

HPV Genotyping in the Prevention of Cervical Cancer—How and When Can It Be a Useful Marker?

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See related article by Schiffman et al., p. 1304

Persistent infection with high-risk human papillomavirus (hrHPV) types is the known cause of cervical cancer (1), a neoplasia suitable to effective primary and secondary prevention. For many decades, cervical cancer screening has been performed by cytology as the primary test, with significant reductions in cancer incidence (2), and, more recently, the use of hrHPV testing with cytology triage in large randomized controlled trials (RCT) has been demonstrated more effective than cytology in preventing invasive cervical cancer (3). The aim of screening is the prevention of cervical cancer through detection and excision of precursor lesions (namely, CIN2 and worse), and its effectiveness, besides primary test performance, depends on target population coverage and adherence to quality-controlled protocols; organized population-based screening is more cost-effective than opportunistic testing.

HPV-based screening is more sensitive than cytology-based screening given the use of clinically validated tests for hrHPV types (4), in women 30 years and older, and triage of HPV-positive cases to counterbalance the 2.5% to 4% lower specificity (3). HPV infection is transient in the vast majority of the women (and particularly in those younger than 30–35 years of age) and only a minority harbor a persistent infection and have or are at risk of having a high-grade lesion (5). Spontaneous regression of CIN2 and, to a lesser extent, CIN3 lesions also occurs in a proportion of women and is more frequent in the youngest. Therefore, triage is necessary to select the women at higher risk of precancer who need immediate colposcopy, thus limiting excessive referral and overdiagnosis in women with transient and not (or less) clinically relevant HPV infections. Cytology is actually the most widely used test to triage hrHPV-positive women attending organized screening (6), but search for alternative (and less subjective) tests is advocated. Several studies, investigating p16 expression, HPV genotyping, HPV mRNA expression, and methylation of cellular and/or viral sequences as triage markers (used alone or in combination) have been published so far (7–12). These markers have been analyzed in terms of immediate or subsequent risk of CIN2⁺ or CIN3⁺, sensitivity, specificity, positive predictive value, and cost-effectiveness (colposcopy referrals, overdiagnosis, and harms). These analyses have been performed on different populations (clinical settings or population-based screening), of different ages, cross-sectionally only or longitudinally. Overall, HPV16 has always been associated with the highest risk of CIN2⁺ and CIN3⁺, with a three-tier ranking of the other hrHPV types; risks were highest in the first screening round, gradually decreasing over

time but still persisting after more than 9 years (12). Moreover, an inverse relationship between sensitivity and specificity of the triage tests was always registered, and different combinations have been proposed. Indeed, the ideal triage test/strategy should allow selection of women at highest risk to be immediately referred to colposcopy, while referring the other hrHPV-positives to a follow-up step that will later allow additional risk stratification. Subsequent controls entail the risk of loss to follow-up of women at risk of high-grade lesions in the medium- to long-term period; thus, reflex tests feasible on the baseline cervical sample have the potential to increase compliance.

Schiffman and colleagues (13) present in this issue a large evaluation on the use of HPV genotyping in three clinical settings: (i) women 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cytology and positive hrHPV test; (ii) women 30 years and older with positive hrHPV test and negative cytology; and (iii) women 25 years and older with positive hrHPV test. In all three scenarios, infection by HPV16 was associated with a higher 3-year risk of CIN3⁺ than by infection with the other hrHPV types. This strong association however does not automatically translate into effectiveness, cost-effectiveness, and utility of partial genotyping as triage marker in all scenarios. In particular, triage of women with ASC-US by hrHPV testing is effective and common practice in many countries; specific detection of HPV16 by HPV-DNA (14) or HPV-mRNA (15) tests allows stratification of hrHPV-positive women, and could eventually be implemented. On the other hand, management of hrHPV-positive/cytology-negative women older than 30 years is indeed the main challenge of HPV-based screening programs, recently implemented in some European countries; actually, in Italy, these women are referred to hrHPV retesting at 1-year interval. Partial genotyping (alone or in combination with cytology) would further stratify hrHPV-positive women, at the cost of increasing the complexity of the protocol. Indeed, within population-based organized screening programs, it is of utmost importance to use simple and widely accepted (by health-care providers within and outside the screening setting) protocols to ensure compliance and screening effectiveness. Longitudinal data from RCTs on persistently HPV16-positive women with no lesions detected should also be evaluated to define their long-term risk and best follow-up strategy before implementation of triage by partial genotyping. Finally, in the screening context, two additional caveats must be kept into consideration in the near future; namely, the different risk of precursor lesions in the first versus the subsequent hrHPV-based rounds, much lower in the second (16), and the screening strategy for vaccinated women, in whom lesions caused by types 16 and 18 will gradually disappear, and specific protocols will have to be designed.

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Disclosure of Potential Conflicts of Interest

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