New Biomarkers Improving Cervical Cancer Screening Efficacy

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Carcinoma of the uterine cervix is the third most commonly diagnosed malignant neoplasm in women and the second cancer-related cause of deaths in many low-resources geographical areas [1]. Cervical cancer cytological screening programs, since the introduction in clinical practice of the Papanicolaou vaginal smear – the Pap test – have represented one of the major public health advantages and improvements of the last century; where cervical screening is realized, incidence and mortality due to this disease have demonstrated a dramatic reduction [2]. Despite this observation, invasive cervical cancer still accounts for almost 500,000 new cases per year worldwide, with approximately 11,000 and 4,000 new cases and deaths respectively in the USA per year [1].

The reason for this unsatisfactory results are attributable to many independent factors: women’s incomplete adherence to screening, inadequate samples, insufficient time devoted to screening, human fatigue, inadequate clinical component, inadequate patient compliance, poor reproducibility of diagnoses, and ineffective aftercare [3].

The Pap test itself has demonstrated inherent limits, the most important of which are the low sensitivity, the low Negative Predictive Value (NPV) and the low interobserver reproducibility; in brief, it has been widely demonstrated and strongly supporting evidence exists, that the rate of false-negative cytological vaginal smears accounts for almost 40% of all the performed Pap tests, and that almost 40% of new cases of invasive cancer are diagnosed among women who had a recent negative Pap test [2]. The understanding of the causal role of Human Papillomavirus (HPV) for the development of cervical cancer in women has substantially modified the scenario of the screening in recent years: the biomolecular diagnosis of HPV infection has gained an increasing consideration in the scientific and clinical community, mainly because of the very high sensitivity and very high NPV; women testing negative for HPV-DNA have been demonstrated to have a long interval – up to 6 years – of risk-free reassurance towards the onset of preneoplastic or neoplastic disease of the uterine cervix [4]. Of note, HPV-DNA testing in primary screening has been strongly demonstrated to have a superior efficacy compared to cervical cytology. Beside this, other diagnostic assays targeted to the identification of true-positive Pap tests have recently been matter of study and promising results have been reported; in particular, p16^ink4A^ and Ki-67 cytological immunostaining of cervical samples seem to be positively responding to the needs of improving cervical screening efficacy and biologically linked to the effects of HPV upon cervical cells. The p16^ink4A^ protein acts as a cell cycle regulator owning an inhibiting capacity upon the progression of the cell cycle itself; in particular, p16^ink4A^ is synthesized during the mitotic phase. Thus, p16^ink4A^ hyperexpression may be interpreted as a marker of cellular multiplication without control. In case of HPV infection due to oncogenic viral strains, the E6 and E7 viral oncoproteins directly interact with the host cells cycle, inhibiting the regulatory effect of p16^ink4A^, promoting its overexpression; high levels of p16^ink4A^ are detectable and directly correlated with the HPV transforming action [5]. The Ki-67 protein is a well established nuclear marker of cellular proliferation, already utilized in oncological histology to define a rapidly growing neoplastic population: the Ki-67 labelling index is a marker of negative prognosis for several malignancies (breast cancer, prostate cancer and some brain cancers). On these basis, the contemporary hyperexpression of both p16^ink4A^ and Ki-67 in cervical cytological samples have been proposed as a biologically applicable and valuable detection tool of the deregulation of the cell cycle secondary to HPV transmision. Several large-scale trials have been designed in recent years to test the performance of the p16^ink4A^/Ki-67 dual staining of cervical smears both in screening and in triaging atypical cytology [6-8]. Consistent results from these trials have showed that p16^ink4A^/Ki-67 cytological staining has comparable sensitivity, but significantly higher specificity than HPV-DNA testing; this lead to a better identification of cases very likely to progress to invasive cancer. Since cervical cancer screening strategies in women will probably be updated according to HPV testing high sensitivity in the near future, these novel biomarkers represent a very promising option to overcome the current limitations of cervical screening.

References
