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PRIMARY CERVICAL CANCER SCREENING

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ABSTRACT

With detection by cytological test, the incidence of cervical cancer was reduced more than 50%; the cause of this cancer are high risk human papilloma viruses; required a sensitive test that provide sensitivity and specificity sufficient for this cancer, not to develop increasing screening intervals when the results are negative. High risk human papilloma virus testing, is safe and effective because of their excellent sensitivity and negative predictive value together with an optimum reproducibility, mainly when combined with cytology based liquid with biomarkers and viral load, will have greater sensitivity and specificity, and reduction of false positives for the detection of cervical intraepithelial neoplasia grade 2 or more and excellent clinical benefit for cancer detection cervical and other related diseases with the infection of the the human papilloma virus, such as the detection of anal intraepithelial neoplasia and cancer anal in high risk groups; He is currently the best tool for early detection of HPV infection and the risk of carcinogenesis.

Keywords: human papilloma virus high risk, methods of early detection of cervical cancer, biomarkers, cervical and anal intraepithelial neoplasia

INTRODUCTION

In the past 30 years, the mortality rate (TM) cervical cancer (CC) in the United States fell by more than 50% detection with the Pap test (Pap) or cytology, which develops in most women who have never done it. Since 1928, when Dr. Papanicolaou [1-4] reported for the first time the cancer cells in vaginal smears and published their

results in 1941; cytology evolved into liquid-based cytology; human papillomavirus (HPV) virus testing was approved in 2000, and the first vaccine against HPV, came to the market in 2006 currently are in draft new vaccines with greater protection. [5.6]

EPIDEMIOLOGY

Cytology reduced the incidence and mortality by CC in developed countries with organized screening programs, even though more than 68,000 and 12,000 new cases are reported each year in Europe and the United States respectively, over 4000 deaths in 2013 CC in USA [4]; although there is evidence that the mortality by CC was declining even before the introduction of the HPV vaccine, the overall rate in July fell from 10.2 to 8.5 cases per 100,000 women between 1998 and 2002, as technologies evolve also screening recommendations for change, the sensitivity of a single Pap for detecting cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN-2+) or squamous intraepithelial lesions (SIL) of high-grade [HSIL) [2.8-10] is low, it requires frequent repetition intervals, highly organized, and the cost is high, requiring the existence of effective biomarkers as a predictor of the risk of CIN; these important, are the determination of HPV genotyping high-risk (HPV-hr), identified in 90 % of CIN or CC [11]; clinical development of new screening strategies based on HPV-hr testing, mortality reduces CC, there are more than 40 genotypes of HPV-hr causing persistent cervical infections and the risk of progression of CIN differ significantly by genotype HPV-hr, but most HPV-hr are rare and not all are included in most HPV testing [12]. Numerous studies have shown that HPV testing offers high sensitivity for detection [13-16] CIN -2 +, but the specificity for HSIL is limited because most HPV infections are transient , and only a small proportion HPV infection persists and progresses to HSIL persists. Due to the high prevalence of HPV infections in women under [30], the HPV-hr tests, is not currently recommended for screening women under 30 years [17].

Detection of HPV-hr in women with abnormal cytology, has a role in identifying women at risk of residual or recurrent disease after treatment of CIN, although HPV-hr, is less specific than cytology, because many infections HPV-hr, return and do not progress to HSIL and positive HPV-hr test not always distinguish between a transient infection of chronic [16,18- 22]. It has been shown that expression of the E6 and E7 oncoproteins of HPV-hr genotypes, squamous epithelial cells of the cervix causes the development of neoplastic growth [12] biomarker overexpressing p16INK4a (p16) that is one of 23 to 28 inhibitors of cyclin dependent kinase prevents phosphorylation of the retinoblastoma protein pRb) and thus plays an important role cell cycle regulation , the p16 biomarker overexpression is frequently observed in the NIC associated with infection by HPV -ar and is associated with dysfunction of the pRb protein through mutations that arise naturally, or associated with the E7 oncoprotein of HPV-16 which induces abnormal cell cycle progression and overexpression of p16 , this biomarker to predict the risk of progression of CIN, compared with the genotypes of HPV-hr [12,29,30] is unclear, but it has been reported that the rate of p16 overexpression increased with greater injury CIN-1 (20.7%), CIN-2 (80.0%) and CIN-3 (89.2%), the overexpression of p16 is significantly greater in CIN-2 and 3 in CIN-1 ($p < 0.001$) reported 46.6% of p16 overexpression and during follow-up, 23.0% with p16 overexpression progressed to HSIL and 8.6 % of patients without p16 overexpression showed progression, this

biomarker is effective compared with HPV-hr testing, in patients with CIN-1 and 2, in patients who were tested with the HPV-hr test, 80% were positive and the rate of HPV-hr also increased in higher-grade lesions in NIC-1 65.1% and CIN- 2 and 3 87.7% ($p < 0.001$) [31,32].

Although patients infected with HPV-hr showed higher prevalence of progression of the lesions, there was no significant difference between groups HPV-hr test, positive and negative. There were no significant differences in the rate of progression or regression of lesions among patients infected or not with HPV-16 or HPV-18 ($p = 0.60$) [8]. Detection of p16 overexpression , a biomarker of prognosis transforming HPV infections precancerous lesions of the cervix , which is effective in the management of cytology with atypical squamous cells of undetermined significance (ASC -US) or injury report low-grade squamous intraepithelial lesion (LSIL) and [23-28] for the study of women with HPV-hr positive tests; sensitivity for CIN -2 + is 18% higher compared to cytology ($P < 0.001$) in women all ages, with specificity of 95.2% (Table 1) [33], the specificity of p16 cytology is higher compared to the HPV-hr test, with fewer false positives by 50%. The double staining cytology p16/Ki-67 combination of biomarkers indicative of transforming HPV infections, have excellent sensitivity and specificity for the detection of CIN -2 +, mainly in women under 30 years, where currently no alternative to cytology or complementary test is available or are limited [8,19-22,31,32,34] .

The CIN is the precancerous lesion that is treated effectively to prevent progression to cervical cancer , CIN -1, is an injury that requires only monitoring without treatment 10% of the CIN-1 progress to CIN -3, or CC; 20 % of CIN -2, CIN-3 progress to or CC , and 40 % of CIN -2 regress spontaneously, making the management of CIN 1 and 2 controversial, some are observed until spontaneous regression or treated with destructive procedures or excisional, but only patients who are at high risk of progression are treated, and observed the low-risk regress spontaneously, but it is difficult to predict the individual result of each patient [34] .

PRIMARY CERVICAL CANCER SCREENING

HPV-hr testing, for the detection and prevention of precursor lesions CC compared with cytology, offer 60 to 70% more protection against CC, especially effective in women 30 to 34 years old and when performed every 5 years provides greater protection than the Pap performed at intervals of 3 years [35]. The incorporation of HPV-hr testing in developed countries, strategies for screening women vaccinated at older ages (18 years or more) has not yet been determined, and should be similar to unvaccinated women, short-term screening with HPV-hr testing will be cheaper and provide greater security than conventional cytology, despite these benefits, public health programs have logistical problems for screening including what type of HPV-hr test used, determine the appropriate ages and intervals for screening, management of HPV-hr positive women, and ensure quality, adherence and implementation of the HPV-hr test to CC prevention programs. The HPV-hr test is more effective in detecting HSIL and prevention of CC than cytology in women older than 35 years has also proven to be more effective than cytology or visual inspection of the cervix with acetic acid and reduced mortality and incidence CC in advanced developing countries [2,16,36] .

NEW GUIDELINES FOR CERVICAL CANCER SCREENING

New recommended by various groups such as the American Cancer Society, the American Society for Colposcopy and Cervical Pathology and the American Society of Clinical Pathology for the early detection of CC guidelines [2.17]; recommended HPV-hr testing in combination with cytology in women 30 to 65 years of age, s randomly assigned to screening with HPV-hr test or cytology (control group) conventional or liquid base; CC cases identified in cytology negative women, the incidence of CC cancer was 15.4 × 10^5 after 3.5 years and 5.5 years, 36.0 x 10^5, and in those with evidence of HPV-hr negative, the incidence was 4.6 x 10^5 after 3.5 years and 8.7 x 10^5 after 5.5 years, indicating that the incidence of CC was less than 5.5 years of follow-up after a test HPV-hr, negative, compared with 3.5 years follow-up after a negative cytology, indicating that screening intervals to 5 years with HPV-hr test are safer than the intervals of 3 years with the cytology alone.

With these recommendations the proportion of cervical adenocarcinomas decreased with age in women younger than 30 years was 40 %, between 30-34 years of age was 35%, between 35 and 49 years was 30% and at age 50 was 23%. The prevention of CC in women of reproductive age is a priority and detection with the HPV-hr test, should begin at age 30 years, 2012 New guidelines on the detection of precursor lesions and cervical cancer have substantially changed practices health of women. The new guidelines take into account HPV infection and the natural history of CC [2.17].

Most HPV infections are transient and the body is able to eliminate them and only persistent HPV infections lead to CC. HPV infection is common in teenagers and women in their 20s. Most women, especially those under 21 years of age, are able to eliminate the infection in 1-2 years. In women over 30, HPV infections are more likely to be persistent and rates of high-grade lesions are increased. Most HPV-related lesions progress to cervical cancer slowly, it takes, on average, 3.7 years for a HSIL progresses to CC. [2,12,17]. The new guidelines are:

Home of screening until age 21, regardless of the conduct, risk factors and age of first sexual intercourse.

For women 21-29 years of age, cytology every 3 years and do not perform HPV testing.

From age 30 to age 65, combined test (cytology and HPV Test) every 5 years. The HPV-hr test is the preferred recommendation but cytology alone every 3 years is also acceptable and HPV testing alone is not indicated.

After age 65, the future screening recommendations dependent upon the on the screening results of previous citology. If the above tests have been negative, these women do not need and do not need screening, a negative pre-screening means three consecutive negative cytology results or the combined results of two consecutive negative tests over the past 5 years. Women with a history of HSIL or CIN -2 -3, or adenocarcinoma can not be left without screening at age 65 and should continue screening. Hysterectomy in women with no history NIC- 2 or higher, the woman no longer performs screening, for patients with HSIL before hysterectomy, screening remains cytology every 3 years for the next 20 years because the cancer recurring may develop in the vaginal vault even years later, HPV testing in this setting is unclear. These patterns of routine women with immunosuppression, human immunodeficiency virus (HIV) positive, exposed to diethylstilbestrol (DES) in utero, or a history of

CC do not apply. The incidence of CC in women of reproductive age has increased recently [2,9,10,17] .

HEALTH PROMOTION

The education of women and health professionals are essential to the use of HPV-hr testing during primary screening, clinical and psychological management of women with normal cytology tests and HPV-hr positive aspects, especially if included women (<30 years), HPV infection and related diseases are certainly newsworthy and the media. The psychological effects of CC screening, including doubtful results are harmful to women, reducing their quality of life and increase cell monitoring even with inadequate results, anxiety and concern of the woman on the CC [37.38]

The best time to provide information on HPV infection before testing HPV-hr , it has the highest level of care, understanding and ability to decrease anxiety, specifically taking positive HPV-hr test so persistent is one of the most important indicators of risk to a woman, over time, develop CC, aids correctly provide other follow-up procedures (eg, repeating the HPV-hr test, cytology, colposcopy, and other markers biological) associated with risk stratification [34], a positive HPV-hr test not a disease but is a risk factor when the HPV-hr test positive persists a year after the first shot, it takes a cytological triage or noninvasive tests, screening prevent the development of CC. The current algorithms are designed for women who are conscious, easy clinical control with monitoring, but in marginalized communities that are most affected by CC, Latin American , Asian and African countries, and low socioeconomic and cultural level, where rates prevalence are highest in CC compared with white women in developed countries [39] .

DISCUSSION

Reports in the past two decades on HPV-hr testing, have definitely shown an association between HPV-hr genotypes CC and [12], also have excellent performance in various clinical applications for monitoring patients treated, comparing with conventional cytology or colposcopy in symptomatic or asymptomatic women for the detection of precursor lesions of CC [35], both for primary cervical screening and management of cytology 'borderline' or ASCUS (atypical squamous cells of undetermined significance), the evidence HPV-Hr not always lead to clinical practice and in national screening programs, although they have higher sensitivity than the cytology [13-15] in the detection of CIN -2 +, the combined HPV and cytolog tests showing high values negative predictive (NPV) [16] for CIN-2 +, some CIN-2 self-limiting and increased sensitivity to these precancerous lesions, and CC grouped as CIN -3 +, is simply over-diagnosis, as there is a lower incidence future of [17.40] CIN-3 +.

The increased sensitivity has two important clinical outcomes: reduction and elongation, mortality screening interval with greater compliance in the detection and lower cost, another added value of HPV testing on cytology is its high reproducibility. The HPV test is more sensitive than liquid-based cytology for detection of CIN -3 +, but less specific than liquid-based cytology (92.0 % versus 53.3 %, difference 38.7%). Although the addition of liquid-based cytology to HPV testing increases the sensitivity for CIN -3 +, 96.7%, also increased the number of positive tests 35.2%, although the use of evidence of HPV-16 or HPV-18 gives better information and is more reliable for identifying women with CIN-3 + [15,29,30].

Determination of p16 positive women in the Triage Study ASCUS/LSIL (ALTS) designed to compare three management options [26.] The HPV-hr test showed highest sensitivity and identified 96.3% (95% CI 91.6 to 98.8) of women with CIN-3 +,[27] the same positive predictive value (NPV) that detection with conventional cytology (no substantial increase in referral to colposcopy), while retaining the highest detection VPN HPV testing [29]. According to the scenario of post was HPV vaccination is to mention the particular value of the HPV test -ar as test more suitable for vaccinated women detection, which is expected to vaccination in the near future, low prevalence of HPV-related diseases, represents another value added [7,19,20-22,41-43] this option selection has been observed that the residual or recurrent disease in women with HPV-16 and/or HPV-18 persistent is higher (82%) than in women with persistent HPV-hr other types such as HPV 31,33,35,45,52 and 58 (66.7%) or HPV 39,51,56,59,68,26,53,66,73 and 82 (14.3%), suggesting different levels of risk for progression of CIN, the detection of persistent infection with certain HPV-hr genotypes has the potential to improve the management of these patients obviously post - treatment follow-up should include conventional cytology and HPV-hr test, to identify patients at increased risk of disease recurrence [12 , 42,43.]

In the past 50 years, the relative proportion and the absolute incidence of glandular pre- invasive and invasive lesions of the cervix has been increasing in Western countries for the years 1950-1960 cervical adenocarcinomas represented 5% of the cases of CC in 1970 represented 20-25% of all CC in most women of reproductive age who require fertility sparing surgery, although the management of adenocarcinoma in situ (AIS) is controversial follow up of patients with AIS who wish to preserve fertility [44], the combination of HPV-hr test and cytology showed greater sensitivity to detect persistent lesions, with 100% NPV is useful and avoids unnecessary hysterectomies. The HPV-hr testing has been introduced into clinical practice as a test of cure, where the persistence of a specific genotype predicts recurrence in the short term and on the contrary, the absence of HPV genotype associated with the preoperative diagnosis involves a successful treatment and low risk of recurrence. [34.42]

CONCLUSION

HPV is necessary for the development of cervical cancer screening and HPV-hr testing versus conventional cytology or liquid foundation cause, sensitivity, and reproducibility VPN as well as management of borderline or ASCUS cytology and follow-up after treatment IAS, HPV-hr testing have nearly 100% sensitivity and NPV for identifying preneoplastic lesions or cervical cancer and is the primary test in the early detection of these squamous and glandular lesions or adenocarcinoma in situ (AIS) , their detection is difficult in national surveillance programs. HPV testing with genotyping of the 14 high-risk viruses, and viral load [45], reduce the number of false positive results respectively. The sensitivity for CIN -3 + remained at 100%, be effective and safe for the detection of CC, especially in combination with liquid -based cytology with p16/Ki-67 biomarkers have the greatest sensitivity and specificity for detection of CIN-2 + and better clinical performance for detection of CC and related to HPV infection, such as anal intraepithelial neoplasia detection of anal cancer and high-risk groups diseases.

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TABLE 1. SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR THE DETECTION OF CIN-2 AND CIN-3 + IN WOMEN 30 TO 65 YEARS

Test for CIN-1+*				
	Sensitivity	**Specificity**	**PPV*** **	**VPN**** **
Cytology or Pap	55.9%	96.3%	12.5%	99.7%
P16	84.7%	96.2%	15.3%	99.9%
HPV-hr test- **	93.3%	96.2%	92.7%	99.9%
Test for CIN -3+*				
	Sensitivity	**Specificity**		
Cytology or Pap	59.0%	96.1%		
P16	87.2%	95.9%		
HPV-hr test-	96.2%	92.7%		

* CIN-2/3 + (cervical intraepithelial neoplasia grade 2 or 3, or worse,
Hpv-hr ** (human papillomavirus high-risk)

*** PPV (Positive Predictive Value)
**** NPV (Negative Predictive Value)

PNV: POSITIVE NEGATIVE VALUE
PNV: POSITIVE NEGATIVE VALUE