New Methods in Cervical Cancer Screening

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*Extremes are not good even in virtue.
Santa Teresa de Ávila (1515-1582)

The fundamental pillar of cervical cancer prevention, in addition to prophylactic vaccination, is the diagnosis of pre-invasive lesions, whose treatment would prevent progression to malignancy. Periodically, reviews are made on what is the most efficient screening scheme to recognize the greater number of patients with premalignant lesions. Screening programs have changed thanks to constant research in recent years. In April 2014, the FDA approved the use of the Cobas ® HPV test for detection of 14 types of high-risk HPV as sole test for screening of cervical cancer, based on the results of the ATHENA study, discussed previously in an article written for this blog. This type of screening was recommended for patients older than 25 years rising three possible scenarios:

a) If the patient presents a positive test for HPV 16 or 18, which are those more often associated with cervical cancer, it must be referred to a colposcopy.

b) If patient has a positive test for the other 12 types of high-risk HPV, she must perform a Pap test, in order to identify cellular changes that justify the need for colposcopy.

c) If the HPV test is negative, would remain the preferred periodic control.

A year later, in April 2015, it was published a study that questions the utility of the detection of HPV as primary and unique evaluation for cervical cancer screening. Were evaluated 256,648 samples of patients between 30 and 65 years who underwent cytology, hybrid capture for HPV and biopsy of cervix. Of the total of patients 98.4% had a biopsy that reported negative or a lesion equal to or lesser severity than cervical intraepithelial neoplasia 2 (CIN2). 1.5% of the total sample had a CIN3 or more severe lesion (CIN3+). This retrospective study compared three types of cervical screening: Pap test alone, HPV test alone and combination of both tests what is called simultaneous test or cotesting. To compare the three groups, when one of the two tests, or both, were positive it was found a 98.8% sensitivity to diagnose CIN3 +, to a sensitivity of 94% with the
HPV test or 91.3% with Pap test alone (p < 0.0001). However, the specificity of single cytology was greater, being 26%, compared with 25.6% of HPV testing and 10.9% of the cotesting (p < 0.0001). In the group of patients with cervical cancer, 18.6% had a negative HPV test, 12.2% reported a negative Pap test and 5.5% had both tests negative, meaning that the proportion of false negative results was less using the cotesting as screening. The conclusion of the study is that the simultaneous test is more sensitive than perform only the detection of HPV or Pap test for the diagnosis of severe cervical injuries, that is, the positive result in both or one of them, has greater sensitivity for diagnosis of CIN3+ lesions.

Since this series makes mention of the algorithm proposed in the ATHENA study, it is worth highlighting some aspects. The study of comparison of tests used hybrid capture test (HC2 Digene) for the detection of HPV infection, while the ATHENA study used the Cobas ® HPV test (Roche) for the detection of infection by HPV, which has higher sensitivity and allows to genotype HPV 16 and 18 types with Real Time PCR and in addition detects another 12 high risk types. The screening algorithm presented in the ATHENA study is valid only for this test based on its sensitivity and specificity. The hybrid capture, which is very useful for screening, only determines if the sample is positive for a group of high-risk HPV types, without discriminating of what type it is, i.e. does not identify what type of HPV is involved. In the case of the Cobas test, it determines types 16 and 18, which are the types most frequently associated with cervical cancer, or whether the other 12 high-risk types are present, and based on the result the patient is subjected to a colposcopy or a PAP. The ATHENA study followed screening for 3 years, and in the study of comparison of tests were evaluated patient specimens obtained during one year but with a much larger study population. It is for this reason that both studies have some methodological differences that make difficult the comparison. However, the use of one or two tests for screening of cervical cancer remains a controversy that must be addressed.

While it is true that types 16 and 18 are those who are most frequently associated with cervical cancer, they are the most common types in transient HPV infections. It is the persistent high-risk HPV infection that will eventually lead to the development of a pre-invasive lesion that could progress to a malignant neoplasm. This is probably the most forceful argument justifying the simultaneous testing or cotesting. The largest number of infections associated with types 16 and 18 was evident in the study of ATHENA, presenting a greater number of referrals for colposcopic evaluation in women between 25 and 30 years, where transient HPV infection is more common. In this group was detected a greater proportion of CIN3 +, what motivated, despite a higher number of colposcopies, to justify the screening with HPV in this range of ages.

To document a high-risk HPV persistent infection, which is the most important risk for development of cervical cancer, interrelated dynamic screenings should be done, i.e., the evaluation of the progression of the infection in time, as performed in the ATHENA trial, although only for 3 years, because a static or a single measurement research does not provide a comprehensive overview of the problem. The sensitivity of any test for the diagnosis of CIN3 + improves if it is repeated at certain time intervals, and the study of the comparison of tests made a cross section of the search results in a single time.

It is also important to consider that a negative HPV test correlates better with absence of CIN3 + to a negative Pap test, i.e. that escape fewer cases of CIN3 + with the detection of HPV than with Pap test, However, it is higher with the simultaneous performance of the two tests, so the cotesting would result in fewer false negatives because they use two tests instead of one.
According to an analysis of several studies involving researches with HPV test, made by several American scientific societies dedicated to the cervical pathology, the following must be considered:

a) No test has the ability to discover all cases of cervical cancer, i.e. always are going to slip away some cases.

b) It is ideal that a test has a high rate of detection of CIN3 + in the first screening and a lower detection for CIN3 + in subsequent screenings.

c) One greater number of referrals for colposcopy is considered as a negative side effect of the screening.

Based on these parameters the screening with cotesting or HPV test, are equivalent in these terms, so it could be interchangeably. In conclusion, both schemes are valid depending on the context in which are carried out, provided in a way that ensures the greatest coverage possible of patients at risk.

Another important aspect to be considered is the cost of screening with Pap test detection of HPV test in comparison with the HPV test only. Probably costs are lower when performing a single test than carried out two. However, HPV test screening can generate costs of the technology needed to process the sample which may not be similar in all countries, being higher in the places where the technology has to be imported, which would make the screening with HPV test only or simultaneously with Pap test, unworkable. In some regions, fewer costs to perform cytology and colposcopy are generated comparing to HPV testing what should be taken into account when recommending a cervical cancer prevention program.

These studies on most convenient screening scheme were carried out in countries, as in the US, where the incidence of cervical cancer is low. To assess the impact of a screening scheme, it would be advisable to do so in regions with higher incidence of cervical cancer, to better evaluate the sensitivity of one or more tests, as well as the costs of the implementation of them.

The ideal test is one that is sensitive, economical and feasible to ensure an adequate coverage of the population at risk. Besides, such as the development of cervical cancer is preceded by a persistent infection with HPV, a dynamic screening in well-defined time intervals, seating information in a database that allows to know which patients have been evaluated and how often they should be reviewed, it would, together with prophylactic HPV vaccination, drastically reduce cervical cancer figures in a few years.

1. Cervical cancer screening: redefining the legacy of Papanicolaou. [https://intervalolibre.files.wordpress.com/2014/05/la-evolucic3b3n-de-papanicolaou-ingles.pdf](https://intervalolibre.files.wordpress.com/2014/05/la-evolucic3b3n-de-papanicolaou-ingles.pdf)

