CERVICAL HUMAN PAPILLOMA VIRUS (HPV) DNA PRIMARY SCREENING TEST: RESULTS OF THE EXPERIENCE OF A REGIONAL LABORATORY IN CENTRAL ITALY

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Introduction and objectives
Cervical cytological screening has significantly decreased the incidence and mortality of cervical cancer. In 2014, about 3000 new cases of cervical cancer will be diagnosed and about 1000 deaths will occur in Italy (1). Persistent infection with high-risk (HR) human papillomavirus (HPV), particularly genotypes HPV16 and HPV18, is the major cause of cervical cancer. HPV detection has been proposed as an alternative or complementary to cytology, according to a better sensitivity for the detection of precancerous lesions, so-called high-grade cervical intraepithelial lesions (CIN 2 or CIN 3) and cancer in cervical screening (2). A large population-based randomized controlled Italian trial performed on almost 95,000 women aged 25-60 years evidenced that HR-HPV DNA detection is more effective than Pap test in detecting both CIN and invasive cervical cancers, and in predicting a longer lower-risk period (3). Although confirming the lack of over-diagnosis in women aged 35 years or older, this trial evidenced an over-diagnosis of eventually regression CIN lesions in the younger group of studied women, aged 25-34 years (3). Moreover, the ATHENA trial is the largest U.S. cervical cancer screening registral trial with the goal of evaluating HPV and it is the only trial to assess the value of simultaneous HPV 16 and HPV 18 genotyping in risk assessment of women (4). The ATHENA study showed that nearly one in 7 women with normal cytology who were HPV 16+ had high grade disease that was missed by cytology (5). Women with ASC-US cytology who were HPV 16 + were more than twice as likely to have ≥CIN2 than women with ASC-US cytology who were positive for at least one other HPV subtypes (5).

Methods
During the period August 2010 October 2011 at the Laboratorio Unico di Screening of Perugia, Umbria, Italy a pilot study was conducted on the population of women 35-64 aged with HPV test as primary screening test. Results were compared with those obtained with Pap test as primary screening test in the same cohort from January 2008 to June 2010, following the screening programmes used since 1999. The usual algorithm with cervical cytology as primary test is described in the fig.1a, whereas fig.1b shows the high-risk human papillomavirus (HR-HPV) DNA test algorithm used as primary screening. The two methods were compared in terms of acceptance rate of invitation, cytological results, molecular results including HPV genotypes, detection rate of histological lesions.

Results
During the tested period were invited 21,249 women to undergo classical cervical cytology screening of 9,979 HR-HPV DNA test as primary screening. A similar rate of adhesion (56.6% vs. 56.5%) was observed Tab 1. Age-related differences were evidenced, with younger women 35-49 year old more prone to accept the invitation to HR-HPV DNA testing compared to 50-64 years old (61.6% vs. 55.5%; p<0.0001 - Tab 1). Among 15,276 women tested with Pap test, 230 (1.5%) had a positive test (105 high grade lesion and 125 low grade lesion). 157 women were referred to colposcopy after triage with HPV test, 119 (79%) accepted the colposcopy. Among those 58 (49%) had CIN2+ histology result. Among the 6,272 HR-HPV DNA testing women, 396 (6.4%) were positive, and, among them, 141 (36%) featured an altered cytology. All patients with altered cytology were suggested to undergo colposcopy and 130 out of 141 (92.6%) answered to the invitation. Among them, 52 (30%) had CIN2+ histology result (Tab 2); HPV-DNAhr 16 was observed in 69% of the CIN2+ lesions. Data comparison shows an implementation in the colposcopy referral rate after HPV-DNAhr test but a doubled CIN2+ detection rate (0.88% vs. 0.37%; p<0.0001 - Tab 3).

Primary Screening Algorithm with Cytology

Primary Screening Algorithm with HR-HPV DNA test

Table 1: comparison between the two screening programs in terms of adhesion rate.

<table>
<thead>
<tr>
<th>Screening Algorithm</th>
<th>Screening period</th>
<th>Women invited</th>
<th>Adhesion rate</th>
<th>Adhesion rate younger (35-49)</th>
<th>Adhesion rate (50-64)</th>
<th>Tested women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Jan 2008-Jun 2010</td>
<td>21249</td>
<td>56.6%</td>
<td>55.5%</td>
<td>61.6%</td>
<td>15276</td>
</tr>
<tr>
<td>hHR-HPV DNA</td>
<td>Aug 2010-Oct 2011</td>
<td>9979</td>
<td>56.5%</td>
<td>52.0%</td>
<td>52.0%</td>
<td>6272</td>
</tr>
</tbody>
</table>

Table 2: comparison between the two screening programs

Conclusions
Although with some limits, the introduction of HR-HPV DNA primary testing resulted feasible and effective, significantly increasing detection of severe lesions compared with the cytology screening program.

References
1. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information centre). HPV and related cancer in women

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