New guidelines in regard to cervical cancer screening

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ABSTRACT
Cancer screening programs have been successful in reducing the incidence and mortality due to cervical cancer. For more than a decade, the human papillomavirus test has been recommended as part of these programs; however, Pap tests is not currently recommended for women < 21 years of age or in those with total hysterectomy for benign disease, unrelated to cancer or precursor lesions of malignant diseases. This is because most of the anomalies observed in adolescents regress spontaneously, and cytological screening tests for this age group cause unnecessary anxiety, additional testing and, therefore, a higher cost. Moreover, there is little evidence that cytology is useful in women after hysterectomy, finding that outcomes are not improved. In women > 65 years of age who participated adequately in screening programs, continuing with these screening programs is not needed. Screening programs will be different in special populations at greatest risk where tests are frequently needed or use of alternative methods.

Key words: Cytology, Papanicolaou, cervical cancer screening, vaccine, prevention.

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BACKGROUND

Cervicouterine cancer has a great impact on the lives of all women; 493,000 new cases are reported yearly worldwide, of which 274,000 women will die.1 Eighty three percent of these deaths occur in developing countries because cancer screening programs are not applied in an effective and efficient manner, indicating that the leading cause of death for women is cancer.2,3 This lack of effective programs is the main reason for the high incidence of cervicouterine cancer in these countries because women only seek medical care when they have obvious symptoms; i.e., when cervicouterine cancer is advanced and difficult to treat.1-3 Despite these obstacles, cervical cancer can be prevented at a low cost.

Prevention of cervicouterine cancer is part of public health strategies to improve women’s health. When not detected and treated early, this type of cancer is fatal. In developing countries a mortality rate of 11.2/100,000 women is reported, which is three times higher than in developed countries;4 with 40% deaths. From 80-90% occur in women during the productive age from 35 years or older. Precancerous intraepithelial lesions slowly progress until cervicouterine cancer is identified in advanced stages. For this reason the incidence of this disease in women < 25 years of age is lower and increases at about 35 to 40 years of age, reaching its maximum point at 50 to 60 years of age.2,5

Early cancer screening programs have managed to successfully reduce the incidence and mortality rate for cervicouterine cancer and, for more than a decade, the combined use of DNA testing for the high-risk human papilloma virus (HPV-hr) has been recommended in these programs.2,6-9 High quality cytology or Papanicolaou tests as a secondary screening in the detection of cervicouterine cancer have significantly reduced the mortality rate of the squamous cell variety, which is the most common type accounting for ~80-90% of all cervical cancers.10-12 This reduction in mortality rate is the result of the detection of cervicouterine cancer in early stages when the 5-year survival rate is 92%. Furthermore, detection and treatment of squamous intraepithelial lesions of the cervix also decrease the incidence of this type of cancer.13,14

At present it is believed that persistent infection with HPV-hr is necessary for the initiation of cervicouterine cancer. This is the same as with precancerous lesions, mainly cervical intraepithelial neoplasia (CIN) grade 3 (CIN-3), where it has been shown that 100% of these lesions were positive for HPV-hr.15 The genotype of HPV-16 is the most carcinogenic as it is identified in 55-60% of all cervical cancers.15-17 Another genotype, HPV-18, is the second most oncogenic genotype, found in 10-15% of cervical cancers15-17 and 10 other genotypes of HPV-hr cause 25-35% of the remaining cervical cancers.

Advances in research of the relationship between HPV-hr and cervicouterine cancer, knowledge of the epidemiology and natural history of persistent HPV infection allow greater understanding of the carcinogenesis of cervicouterine cancer. Regarding infection with HPV-hr, its persistence vs. treatment and progression of precancerous lesions to invasion2,9-19 allow for orienting the directives of the detection and treatment of precursor lesions and cervicouterine cancer.20

Genital HPV infection is acquired through sexual contact and skin contact with infected skin. The peak prevalence of HPV infection is present usually within 2 years of initiating sexual activity9 where 90% of people are infected. However, HPV infections are transient, go into remission and remain undetected for 1 or 2 years.10,11 Only those women with persistent HPV-hr infections are at higher risk of precancerous lesions, especially when it persists for > 1 to 2 years where it is predicted that a CIN-3 or higher lesion will
be diagnosed in later years. If the CIN-3 is treated, the probability of developing cervicouterine cancer is 30% over a 30-year period. Only 1% of patients treated for CIN-3 will convert to cervicouterine cancer.

Some of the key objectives of the programs for early detection of cancer are the prevention and reduction of mortality and morbidity. The cytology test (or Pap smear) has been successful in reducing the incidence and mortality rate of cervicouterine cancer in countries with good quality programs for early cancer detection.

Tests using molecular biology techniques are clinically useful in the detection of DNA of the HPV-hr genotypes. These HPV-hr DNA tests better predict which women are at risk of developing a CIN-3 in 5-15 years compared with cytology-based screening. Incorporation of DNA tests for HPV-hr as a strategy for the detection of precursor lesions and cervicouterine cancer improves the treatment and increases the duration between the intervals for the detection of these diseases. In addition, it decreases the psychosocial impact compared with the Pap smear. When the result of the Pap smear is abnormal, additional visits along with clinical and therapeutic procedures are required for the lesions that are destined to spontaneously return.

Regardless of the different methods for early detection of cancer, 50% of the cases of cervicouterine cancer is diagnosed in patients who have never had any method of early detection of cancer; 10% have not had a screening test in the last 5 years. This happens primarily in women from marginalized groups or regions lacking medical services, with low socioeconomic resources and racial differences. The annual incidence rates of cervicouterine cancer and the mortality rate is higher than in the general population. Although there are programs where molecular biology techniques are carried out for early cancer detection, there will be no substantial impact on the mortality rate if its scope and benefits do not reach all sectors of the population.

The immediate benefit in reducing the incidence and mortality rate for cervicouterine cancer relies on increased access to screening programs for this disease, regardless of the method used. Where programs are currently limited, addition of the DNA test for HPV-hr will demonstrate greater advantages. With routine screening there will be greater safety in the long term compared with only cytology or Pap test. When the DNA test for HPV-hr is negative, the timeframe for screening tests will be done with less frequency.

**Tests for Early Detection of CUC**

Secondary screening for detection of precursor lesions or cervicouterine cancer based on yearly cytology or Pap smear has changed. Currently, management for prevention and timely detection is based on the age of the patient and on the HPV-hr DNA tests. The age at which it is recommended that the screening begins, based on cytology or Pap smear for the detection of precursor lesions or cervicouterine cancer, is 21 years of age and is not recommended before that age. For women between 21 and 29 years of age, high quality cytology screening or Pap smear is done every 3 years and the HPV-hr DNA test is not used for cervicouterine cancer detection in this age group.

The preferred screening methods for early detection of cervicouterine cancer in women 30-65 years of age are cytology and HPV-hr test, which are done every 5 years, but Pap smear is also acceptable every 3 years. One hundred percent of cervicouterine cancers are squamous cell and are positive to the HPV-hr test. This test has the advantage of early detection of cervical adenocarcinomas and its precursor lesions, which are difficult to detect.
with the Pap smear or cytology test as well as with colposcopic findings.\(^2\)

When the cytology is abnormal or positive and the HPV-hr test is negative, it is not necessary to perform another study. Routine screening will be done according to the age of the patient. Nevertheless, if both tests are negative (cytology and HPV-hr) or if the result of the HPV-hr test is positive, there are two options: 1. Repeat the cytology and HPV-hr test at 12 months and if either is positive the patient is sent for colposcopy. If both are negative, routine screening tests are continued according to the patient’s age. 2. Perform the immediate HPV-hr test for HPV-16 alone or HPV-16/18 genotypes. If they are positive it is recommended that the patient be sent for colposcopy. If both HPV-16 and/or HPV-16/18 are negative, cytology and HPV-hr tests are done at 12 months and treatment will be based on the results according to what is described in the first option.\(^2,18,21,22\)

No method of early detection for cervicouterine cancer for women > 65 years of age who have had an adequate prior negative screening and no history of CIN-2 or a greater lesion in the last 20 years is required. Once the screening is stopped, it should not be restored. Adequate cytology screening is defined as the prior report of three consecutive negative results or two cytology results, plus a consecutive negative HPV-hr test in the 10 years of its interruption, with a recent negative HPV-hr test in the last 5 years of monitoring.\(^2,21,22\)

Routine screening should be continued for 20 years after presentation of a CIN-2/3 or adenocarcinoma in situ even if clinical control monitoring is extended for 20 years after 65 years of age or in women of any age who have not had a history of CIN-2 or greater lesions. However, routine cytologic screening is no longer necessary in women with total hysterectomy.\(^2,21,22\)

It is recommended not to change the routine screening in women vaccinated against HPV. The fundamental reason is that the two licensed vaccines are highly effective in preventing infection with HPV-16 and HPV-18 (two of the HPV-hr genotypes that cause 70% of all cervical cancers). The vaccine is effective in preventing CIN-2 and -3 in women with no previous exposure to these HPV-hr genotypes (HPV-16 and HPV-18).

In populations of vaccinated women it may not be so important to start screening at the recommended age, but to start at an older age due to the future risk of cervicouterine cancer. However, ~30% of cervicouterine cancers will continue to develop because the first generation vaccine only covers HPV-16 and -18 genotypes. In addition, recommendations for implementation include vaccination in women up to 26 years of age, so many are vaccinated after acquiring HPV infection. For this reason, coverage of the vaccination against HPV has not yet reached levels comparable to all countries. It is necessary that greater coverage in young girls, adolescents and women of reproductive age be guaranteed.

In developed countries, it is reported that 32% of young girls and women of reproductive age have received three doses of the vaccines and vaccination against HPV, which is not necessarily aimed at girls or young women before the onset of sexual activity.\(^2,21-23\) In addition to geographical and socioeconomic differences necessary for its coverage, there are no data to support the modification of the intervals in screening programs at the time in which the women have been vaccinated.\(^2,18,21,24-26\)

The new guidelines that need to be implemented in cancer screening programs for prevention of cervicouterine cancer are as follows: take the first cytology at 21 years of age without regard to prior sexual activity; perform cytology every 3 years from age 21 to 29 years of age. During this time
period no DNA test for HPV-hr is done, but the cytology and HPV-hr DNA test should be done every 5 years from the age of 30 to 65 years of age. Suspension of routine screening is recommended in women with total hysterectomy for benign reasons and in those women > 65 years of age with history of prior negative routine screening tests.

DISCUSSION

In order for the cervicouterine cancer prevention programs to be effective, it is necessary to include a program of sexual education, detection and treatment for the precancerous lesions and to have contact with the majority of women at risk for contracting the disease. It is necessary to inform women so as to encourage them to have the test performed and for these women to attend screening services for follow-up and treatment to insure correct treatment for the detected precancerous lesions.

The evolution and natural history of cervicouterine cancer serves as an important guide to decide when to initiate screening tests, the frequency for carrying them out and when to recommend further treatment and evaluation.

Cervical cancer screening programs need to address cultural, psychosocial and clinical barriers that influence women to use early detection cancer screening services. It is possible to carry out organized prevention programs for cervicouterine cancer in women from a low socioeconomic status that will reduce the disease burden. The preventive approach for detection and treatment with one or two clinical visits is safe and effective when resources are limited. Visual inspection and HPV-hr tests are promising alternatives to cytology and to the cost, but are especially effective in saving women’s lives. Cryosurgery and electrosurgery or excision using loop electrosurgery are safe methods for treatment of women with precancerous lesions. In developing countries, clinical tests can be done to obtain data on the impact of different methods of prevention of cervical cancer.

Routine screening intervals require changes in the thinking of patients, clinicians and health organizations. It is important to know that if this treatment is supported the reasons for noncompliance will be part of the acceptance. In the treatment of precursor lesions and cervicouterine cancer, screening programs in the general population are different from those of special high-risk populations. This population includes women with a history of cervicouterine cancer, women exposed in utero to diethylstilbestrol or women with immunological abnormalities such as those infected with human immunodeficiency virus where more common alternative methods or tests are necessary.

Current criteria are needed for the prevention of CIN or cervicouterine cancer, but it is also imperative to decrease the resources for early cancer detection and use them for other public health programs that favor the majority of women and where these are used in other health programs aimed towards diffusion and teaching of breast self-examination with the purpose of improving the quality of life for women. We must increase awareness of the need for changes in lifestyles that include adopting a healthy diet and proper nutrition, promoting exercise, avoiding risky behaviors, using family planning, managing the transition to menopause, preventing osteoporosis, participating in colorectal cancer screening and evaluation of pelvic floor function, which will improve the baseline reference for mammography and, above all, the quality of life of the women.

In conclusion, changes in the methods of routine and timely methods of cancer, precursor lesions and cervicouterine cancer are of great benefit for the majority of women and for public health programs. These recommendations reflect
the evidence reported in regard to prevention, decrease in mortality and morbidity rates of cervicouterine cancer with the available screening test that reduce the potential damage associated with false positive or false negative results of early cancer detection tests and overtreatment where the resources will be used for other early cancer detection programs and to improve the quality of life for women.

REFERENCES

