Editorial

The Pap Test: Is it Time to Move on?

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The Papanicolaou vaginal smear – the Pap test – for the early detection of cervical cancer in women, represents one of the milestones of the modern medicine and the turning point towards the applicable concepts of preventive oncology [1]. During the 20th century, cytological screening for cervical cancer has been the gold standard and is now widely recognized to have represented one of the major public health advances. Where cervical cancer screening has been realized, a dramatic decrease in incidence and mortality from this disease has been observed; despite this, cervical cancer still accounts for the third most commonly diagnosed malignancy in women worldwide and for the second cause of cancer-related deaths in some low-resources geographical areas [2]. Low sensitivity, high false-negatives rates and very high interobserver variability, are the most commonly reported biases associated with the Pap test efficacy; of note, perfectly synthesizing an emerging impression, in the 1980s, Dr. Louis zur Hausen published an editorial in the JAMA journal titled “The Papanicolaou test for cervical cancer detection. A triumph and a tragedy” [3]. Many studies have reported that up to 40% of incident cases of invasive cervical cancer are detected in patients regularly attending screening programs and testing negative [4,5], and that the overall sensitivity of cervical cytology is rarely higher than 60% [6]. In 1975, zur Hausen firstly hypothesized the importance of a viral agent as the biological cause of invasive cervical cancer, and identified the Human papillomavirus (HPV) as potentially responsible for the neoplastic transformation of the superficial cells of the uterine cervix [7]. From that moment, the importance of HPV in representing the necessary cause for cervical cancer became one of the major research interests worldwide, accounting for more than 10,000 published papers till today. The better understanding of the causal role of Human Papillomavirus in the development of cervical cancer has deeply modified the approach to its prevention: from the “early detection” of preneoplastic disease with cytology, to the “at high-risk women” identification and management with biomolecular assays long before the onset of the disease. Strong evidence now exists supporting the introduction into cervical cancer prevention strategies of diagnostic tools specifically targeting the detection of oncogenic, or “high-risk” HPV strains; large randomized recently published trials have consistently demonstrated the higher sensitivity, very close to 100%, and negative predictive value (NPV) of HPV-DNA testing compared to conventional and liquid-based cytology [8,9]. Among the several demonstrated improvements correlated to the use of HPV-DNA testing, lengthening of screening intervals, overall costs reductions, and stronger and longer patients’ reassurance must be underlined and strengthen the newly emerging scenario in this field. At present, the validated and recommended use of HPV-DNA testing in clinical practice essentially covers three settings: primary screening, triage of equivocal cytology and follow up of conservatively treated patients for high-grade cervical cancer precursors; in all these situations, HPV-DNA testing has been proved to have a better efficacy in predicting cervical intraepithelial neoplasia of high grade (CIN2-CIN3) or cancer than cytology or colposcopy [10]. Another particularly interesting aspect of the positive impact of HPV-DNA testing will be expected following the recent introduction of HPV vaccines: once the results of vaccination campaigns against HPV will be obtained, with the awaited significant HPV prevalence reduction in vaccinated subjects, the relevance of identifying the large numbers of HPV-negative women will be even more important than today. Even in low-resource regions, considerable improvements in terms of cancer-related deaths and morbidity will be obtained: in these settings, where no screening strategies are available because of unaffordable costs, a single round of HPV-DNA testing would significantly perform [11]. On these basis, from a public health perspective, the optimal design of an efficient cervical cancer prevention strategy should without any hesitation include HPV-DNA testing as a fundamental diagnostic option that would allow saving thousands of women worldwide.

References


