Online Journal of Gynecology, Obstetrics and Maternity Care
ISSN: 2642-0163

*Review Article* *Volume 3 Issue 1*

# Towards a Better Screening for Cervical Cancer

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**Received Date:** January 10, 2020; **Published Date:** February 04, 2020

## Abstract

As cervical cancer screening changes from cytology or Pap test to high-risk human papillomavirus (HPV-ar) test, primary worldwide, effective classification tests to decide who of the positive HPV-ar women should receive additional diagnostic evaluation to avoid unnecessary colposcopies and biopsies; with the evaluation of the performance of the dual staining p16 / Ki-67; and partial genotyping, HPV-16/18 for the triage of women with HPV-ar, positive; for the detection of cervical intraepithelial neoplasia grade 3 or more severe (CIN-3 +) and CIN grade 2 or more severe (CIN-2+), diagnosed within 3 years after taking the sample; better risk stratification for CIN-3+ was demonstrated, compared to Pap; in women with positive results they have a higher risk than with Pap, for CIC-3 + (12.0 vs. 10.3%; 11.6%; P = .005); even with better risk stratification for NIC-3 +, compared with Pap in women with HPV-ar, positive, regardless of genotype. The greatest balance against CIN-3 + was observed in HPV-16/18 negative women or with dual negative staining, with a low risk to extend the screening intervals.

Double staining triage strategies required substantially fewer colposcopies for the detection of CIC-3+ compared to Pap, with a 32.1% reduction in colposcopies compared to the triage strategy currently recommended in the detection of HPV-ar, with the Pap. The results for CIN-2+ are similar. Conclusions; the management of women with HPV-ar test, positive in the detection of cervical cancer; with support from the Pap and dual staining p16 / Ki-67, alone or in combination with HPV-16/18 genotyping, it provides better risk stratification than strategies based only on the Pap and in countries such as Mexico, where there is organized infrastructure can detect and prevent the cervical cancer.

**Keywords:** Dual staining p16 / Ki-67; Cytology; Pre-cancerous lesions; Cervical cancer; HPV tests; screening; Colposcopy and management

**Abbreviations**: HPV: Human Papillomavirus; HIV: Human Immunodeficiency virus; HSIL: High-Grade Squamous Intraepithelial Lesions; DES: Diethylstilbestrol; LSIL: Low-Grade Squamous Intraepithelial Lesion.

## Introduction

Cervical cancer is among the most preventable human malignancies, but remains one of the leading causes of death among women worldwide, with more than 300,000 deaths annually [1]; unlike elimination in developed countries, cervical cancer still mainly affects women in emerging countries [1-3], where limited access to vaccination against human papillomavirus (HPV), lack of screening and treatment programs have become a public health problem in marginalized women, without access to medical care; mainly in regions, where human immunodeficiency virus (HIV) infection is endemic and cervical cancer is the most common

and deadly cancer in these women [4,5].

Screening is associated with decreases in incidence and mortality rate by cervical cancer during the last decades [6,7]. The evidence implies that persistent infection with human papillomavirus with high-risk genotypes (HPV-ar) are the causative agents of cervical cancer; however, these HPV-ar infections are common and occur in most women with active sex life throughout their lives; Most of these infections resolve spontaneously without clinical consequences during the first 2 years and only persistent infections can lead to high-grade squamous intraepithelial lesions (HSIL) or cervical intraepithelial neoplasia grades 2 and 3 (CIN-2/3), which they are precancerous and can progress to cervical cancer; 30% of CIC-3 progress to cervical cancer over a period of 30 years [8-11]. This slow progression allows many opportunities to detect and treat these lesions, which interrupts the development of cervical cancer [6-10].

The screening test for the detection of cervical cancer is changing from the cytology or Pap test (Pap), primary by the high-risk human papillomavirus (HPV-ar) tests, primary worldwide [12-16]. Women with HPV-a test, with negative results, have a low risk of cervical cancer for many years and the detection intervals can be safely prolonged compared to detection with primary Pap [2]. Most HPV infections are common and transient in the population, the three main detection strategies; Pap, HPV-ar tests, or HPV-ar tests, and Pap (Co-testing) and partial genotyping HPV-16/18; [2,4,7] for all screening approaches, require screening tests to decide which patients are sent to colposcopy for diagnostic evaluation [17,18].

The current recommendations for screening with HPV-ar tests, HPV-16/18, positive women are sent to colposcopy, while women with HPV-ar, positive for other HPV-ar genotypes, not HPV-16/18 Pap is performed; partial genotyping for HPV-16 and 18; genotypes with a higher risk of cervical cancer, does not distinguish a transient infection from a prevalent precancerous lesion. Triage or support with Pap is subjective and its sensitivity varies widely, which requires reassessing HPV-ar women, positive with negative Pap results [19,20].

Primary screening and triage strategies must be evaluated together, because the safety and efficiency of a screening approach and subsequent management depend on the combination of the results of the components of both tests. An ideal screening and triage approach should identify as many precancerous lesions as possible, while sending as few women as possible to a colposcopy. Detection with dual staining p16/Ki-67, in Pap samples is an accurate marker of cervical precancerous lesions [21-24].

## Recommendations for Screening Cervical Cancer

Screening tests that apply to women at average risk; without prior diagnosis of HSIL or cervical cancer, without immunosuppression or in utero exposure to diethylstilbestrol (DES) and suspension of screening when these women have had total hysterectomy with cervical removal; for women at higher risk, these screening recommendations are extended by 8.20 and the clinical management of the common results of abnormal screening tests is according to the following recommendations (Table 1).

| **Pap Every 3 Years for the Ages of 25 to 29 Years and 25 to 65 Years** | |
|---|---|
| **Abnormal Pap Follow-up** | **Recommendation** |
| ASC-US | Pap in 1 year |
| | HPV-ar; yes it is; |
| LSIL + | HPV test (+) => Colposcopy |
| | HPV test (-) => Pap in 3 years Colposcopy |
| **HPV-Ar Test, Primary Every 5 Years for Ages 25-30 to 65 Years** | |
| **Test HPV-ar abnormal follow-up** | **Recommendation** |
| Genotyping (HPV-16/18): | HPV-16/18 (+) => Colposcopy |
| | HPV-16/18 (-) => Pap yes it is; |
| | Abnormal => Colposcopy |
| | Normal => Repeat in 1 year |
| **HPV-Ar Test, Primary Every 5 Years for Ages 30 to 65 Years** | |
| **Test HPV-ar abnormal** | **Recommended follow-up** |

| | |
|---|---|
| Genotyping (HPV-16/18) yes it is; | HPV-16/18 + => Colposcopy |
| | HPV-16/18 (-) Pap yes it is; |
| | Abnormal => Colposcopy |
| | Normal => Repeat in 1 year |
| **Co-Testing Every 5 Years for Ages 30 to 65** | |
| **Co-testing yes it is;** | **Recommended tracking** |
| ASC-US and HPV-ar (-) | Co-testing in 3 years |
| LSIL and HPV (-) | Co-testing in 1 year |
| Pap (-) HPV + | Co-testing in 1 year |
| Pap (-) HPV + | Genotyping (HPV-16/18) yes it is; |
| | HPV-16/18 + => Colposcopy |
| | HPV-16/18 (-) => Co-testing in 1 year |
| ASC-US and HPV+; | Colposcopy |
| LSIL and HPV+; | |
| ASC-H, HSIL+ | |

Table 1: Recommendations for the Management of Screening tests for Cervical Cancer [11,24,29].

Recommendations for screening test results abnormal in women at average risk of cervical cancer, from 25 to 65 years [8,17,25,] and indications of delivery and time to perform the colposcopy table 2. The average risk in women without a previous diagnosis of HSIL or CIN-2/3, adenocarcinoma in situ (AIS) or cervical, women without immunosuppression and without intrauterine exposure to diethylstilbestrol (DES). For women 21 to 24 years of age, only colposcopy is recommended for the report of Pap with HSIL or worse lesion (HISL+) that indicates atypical glandular cells, AIS, carcinoma or HSIL) or atypical squamous cells, cannot exclude HSIL (ASC-H) For those with atypical squamous cells of undetermined importance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL), it is recommended to repeat cytology at 12 and 24 months and perform a colposcopy if it is ASC-H, HSIL+, or if the Pap is persistently abnormal at 24 months, LSIL+; Indicates HSIL+, in addition to LSIL, HPV-ar tests are exact, non-specific tests [2,11,16,24].

| Colposcopy indication | Time |
|---|---|
| Macroscopic suspicion of cervical cancer | Immediately (between 1-7 days) |
| Abnormal Pap con cervical cancer | Immediately (between 1-7 days) |
| HSIL | Between 1 month |
| LSIL1 | According to recommendations on the |
| Pap | Results |
| ASC-H | Between 1 month |
| ASC-US | Repeat Between 6 months (2-3 times between 12–24 months or in ≥ 30 years of age with HPV-ar (+) |
| AGC-FN or AIS | Between 1 month |
| AGC-NOS | Between 2 months or according to the recommendations for Pap2 |
| Abnormal endometrial cells | Between 1 month |

**Table 2:** Colposcopy Shipping Recommendations.

[1]In women ≥ 30 years of age, it is sent to colposcopy in 6 months; in < 30 years of age, the recommendations are colposcopy in 6 months or repeat the Pap in 6 to 12 months, if the Pap is abnormal (≥ ASC-US) it is sent to colposcopy in 6 months

[2]Colposcopy recommendations or repeat the Pap in 4 to 6 months; Colposcopy is performed if the Pap is abnormal (≥ ASC-US)

The 3 options for screening strategies adapt to a variety of clinical settings; 3 are recommended for women aged 30 to 65; But, women's preferences are important considerations when choosing a particular strategy and are discussed with the medical doctor; the clinical implications of choosing the HPV-ar test, primary; or to counteract the strategy of the Pap, during a lifetime of detection, the strategies based on the HPV-ar test, avoid 1 case of additional cervical cancer per 1000 women screened compared to the Pap, which represents a "very small" improvement in the years of life gained and the strategies based on the HPV-ar test, women would have more tests and procedures compared to the Pap alone.

Shared decision making is easy to invoke, but it can be difficult to implement 9; explain the trade-offs between prolonged detection intervals and a greater probability of more tests because surveillance is complex and time-consuming, but it is necessary if the informed preferences of women are integrated into clinical practice, many women prefer not to participate in the detailed discussion and seek medical advice regarding which strategy best balances the benefits and harms; when the cost in decision-making is not considered, for Pap or HPV-ar tests, by themselves they are preferable in relation to cost, based on their evaluation of this balance [12,11,16,22,26].

From a public health point of view, the primary HPV-ar screening option requires the availability of at least 1 of the HPV-ar tests approved; Algorithms for monitoring abnormal test results is another factor that determines which strategies are more feasible and efficient shows different clinical actions for women with abnormal test results; It is a challenge for the systems responsible for coordinating follow-up visits and guaranteeing high quality services if the 3 detection strategies 2.5-14 are used. In addition to screening, medical doctors can promote that the goal of preventing cervical cancer is to recommend HPV vaccination and a 2-dose program is recommended for girls and boys who start vaccination at the ages of 9 to 14 years; and 3 doses for people from 15 to 26 years of age, also when they have immunosuppression; Vaccinated women screening is similar to unvaccinated women [27].

The effect on detection, on incidence and mortality from cervical cervical can be achieved by providing women in the general population with easy access to low-cost screening tests; with diagnostic tests and therapeutic procedures. The strategy with HPV-ar tests alone allows the possibility of self-taking, which may be effective and acceptable for some women who cannot attend the clinic. The management of women with HPV-ar test, positive in the detection of cervical cancer; with dual staining p16 / Ki-67, alone or in combination with genotyping HPV-16/18, it provides better risk stratification than Pap-based strategies; positive, double-stained HPV triage leads to lower colposcopy with similar cervical HSIL detection, compared with Pap detection, makes the detection of cervical more efficient [28].

## Discussion

The screening test for the detection of cervical cancer is passing from the primary Pap by the HPV-ar test; a negative HPV-ar test result; provides tranquility for the prevalent HSIL or cervical cancer, most HPV-ar women, positive; they have transient infections that are not associated with cervical HSIL and need additional classification tests; with the detection of the primary HPV-ar test, which includes partial genotyping and Pap for the triage of women with HPV-ar, positive [19,20].

This strategy leads to two thirds of women with HPV-ar test, positive; they are sent to colposcopy immediately, and more than 80% of HPV-ar, positive, they are performed colposcopy immediately after 1 year, this strategy creates a substantial burden with implications for the infrastructure and cost of medical care, since the most shipments to colposcopy do not detect precancerous lesions; on the other hand it is reported that the dual staining of p16 and kI-67 by Immunohistochemistry, has greater sensitivity and specificity; when compared with the Pap for the triage of women with HPV-ar, positive [22].

The performance of the dual staining has been assessed along with the partial genotype, which allows a direct comparison of the currently approved approach for the triage of women with HPV-ar, positive; as an alternative [1,2]. Using a risk-based approach to current management 29, it is reported that performing double staining would accurately identify most women with very low risk of precancerous lesions (with negative results of partial genotyping HPV-16/18 and staining dual negatives, that new tests could be safely performed at prolonged intervals, the small group of women at higher risk who are not high enough to be sent to colposcopy (positive HPV-16/18 results with negative dual staining), and Remaining women whose risk is well above the threshold for colposcopy (all women with positive results of dual staining are at greater risk among women with positive results of dual staining and HPV-16/18 positive).

Normal Pap results, but positive HPV-16/18 results, have a risk above the threshold for colposcopy, much higher than the risk of women with negative results in dual staining and positive HPV-16/18 results; Double staining alone, without genotyping, provides a very similar risk stratification, which indicates that it is also effective for the selection of HPV-ar screening tests, without providing genotyping. In addition, the stratification of the risk of dual staining in HPV-16/18 negative women is better compared to Pap, that dual staining

is a good triage option for vaccinated populations that have a reduced prevalence [5,10,21,29,30] of infections for HPV-16/18.

When the HPV-ar test strategy was evaluated, primary; approved in the detection of cervical cancer and the new classification strategies based on dual staining, with respect to colposcopy and HSIL detection; strategies based on dual staining are more efficient (indicated by a smaller number of colposcopies needed per case of CIN-3+ detected compared to strategies based on the Pap; demonstrating the low efficacy of repeated tests in 1 year in the currently approved strategies, with higher sent to colposcopies after repeated tests that detect few cases [28] of CIN-3+. Compared to a combined approach to genotyping and HPV-16/18 and dual staining, the few additional cases of CIC-3+ that are detected by these strategies involving repeated tests in 1 year, which have HPV-16/18 results and negative dual staining at the beginning, suggests that it is at the risk of HSIL that they will be resolved or detected safely at the next 3-year screening visit [28].

Pap with dual staining and HPV-ar tests, primary; they can supplant a high quality program and provide a sensitive detection of cervical HSIL, while leading to fewer shipments to colposcopy. The Pap with dual staining showed better performance compared to the Pap in both the subset of women who undergo routine screening tests and in the entire population, including women who underwent co-testings to manage results. abnormal detection, after colposcopy or after treatment. Long-term follow-up shows that women with negative results of dual staining have a low risk of cervical HSIL for 5 years [21].

these data, combined with low risk estimates; for women with negative staining results, they support reassessment intervals in women with negative results of dual staining extend safely to 3 years; The significance of the Triage for women with HPV-ar test, positive with double staining lead to lower sent to colposcopy with similar detection of precancerous lesions compared to the Pap screening, which makes the detection of cervical cancer more efficient [28] The use of HPV-ar tests will be useful with the support of the Pap and biomarkers with the dual staining of p16 and Ki-67 in the diagnosis of cervical cancer, if they are implemented in countries that have the infrastructure and organization to carry them out. like Mexico.

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