Liquid-Based Cytology (LBC) was introduced in 1996 to overcome the limitations of conventional Pap tests. Since then, other methods of LBC have been developed and used, including the High-risk Human Papillomavirus (HPV-hr) test, as a method with greater sensitivity that requires less screening.

Cervical cancer can be prevented by early detection and treatment of precancerous lesions that are mainly caused by infection with high-risk strains of the HPV-hr. Screening with Pap and with the use of HPV-hr tests, as an option for women aged 30 to 65, allows prolonged screening intervals. Evidence that evaluates screening programs that involve the HPV-hr test, primary and Co-testing (Pap and HPV-hr test) inform new detection strategies. The evidence supporting the Pap is well established, the HPV-ar test, primary or as Co-testing, compared to the Pap alone, in the detection of CaCu, provide better protection and allow for greater re-evaluation intervals. Cervical cancer rates are low in women who are routinely screened, but not all women do it, and there are significant racial/ethnic disparities in cervical cancer morbidity and mortality; several potential combinations of the Pap results and the HPV-hr test; abnormal is based on the principle of management equal to equal risks, which determine that the risk of cervical cancer is a function of its results, to evaluate subsequent management, including routine screening, close monitoring (more frequent screening and/or tests additional), colposcopy or treatment.

There are several HPV-hr tests available; they can be used as in Co-testing, or as reflex tests for an abnormal Pap, such as atypical squamous cells of undetermined significance (ASC-US), as HPV-hr tests, primary alone, for the detection and/or genotyping of HPV-hr (tests for a particular genotype HPV-16 or 18): A positive HPV-ar test and a negative Pap have an increased risk of Cervical Intraepithelial Neoplasia (CIN) and its management includes repeat Co-testing (HPV-hr test,

Received: Dec 24, 2020

Accepted: Feb 12, 2021

Published Online: Feb 15, 2021

Journal: Annals of Gynecologic Cancer

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

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Keywords: Cervical cáncer; Screening tests; Cytology or Pap test; Human papillomavirus tests; perspectives.



and Pap at 12 months or HPV genotyping. The recurrence of the HPV-hr test, positive, after a period of HPV-hr tests, negative; is usually a reactivation of a latent infection, or a new HPV-hr infection; unlike persistent HPV-hr infection (that is, a positive HPV-hr test; at least 12 months apart) reflects increased risk of development or progression to AIS of Grade 2 or more serious (CIN-2+). They are high-risk patients and their handling with surveillance narrow and active treatment, indicated. If HPV-hr tests are positive for HPV-16 or 18, even if the Pap is negative or reports ASC-US; It implies greater risk and indication of immediate delivery to colposcopy. When the Pap is unsatisfactory, it is repeated even if the HPV-hr test result is negative. An unsatisfactory cervical Pap is considered unreliable for the evaluation of epithelial abnormalities and may also result in a false negative HPV-hr test. The greater sensitivity of primary HPV-hr tests in the first test has the potential to improve results in the high-risk population and only that resources are limited, the Pap (with or without HPV-hr, They are used for cervical cancer detection.

Background

For the detection of cervical cancer, screening tests are used with combinations of cytology or Papanicolaou test (Pap) and tests for the High-risk Human Papillomavirus (HPV-hr), which is Co-testing; The management of these tests varies according to age and previous results, the use of HPV-hr tests, they are used in women aged 30 to 64 years, for primary screening; but, the interpretation of the results, is a common problem for the doctors [1-11].

There are many potential combinations of HPV-hr-HPV test and Pap results, some of these combinations or test results are not included in the guidelines or include tests that detect late biological events associated with High-grade Cervical Intraepithelial Lesion (HCIL) or grade 2 or 3 Cervical Intraepithelial Neoplasia (CIN-2/3) and Cervical Cancer; Such tests are based on molecular markers and when they are negative they do not imply any risk of disease such as dual staining p16/Ki-67 or the E6 and E7 oncoproteins of HPV-hr [12-16].

It is a challenge for physicians to choose the appropriate management and they must be interpreted based on evidence, in order to individualize the management, abnormal results of screening tests for the detection of Cervical Cancer are based on the principle of equal management at equal risks [8]. The risk of Cervical Cancer is determined based on the results of the test, which indicates the evaluation or treatment. Options, including ongoing routine screening, close surveillance (with more frequent and/or additional screening tests), colposcopy, or treatment (example, cervical cone, ablative treatments). To determine the risks associated with common screening test results; some risk calculations cannot be made with certainty and must be extrapolated based on available data and expert opinion. The same approach applies to patients who have a set of Cervical Cancer detection results that are rare or do not exactly conform to management guidelines, and the clinician must estimate the risk of Cervical cancer to manage [15-16].

History of screening for cervical cancer

The incidence rate of cervical cancer by age throughout the world has decreased significantly due to the detection of cytology or Pap smear (Pap) [17].

Screening tests for the detection of Cervical Cancer have a long history, characterized by its natural history of the disease from the precancerous lesions (7 to 20 years) before progressing to invasive cancer and makes its detection possible; the Pap that was used for the first time in 1943, and is used as a screening test for Cervical Cancer; developed countries with organized conventional Pap screening programs have several advantages, including simple procedures, low cost, and high specificity; and it has reduced the incidence and mortality from Cervical Cancer; as reported in a Pap-based screening program for women ≥ 30 years old every two years and the results are reported according to the Bethesda System; the Cervical Cancer diagnosis rate decreases from 0.1 - 0.96; in the intakes of university hospitals and 0.07% -0.09% in commercial laboratories in 1998 to 0.28% and 0.033% respectively in 2016 [15 and the original]; even though deaths related to Cervical Cancer are reported annually raises concerns regarding the limitations of current screening tests [2-9].

Despite the numerous advantages of conventional Pap, this technique requires supplementation due to the high false negative rate (20%) caused by errors that occur during specimen collection, preservation, analysis, and reading; low sensitivity; highly subjective results and low reproducibility; the level of experience of the cytopathologist; better screening is required [8,11]. To overcome these limitations, a Liquid-Based Cytology (LBC) method was developed that involves fluid-based collection and processing; with advantages: low levels of artifacts, each sample is fixed immediately after collection; superior morphology; reduction of unsatisfactory results caused by blood or inflammatory cells; quick and easy detection; better sample due to scattering of cells; and with the potential to perform multiple tests on the same sample. the effectiveness of LBC increases the detection rate of Squamous Intraepithelial Lesions (SIL), especially Low-grade SIL (LSIL), and improves the sample [11,12].

When comparing the clinical utility of LBC with conventional Pap; LBC not only improves the diagnostic rate, it reduces unsatisfactory samples, compared to conventional Pap, and the current use of LBC is increasing [13,15,16].

The unsatisfactory conventional Pap report represents 0.6%, and must be repeated in 2 to 4 months, for adequate follow-up; Although LBC reduces this proportion, diagnostic accuracy is crucial for false positive/negative evaluations [14-16].

Pap alone, its accurate results do not detect Cervical Cancer, additional combined tests are required; colposcopy increases sensitivity, but its limitations (cost, time and training) are impractical, cervicography allows the interpretation of ectocervical photographic images based on the principles of colposcopy; achieves greater diagnostic precision combined with Pap of 90 to 100% for infiltrating Cervical Cancer and 90 to 95% for Cervical Intraepithelial Neoplasia (CIN, its cost), continues to be a significant limiting factor for its use as a general detection method, a despite the lower cost of co-testing [9,15,16].

HPV plays an important role in the development of Cervical Cancer and is found in 90 to 100% of High-grade SIL (HSIL) or invasive Cervical Cancer, the inclusion of ar-HPV tests in the detection of Cervical Cancer is useful to complement the Conventional Pap. Repeating the Pap, performing colposcopy or HPV-hr tests are recommended methods to select high-risk patients when a Pap with ASC-US is reported, where the usefulness of the HPV-hr test is constantly highlighted.

The HPV-hr test, by means of the polymerase chain reaction (PCR), or through the hybridization of the DNA with the hybrid capture II or Hybrid Capture II (HCII) system; are complementary methods for the management of ASC-US and LSIL. The sensitivity and reliability of the have been approved, and it has been used extensively to detect HPV. An HPV DNA microchip test is also being used that allows the identification of HPV genotypes from a single test [1-8,15,16].

Although the majority of ASCUS or LSIL are naturally eliminated, a small portion persists or transforms into CIN-2/3, in patients initially diagnosed with ASC-US or LSIL by Pap, 5 to 15% have HSIL by biopsy, it is important to verify HSIL in patients diagnosed with ASC-US or LSIL by Pap, the HPV-ar tests, had greater sensitivity to detect HSIL from ASC-US than Pap (0.83 vs 0.66), but Co-testing increases the sensitivity (0.92). Pap has higher sensitivity (1.00) to detect HSIL than LSIL compared to HPV-ar (0.93), while Co-testing showed a sensitivity of 1.00. In addition, it was determined that HPV-hr tests are useful only for the management of patients with ASC-US; but, not in LSIL, they must be sent for immediate colposcopy or repeat the Pap every 6 months [15,16,17].

The prevalence of HPV infections with the HPV test; 10.3% were positive for HPV DNA, while 60% had ar-HPV and in order of frequency were HPV-16,33,58,66,18,31 and others, while low-risk HPV genotypes (HPV-lr) observed in order of frequency were HPV-70,81 and others Another report of the prevalence of HPV infections, 48.8% were positive, 86.9% were positive for eVPH-ar, and the genotypes in order of frequency were HPV -16,58,18,52,53,31 and others, while low-risk HPV, in order of frequency were HPV-70,6,11,40 and 42 [2-9,15,16].

Current status of screening for cervical cancer

Screening tests for Cervical Cancer detection using Pap smears were not widely used in the early stages of screening programs, in a report only 88% of women (≥ 20 years) [33] were screened, probably due to the lack of advocacy and monitoring for marginalized groups [8]. The new screening programs carried out in different regions of the participating countries were initially based on Pap, but with the aim of moving towards direct detection of HPV infection [15].

The evaluation of costs and clinical effectiveness showed that HPV-ar-16/18 tests performed together with Pap and dual p16/Ki-67 staining improves the detection rate of Cervical Cancer compared to Pap alone, with a lower total cost annual [18]; HPV tests performed every 5 years are more effective for the detection of CaCu at a better cost than Pap tests performed every 2 years and change the primary detection of HPV with partial genotyping [19].

Even Co-testing can better improve clinical and economic outcomes, HPV-hr, primary; in women older than 25 years; performed every 5 years is the most efficient alternative compared to Pap [20]. In asymptomatic women older than 20 years, conventional Pap or LBC is started with intervals every 3 years until they turn 74 years old, it is suspended, without having had three consecutive negative Pap tests in the previous 10 years [21]; however, Pap smears are underused in marginalized populations where there are inequalities in their access. The cost of HPV-hr testing is lower than the costs associated with establishing Pap-based detection systems and in populations where it cannot be performed, it is replaced by self-testing, with HPV-hr tests. The primary HPV test is increasingly used in some coun-

tries, its efficacy and cost-effectiveness vary in different clinical and socioeconomic settings, and only the Pap test is useful in countries with well-developed detection systems [22-24].

Due to the financial limitation for the national Cervical Cancer detection program and the associated low medical costs, Pap is still used, due to the following factors: Guaranteed quality management, available training for qualified Pap detection personnel, and the relatively high associated cost. with the HPV-hr test. In addition, even in negative cases for HPV, lesions equal to or more severe than LSIL are observed in the Pap and histopathological in 17.5% of cases, despite the high sensitivity of the HPV-hr test, it has the crucial disadvantage of low specificity and its independent result is not useful in most cases, which can cause unnecessary anxiety for patients, the HPV-hr test is not considered an adequate independent screening test [5,9,15,16,17].

Pap management guide and hpv-ar test results

In general, Co-testing is a marker of the current risk of CIN-2 or higher grade lesion (CIN-2 +), even more so the genotype of HPV-hr, (for, HPV-16 or 18) positive control, it is an excellent marker to predict the future risk of CIN-2 +. When making clinical decisions, if there is knowledge of past and/or current HPV-ar results, or if HPV-hr positivity persists, (defined as consecutive positive ar-HPV results, with at least 12 months of difference), it is helpful for making clinical decisions about a patient's risk of having a current or future disease [14,25].

HPV-ar tests, available

There are several HPV-hr tests available; can be used for one or more HPV genotypes; such as Co-testing, reflex tests in response to a Pap with Atypical Squamous Cells of Undetermined importance (ASC-US), HPV-hr, primary tests or HPV-hr genotyping; But, all HPV tests must pass. The term HPV-hr test refers to a test that is reported positive if one or more genotypes of HPV-hr are detected, all tests must genotype 13 or 14 genotypes of HPV-hr, common [15,16]. HPV genotyping refers to testing for individual HPV genotypes, usually HPV-16 or 18, some include HPV-45.

The clinical data varies for each HPV-hr test, and between laboratories with respect to performance, which is a challenge for the physician to individualize its handling, each approved test has its own performance differences to identify CIN-2 +; overall performance is similar. As technology evolves and new tests are developed, future screening guides take on these differences in performance. Currently, knowledge of the Pap results, HPV-hr test, HPV genotyping (if done), and knowledge of the patient's previous HPV results play a role in the management decision. Other antecedents that modify the risk are previous HPV vaccination (reduces risk), previous negative HPV-hr tests (reduces risk) and previous treatment for CIN (increases risk) [5,13,15, 16.17].

Positive results of the Hpv-ar test

Screening guidelines for the detection of CaCu address HPV-hr testing, in women aged 30 to 64 years, in combination with Pap or as a reflex test of a Pap result with ASC-US or the primary test of HPV-hr. every five years, if the test is negative [10].

HPV-hr testing is generally not recommended in women ages 21 to 29. Reflex testing is performed on ASC-US Pap, although repeat Pap in 12 months is preferred. New HPV infections often occur shortly after the onset of active sexual life, HPV-hr infec-

tion is common in women under the age of 25, the related clinically relevant disease in women of this age is extremely rare. If an HPV-ar test is done in young women and it is positive, we use conservative approaches to management. This includes Pap and/or HPV-ar tests, more frequent instead of colposcopy [15,16]. The HPV-hr test, primary, its role varies [2-6]. The first positive result for HPV; it is common and, if there is no previous positive test for HPV, it most likely represents a new infection. Most new infections will test negative again within 6 to 12 months. Women with a new positive HPV-hr can be counseled about the high probability that the test results will be negative again. These patients are managed based on the combination of HPV-hr and Pap test results, according to guidelines [2-6,9,15,16].

HPV-ar test, it is positive, and the Pap negative

In patients ≥ 30 years old with a positive HPV-hr, and negative Pap test have a higher risk of cervical disease in the screening than the general population, the management of this result includes repeating the Co-testing) at 12 months or HPV genotype. If it is positive for HPV-16 or 18, colposcopy is performed immediately [2-6,9,15,16].

HPV-ar test, recurrent positive

It is a common scenario for a positive HPV-ar test to be followed by a negative HPV-hr test; It happens in most women with a positive HPV-ar test, due to the adequate immune response that is generated to make the HPV infection latent and it is likely that the HPV has not disappeared, it is only in a latent state below the detection threshold of the test to be HPV positive. Some patients who have had HPV-hr tests, positive and then negative, the HPV-hr test, positive can reappear. Often it is the same HPV genotype as a previous infection, suggesting a reactivation of a latent infection, it is impossible to define whether a current HPV infection is new or a reactivation of an old latent or a previously acquired reactivation that was latent. The majority of infections detected during the years of detection are reactivations of latent infections that are acquired at or near the onset of active sexual life. Reactivation of a latent infection implies immunosuppression and the patient will have a higher risk of persistence; it is particularly common in immunocompromised patients. When patients have Pap and HPV-hr test results, which are occasionally positive and negative over time, they suggest borderline latent infection and their management is closely monitored with Co-testing and/or colposcopy every 12 months, depending on the results [9,15,16,17].

Persistent HPV infection (defined as consecutive positive HPV results at least 12 months apart) [14] is the etiopathogenic process necessary for progression to CIN-2+. In patients with persistent HPV infection; diagnosed with CIN-2+, almost all women with persistent HPV infection developed CIN-2 + within five to seven years, many within two years. These high-risk women, with persistent HPV-hr infection, should be treated with surveillance and treatment, if indicated [9,15,16]. Co-testing allows the physician to better individualize the management and determine if there is progression to CIN-2 + or its possible regression.

If the patient had a normal Pap in the past and now has a positive Pap and a Pap with LSIL or persistence of HPV-ar, suspect that these patients will have CIN-2+ in the future; but it is also likely to show progression, or continued confusing results, or regression. There are no high-throughput surrogate test mark-

ers to predict the direction infection and disease will take. The patient should be evaluated with colposcopy and, if the results are negative or CIN is identified, they are closely monitored. On the contrary, if the patient had positive HPV-hr and Pap tests with LSIL in the past and the last Co-test with negative Pap and HPV-hr negative test, the chances of CIN-2+ in the future is less; even without recurrence of the disease and its management is based on the principle of equal risks [9,13,15,16].

HPV-hr, positive, low-risk Pap test and negative colposcopy; it is a common and frustrating clinical scenario (for the patient and the clinician). It is important to perform vaginoscopy, if it is negative, they are still at risk of progression, and close monitoring is prudent. Only a small percentage of these patients will progress, but there are no high-throughput clinical markers to predict progression.

HPV genotyping

HPV-16 or 18 genotype positive; indicates high risk of CIN-2 +, current or future and is an indication for immediate referral to colposcopy and should replace other tests, even if the Pap is negative or with an ASC-US report, the risk of clinically relevant disease, with HPV-16 positive is greater than most of the associated risks in immunocompromised HPV-16 negative patients. Other genotypes HPV-16/18 associated with Cervical Cancer; carries a risk, not high like HPV-16/18 and continued close monitoring is recommended, unless Pap warrants immediate colposcopy, some labs use a test that has a combined HPV-18/45 end point instead HPV-18 only. HPV-45 is associated with 3.7% of CaCu and has a risk almost, but not equal to [9,15,16], with HPV-16 or 18.

Unsatisfactory pap with HPV-ar test, negative

The unsatisfactory Pap should be repeated even if the HPV-ar test result is negative; this is considered unreliable for the evaluation of epithelial abnormalities. The low cellularity gives rise to a false negative HPV-hr test [15,16].

Future perspectives on screening of cervical cancer

The socioeconomic, geographic and ethnic differences with respect to developed countries, where the HPV-hr test is used as the primary test for Cervical Cancer detection, the real conditions in emerging countries should be considered before establishing new methods for Cervical Cancer detection; However, there are no systematic studies on the reproducibility and precision of the HPV-hr tests, used in developed countries; the uncontrolled performance of the HPV-hr tests could generate increased costs and anxiety in patients. To determine whether HPV tests should be used as primary screening methods for Cervical Cancer, a quality assurance management protocol should be established for HPV-hr tests, and the results regarding the relative precision and sensitivity of the tests HPV-hr should be available to the public. Consequently, institutions that perform ar-HPV tests must choose a validated and acceptable detection method, and quality control of detection methods must be ensured before using HPV-ar tests, insurance costs HPV-hr tests are extremely high compared to Pap tests, they are important obstacles to the establishment of a national program for the detection of Cervical Cancer [2-9,15,16,17].

The diagnostic precision of Pap as a primary screening test has greater sensitivity and specificity for the detection of SIL and Squamous Cell Carcinoma (SCC) [26]; is one of the most useful, sensitive and confirmed Cervical Cancer tests available.

Some recommend, screening for Cervical Cancer in women over 20 years old, conventional Pap or LBC every 3 years (recommendation A) or Co-testing, is recommended as an option in consideration of individual risks or preferences (recommendation C). Current evidence for HPV-hr testing, primary; it is insufficient to evaluate benefits and harms of CaCu screening (recommendation I). Screening is terminated at 74 years of age if it has been confirmed that the patient has more than 3 consecutive negative Pap results within 10 years [21], HPV-hr tests, in some emerging countries are considered useful secondary tests when they are done as co-testing.

In addition to Cervical Cancer detection methods, HPV vaccines prevent future cases of Cervical Cancer; Gardasil against HPV-6,11,16 and 18. Gardasil 9 against HPV-6,11,16,18,31,33,45,52, and 58, while Cervarix against HPV-16 and 18. genotypes HPV-16 and 18 represent 55 and 70% of the main cause of Cervical Cancer; 30% of CaCu contain other HPV-ar genotypes, and would not be prevented by current vaccines. Therefore, unvaccinated women as well as vaccinated women should undergo regular screening tests using the best, most sensitive and specific screening tests available in the current era, HPV vaccines have no effect against genotypes HPV-53/66, and more effective vaccines against HPV should be developed [2-9,15,16].

Cervical biopsy specimens that aid pathologists in diagnosis, such as dual immunostaining for (p16INK4a / Ki-67); p16 is associated with the presence of CIN-2+, and Ki-67 this is a proliferative marker that improves specificity. Another test is based on the expression of the mRNA of the E6/E7 oncoproteins, which is present in CIN-2+ [18,19]. They are sensitive to precisely and specifically identify women who need colposcopy due to the increased risk; high-throughput viral methylation tests correlate with CIN-2+ [20,21]; These and other technologies should lead to less referral to colposcopy, to efficiently identify CIN-2+, a negative test does not mean the lack of presence of CIN-2+; Only p16 is recommended for diagnosis, with an increase in the positive predictive value that the precancerous lesion is progressing and should be treated according to the histopathology [9,15,16,17].

Dual immunostaining can be used both in biopsy histopathology and in support or triage Pap for women undergoing detection with HPV-hr, primary; was more sensitive than a Pap test for evaluating women with a positive HPV-hr test, the specificity was comparable [23]. The primary detection of HPV-hr, with dual immunostaining on Pap was significantly more sensitive than the Pap alone (74.9 versus 51.9%) for the triage of women with a positive HPV-hr test, whereas the specificity is comparable (74.1 versus 75.0%) [9,15,16,27-29].

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