CORRESPONDENCE

Human Papillomavirus DNA and Pap Tests: The Need for Cotesting in Opportunistic Setting During the Transition Time

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The knowledge of the etiologic role of high-risk human papillomavirus (HPV) infection in cervical cancer generated 2 important clinical tools concerning primary and secondary prevention: HPV vaccine and HPV DNA testing, respectively. Although cytology-based screening has been universally recognized as the cornerstone of cervical cancer prevention, oncogenic HPV DNA testing in the last decade has been consistently shown to be more sensitive (about >30%) than Pap test [1]. Moreover, randomized trials found that, although some of the cervical intraepithelial neoplasia 2 (CIN 2) may spontaneously regress, the increased sensitivity for precancers and cancers, grouped here as CIN 3+, is not merely an overdiagnosis because there is a corresponding lower incidence of future CIN 3+ [2–4]. Increased sensitivity has 2 important clinical outcomes as follows: reduced mortality and an elongation of screening intervals; the latter implies better compliance with screening and lower costs. Recent articles supported these assumptions; the New Technologies for Cervical Cancer screening study showed that HPV-based screening is more effective than cytology in preventing invasive cervical cancer, by detecting persistent high-grade lesions earlier and providing a longer low-risk period. The detection of invasive cervical cancers was similar for the 2 groups in the first round of screening (9 in the cytology group vs 7 in the HPV group, $p = .62$); no cases were detected in the HPV group during round 2, compared with 9 in the cytology group ($p = .004$) [5]. Finally, a recent meta-analysis of 7 European population studies showed that primary screening by HPV testing allows for an increase in the interval between 2 screenings of up to 6 years, while keeping the cumulative incidence rate of CIN 3+ in HPV test–negative women almost 2 times lower (0.27%) than in women screened by cytology (0.51%) at 3-year intervals [6]. In this way,

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even an increase of costs related to the new technology is balanced by an extension of intervals between 2 different screens.

Better sensitivity means earlier detection of clinically relevant cervical lesions and, as a consequence, a reduced cancer incidence; therefore, the introduction in cervical cancer screening programs of primary HPV DNA–based screening with cytology triage and repeated HPV DNA testing of cytology-negative women seems to be the most feasible strategy [7], minimizing the number of unnecessary referrals to colposcopy [5].

As a matter of fact, in the very near future, this approach could be adopted in large-scale pilot studies in countries where organized cervical cancer screening programs are well established, starting at the age of 30 years, moving cervical screening toward better effectiveness and reproducibility. Such strategy has been recently approved by the Health Council of the Netherlands [8] as well as pilot phase in some Italian regions.

In Italy, cervical cancer prevention is pursued through direct personal invitation by organized triennial regional screening programs (which cover approximately 60% of the target population) or via the so-called *opportunistic* screening, proposed to a single individual by her family physician or—more often—private gynecologist with a circa annual periodicity. Overall population coverage and response rate (70% of the covered population) of organized screening are still less than optimal, accounting for approximately 5.6 million of Pap tests per year. On the other hand, opportunistic cervical screening is a well established and widely performed preventive intervention among Italian women, accounting for more than 5 million tests taken each year. Although many attempts have been advocated to discourage opportunistic screening, it is realistic to expect that it will remain part of our health preventive scenario for the next years to come.

At this time, a relevant question is how to introduce the new instances of HPV DNA–based prevention strategy in these 2 different settings, taking into account the difficulties existing at this transition time. Indeed, at the national level—organized programs, it will be easy—and mandatory—to implement the evidence-based approach with HPV DNA testing as the primary step and long-time interval (3–5 years and more) between the rounds, whereas in the opportunistic setting, one may expect to encounter more resistance, considering the tendency to overscreen patients with conventional cytology, every 12 months (or even less) [9]. This translates to higher costs, increase in harms, no additional benefits, and treatment of transient lesions. Human papillomavirus–based screening, adopting longer interval (3–5 years), can interrupt that financially driven strategy and a discrete effort to achieve substantial changes in the private setting.

Therefore, it is not unrealistic to anticipate in the near future a somehow "double-track" scenario in cervical cancer prevention (public vs private), with different methods used and uncoordinated interval timing: HPV DNA testing every 5 years versus annual conventional Pap test. There is no doubt that such scenario could be harmful from a public health point of view, would possibly limit the expected results of cervical cancer prevention, and, even more, could confuse the public opinion and perception of the tests. There is basically a single option to counteract such a situation, and it is, during these years of transition, to strongly support the use of the 2 tests together (Pap test and HPV DNA testing) in the opportunistic screening set.

The so-called *cotesting* strategy (although approved and supported as optimal primary screening in the United States for women 30–65 years [10]) has been recently judged ineffective in organized screening, mainly owing to overreferral to colposcopy of women presenting a low incidence of cervical lesions [11] (i.e., cytology-positive, HPV-negative women), thus resulting in a unfavorable cost-benefit ratio. Although this perspective is reasonable at a national, cost-conscious level, in the private—opportunistic—arena, the exclusion of an invasive disease in that single woman requiring the test is the primary goal, and costs might not be the only variable to be taken into account. In fact, even those few cases of high-grade cervical lesions testing negative for HR HPV DNA are important at the individual screening level. Indeed, in all studies published so far, double testing resulted in an increased detection of cancer precursor lesions, either CIN 2+ or CIN 3+. In the ATHENA study, Castle et al. [11] reported 2 (12.5%) of 16 in situ adenocarcinomas and 20 (4.8%) of 411 CIN 2+ found in liquid based cytology-positive+/HPV-negative patients. In similar group of patients in Kaiser Permanente Northern California study, Katki et al. [12] showed a nonnegligible rate of squamous cervical cancers (8 of 49, 16.3%) and of CIN 2+/in situ adenocarcinoma (91 of 2,223; 4.1%). Although cytology is much more useful in HPV-positive rather than HPV-negative women, the identification of such "extra" high-grade lesions in the latter group (adding cytology) fits into the clinical objective of individual screening.

It is important to emphasize that, within the cotesting strategy, an option to reduce unnecessary referrals to second-level procedures in women at low-risk of

significant disease (Pap positive/HPV negative) could be to send to colposcopy only those presenting high-grade squamous intraepithelial lesion, atypical squamous cells-cannot exclude high grade lesion, or atypical glandular cells cytology. Exclusion of borderline cytology (atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion) from further examination reduces, in such a group of patients, management costs, improving overall positive predictive value. In addition, 2 factors should be taken into account: in the study published by de Sanjose et al. [13], only 62% of invasive cervical adenocarcinomas had positive HPV test results.

It is anticipated that approximately one half of the cervical adenocarcinoma that are currently diagnosed by cytology would be missed by the introduction of HPV testing alone. These numbers have minor impact in population screening, which is directed to the most frequent types of cervical cancer, the squamous and adenocarcinoma HPV-related cervical cancers, but represent not only a loss of diagnostic chance for the individual woman who planned and asked to undertake Pap testing and instead will receive an HPV DNA test, with all the pluses of the new tool, but also the potential disadvantage of missing some rare types of cervical cancer.

In conclusion, according to the existing double-track screening, the introduction of a cotesting strategy in the opportunistic setting (HPV DNA test and cytology, preferably on the same vial of liquid based cytology) could potentially represent the best option to overcome the challenges related to the transition time from cytology to HPV DNA–based screening, giving some homogeneity between the 2 existing screening scenarios. In the HPV-negative group, the indication to refer to colposcopy patients with high-grade squamous intraepithelial lesion (and atypical squamous cells-cannot exclude high grade lesion/atypical glandular cells) cytology will result in more cost-effective management. Moreover, this combined strategy could also be well accepted by cytopathologists. In the meantime, private gynecologists will educate themselves to bypass the habit of annual Pap testing and will appreciate different reasons to see the woman regularly; they will learn how to manage HPV DNA positivity and become experts in HPV counseling. This will help everyone be prepared to switch to the next steps, every 5 years HPV DNA–based cervical cancer screening and screening of the vaccinated population.

Human papillomavirus testing carries better protection against cervical cancer, a real advantage to women's health. Any strategy that can smooth and speed up the adoption of the new technology by gynecologists will result in a quicker transfer of scientific evidence to women and better care for them. Supplementation of Pap smear screening with HPV testing is the fastest track to achieve this goal, despite the fact that epidemiologic evidence says that HPV testing can do equally well alone, without cytology.

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