HJOG An Obstetrics and Gynecology International Journal

Review

# HPV DNA testing *versus* Cytology: A new era in cervical cancer screening

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## Abstract

Cervical cancer screening tests are growing at a rapid pace, reflecting the importance of the HPV virus in the development of cancer. Four randomized studies in Europe and one perspective study in the USA have substantiated the application of HPV DNA screening (HPV testing), as a triage trial for cervical cancer. According to the results, HPV DNA testing displays higher sensitivity in comparison to the Pap-test, when it comes to early detection of precancerous lesions, a fact which promotes the maintenance of longer intervals of screening. On the other hand, HPV DNA testing exhibits a lower specificity and thus increases the number of unnecessary colposcopies. In order to counteract this shortcoming, new biomarkers could be used, while vaccination against the HPV virus will undoubtedly promote the eradication of the disease.

**Key Words:** HPV DNA testing; cytology; Pap smear; cervical intraepithelial neoplasia; cervical cancer screening

In the United States, approximately 33,000 cases of cancers that are associated with the human papillomavirus (HPV) are diagnosed annually[1] while cervical cancer is considered to be the cause for about 275,000 deaths per year, ranked fourth after breast cancer. The persistent infection with high-risk HPV types is necessary but not sufficient for cancer development, considering that more than 70% of cervical HPV infections will clear spontaneously within one year[2]. Besides cervical cancer, oncogenic HPV types are detected in the majority of vulvar, vaginal and anal cancers[3].

Since George Papanicolaou correlated cervical cell changes with cancer development, cervical cytology constituted the cornerstone of cervical cancer prevention and led to a dramatic decrease in mortality and morbidity from the disease, after its implementation in organized screening strategies. A striking example comes from the UK as cytology aimed to reduce cervical cancer mortality from 6.4 per 100,000 population in 1988 to 2.2 per 100,000 in 2012[4].

The reveal of the strong bond between high risk HPV (hrHPV) and cervical carcinogenesis induced primary prevention strategies based on HPV immunization and finally shifted secondary prevention to the direction of hrHPV detection which reflects the risk stratification for cervical cancer development.

In January 2016, the UK National Screening Committee modified its recommendation as to use HPV testing as the primary screening test in the place of

cytology[5]. In the United States HPV testing is recommended to triage women with atypical squamous cells of undetermined significance (ASC-US) and as an adjunct to cytology when screening women ≥ 30 years ("cotesting")[6,7].

Scientific research has indicated that there is a comparable efficacy between HPV testing and cytology, regarding the prevention of cervical cancer and the aim of this review is to enlighten the different aspects of the existing evidence.

A comprehensive systematic bibliographic search was conducted in order to identify international Randomized Control Trials, Meta-analyses and Systematic Reviews, regarding the efficacy of HPV DNA testing versus cytology as screening methods. The Cochrane Library and the U.S. National Library of Medicine were used, as computerized bibliographic databases. The key words that were used were: "HPV DNA test", "cytology", "Pap smear", "cervical intraepithelial neoplasia", "cervical cancer screening".

We found four large randomized control trials that were conducted, in order to evaluate the efficacy of HPV-based primary screening, in the Netherlands (POBASCAM)[8], Sweden (SWEDSCREEN)[9], Italy (NTCC)[10], and England (ARTISTIC)[11]. Women aged 20-64 years old were separated to experimental group (HPV testing plus cytology) and control group (cytology-based). Interventions were done in HPV positive/cytology negative women. The primary endpoint was the precursors of cervical cancer. Ronco et al. in 2013, published a pooled analysis reviewing the data of all four trials and subsequently followed up almost 180,000 women over a six and a half years in average, which resulted in the identification of 107 cases of invasive cancer[12]. Additionally, data from the follow up analysis demonstrated that HPV-based cervical screening provided 60-70% greater protection against invasive cancer compared to cytology based screening and moreover allowed extended screening intervals. More specifically, a lower incidence of CIN3 was recorded in the HPV-testing group, while the results demonstrated that HPV-based screening detected the persistent high grade CIN earlier than cytology and therefore increased the chances of sufficient treatment and prevention from invasion. However, although different screening protocols were applied, the efficacy in cancer prevention was dependent on the screening method and not on the protocol that applied. Regarding the screening intervals, the cumulative cancer incidence 5,5 years after a negative HPV test was lower in comparison to after 3,5 years after a negative cytology-based test.

In 2008, the 3-year prospective ATHENA study was initiated in the U.S. and compared the sensitivity and specificity of primary hrHPV screening with either cytology alone or co-testing (co-testing beginning at the age of 30 and cytology alone for ages 25-29). Approximately 42,000 women were enrolled in the study and followed up for the development of dysplasia. A total of 240 CIN2, 319 CIN3, 20 adenocarcinoma in-situ, and 8 invasive cervical cancer cases were detected. The results of ATHENA study indicated that HPV-testing was more sensitive in detecting high-grade cervical dysplasia. HPV-testing in women ≥ 25 years had the highest adjusted sensitivity over 3 years (76.1%; 95% CI: 70.3-81.8%) for the detection of CIN3+, while the adjusted sensitivity of cytology for CIN3+ was 47.8% (95% CI; 41.6-54.1%) and that of the hybrid strategy was 61.7% (95% CI: 56.0-67.5%). In women ≥ 25 years, cytology had the highest specificity (97.1%; 95% CI: 96.9-97.2%) and HPV-test the lowest specificity (93.5%; 95% CI: 93.3-93.8%) for CIN3+. The hybrid strategy presented intermediate specificity. In women ≥30 years the hybrid strategy and HPV-testing had similar sensitivity and both higher than cytology for the detection of CIN3+. In women ≥30 years cytology had a higher specificity for CIN3+ than hybrid strategy or HPV-testing while the latter presented the same specificity. HPV-test had a significantly higher negative predictive value (NPV) than cytology suggesting that women, whose cervix was not affected by hr HPV, were not likely to develop severe cervical lesions within the next five years[13].

It is obvious that HPV-testing shows greater sensitivity for the early detection of CIN2 and CIN3. It is also scientifically proven that these lesions often regress in young women and progress in a rate of 16% in ages 18-34[14]. Thus, the risk of overdiagnosis of CIN in young women should be thoroughly considered and evaluated.

Pileggi et.al. meta-analyses, concluded that due to the prevalence of transient HPV infections, especially in younger women, HPV-testing is less specific in detecting CIN2 and CIN3 than cytology, whereas both test specificity increases with age and overlaps beyond the age of 30[15].

Still, the main concern is the lower specificity of HPV-testing at the age 25-29 which increases the referral rate of unnecessary colposcopies and further investigation. This results in severe emotional impact between HPV positive women that partially could be managed by comprehensive communication with healthcare professionals. In order for HPV testing to be an efficient primary screening strategy, algorithms are required to avoid over-referral of younger women. Furthermore introduction of biomarkers as HPV E6/E7 mRNA and p16 may help to distinguish transient from persistent HPV infections.

The main weakness of cytology is its low sensitivity which means that a high rate of false negative tests will require repeating screening at short intervals, therefore higher cost for the health system and lower rate of compliance from women. On the other hand, annual visits to the GP or gynecologist for cervical screening automatically offers women a comprehensive medical care, including general gynecological examination, breast examination and consultation all of which benefit their well-being in the long-term.

The use of HPV-testing as a primary screening method and subsequently cytology as a more specific method for a triage of HPV positive women - as demonstrated in the HPV Primary Screening Pilot Protocol Algorithm in England - reassured that only women with abnormal cytology would be referred for colposcopy. The real challenge though, was the HPV positive/cytology negative women, a group that does not require immediate intervention but certainly requires early recall (12 months).

Furthermore, the immunization against HPV is considered to have a positive impact on cervical cancer screening. More specifically, once the vaccinated group reaches the age of 25 and is introduced in the screening program, the overall HPV positivity will be reduced significantly and the screening will be undoubtedly more efficient, as it would overcome the major problem that is the high HPV prevalence in the years of 25-30.

The key role of HPV infection on the initiation and development of cervical cancer is the basic principle that led the scientific community to a radical reconsideration of current screening strategies. There is robust evidence supporting the switch from primary cytology to primary HPV-testing but at the same time there are challenges to overcome, such as lower specificity and over-diagnosis of regressive lesions. Overall, there is a great variety of parameters that should be taken under thorough consideration before implementing a new screening policy, but the ultimate priority is to prevent cervical cancer in women.

## Conflict of interests

The authors declare that they have no conflict of interest.

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