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Rapid Communication

HPV DNA testing in cervical cancer screening: From evidence to policies

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Rationale

Within the past 5 years, guidelines recognizing the value of HPV testing in both primary cervical screening and in the management of abnormal cervical cytology have been established in the US and are being considered in Europe [1–5]. This trend has occurred because of the definitive association of high-risk (HR) human papillomavirus (HPV) with cervical cancer and the overwhelming evidence that the sensitivity of HR HPV testing for lesions with a diagnosis of cervical intraepithelial neoplasia grade 2 or more severe (CIN 2+) is substantially higher than that of cytology [6–8]. This higher sensitivity offers a number of advantages, including, most importantly, the potential of reducing cervical cancer rates while reducing the number of screens in a lifetime necessary to achieve this goal [9,10].

Current evidence base for using HPV testing

Although cervical cytologic screening has been very successful in lowering the rate of cervical cancer in countries with high coverage and good quality control, a number of problems with cytology have been well described. These include: (1) results are dependent on a high quality sample being collected at examination, (2) the reading of the slide is subjective and (3) the repetitive nature of the reading, which can lead to greater number of interpretive errors. The low sensitivity of cytology has major medical, economic and medico-legal implications [6–8]. High coverage remains the most important factor for successful screening programs, but once coverage is high, improving the sensitivity of the screening test becomes increasingly important. A report of Sasieni and colleagues (1996) shows that 47% of women in the UK who developed stage 1B1 or worse invasive cervical cancer before the age of 70 had had an adequate previous screening history [11].

A review by Cuzick et al. (2006) of studies in countries with established cytology-based screening activities, including more than 60,000 women who were tested for both HPV and cytology provides a direct comparison of the sensitivity of these two tests [12]. Sensitivity of cytology was substantially less than for HPV testing and varied considerably between studies. The overall sensitivity of cytology for CIN2+ was 53.0% (48.6–57.4%), but varied enormously from 18.6% in Jena to 76.7% in the HART study [13]. The sensitivity was substantially better in women over the age of 50 than for younger women (79.3 vs. 59.6%). The overall specificity for cytology was 96.3% (96.1–96.5%) and the overall PPV was 20.3% (18.3–22.4%). In common with HPV testing, specificity was better in older women (95.9% vs. 97.1% for <35y vs. 35+) and the PPV was higher in women younger women (23.2% vs. 17.5% for <35y vs. 35+) [12,13].

HPV testing was consistently very sensitive in all studies, with the sensitivity for CIN2+ and CIN3+ both being 96.1% overall (94.2–97.4% and 93.6–97.6% respectively). Unlike for cytology, there was no indication of heterogeneity between studies [8,14–17]. Also, the sensitivity was unaffected by age.

Specificity of HR HPV testing (≥CIN2) was more variable, and was significantly lower in younger women. Overall the specificity was 90.7% (90.4–91.1%) and ranged from 76.5% (72.8–79.8%) in a mostly young population to 95.5% (94.7–96.1%) in an older population. For women 35y and over, specificity was 93.3% (92.9–93.6%) overall and ranged from 87.3% (86.1–88.5%) to 96.4% (95.6–97.1%). Overall the positive predictive value of an HPV test for CIN2+ was 15.5% (14.2–16.8%) and was 12.8% (11.2–14.6%) in women 35y or over and 17.8% (16.0–19.8%) in younger women [12]. In conclusion, HPV testing is more sensitive than cytology at all ages and in every study [8,12–18]. It is also less specific. This

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difference is substantial for women under the age of 35 years, but for older women the differences in specificity between HPV and cytology tests are quite small [12].

Recommendations

General points

- The use of HPV DNA testing alone as a primary screening method has been shown to be more sensitive than cytology in numerous clinical studies. Further trials are ongoing to help define its best use as a primary screening tool.
- The International Agency for Research on Cancer (IARC) stated: "There is sufficient evidence, based on surrogate markers, that the efficacy of HPV testing, using a validated system, as the primary screening modality can be expected to be at least as good as that of conventional cytology" [3].
- Because HPV testing is more sensitive than cervical cytology in detecting CIN 2 and CIN 3, women with concurrent negative test results (Pap and HPV test) can be reassured that their risk of unidentified CIN 2, CIN 3 or cervical cancer is approximately 1/1000 [10,19].
- Cost-effectiveness modeling indicates that HR HPV testing alone is an attractive approach in many settings (Goldie et al.). The development of cheaper HPV tests would make this attractive in even more settings [20].
- Cervical cancer is a rare complication of a common cervical infection with a HR HPV type.
- Persistent HR HPV infection is necessary for the development, maintenance and progression of CIN 3 [21,22].
- The vast majority of HPV infections will regress spontaneously with no serious sequelae.
- Testing for persistent HPV should take into account the usual clearance time reported for transient HPV infections (6–18 months) [19,21,22].
- It is important that HPV testing be conducted with a clinically validated test to ensure that results are objective and highly reproducible.
- HPV testing lacks the inter-laboratory and inter-observer variability of cervical cytology.
- Efficient management of women who are HPV positive but cytology negative remains a key issue for primary screening [23,24]. HPV typing for types 16, 18 and possibly 45 could be useful in managing HPV positive/cytology negative women. The value of typing for other high-risk types is less clear at this time. In the future, tests based on HPV mRNA or p16 may also be useful in this regard.
- Women and clinicians should be educated on the frequent and benign nature of most HPV infections.

Primary screening in US

- Currently cervical screening with cytology is standard in the US, starting 3 years from 1st intercourse or age 21, whichever comes first [1].
- Testing women ≥ age 30 for high-risk HPV is more sensitive as a primary screen than currently practiced cervical cytology.
- For women over the age of 30 years, HPV testing has been accepted as an adjunct to cytology in primary screening, provided the screening interval is extended to 3 years.
- The vast majority of the available evidence and modeling studies support the use of HPV testing alone as the primary screening test, starting no earlier than age 25. Ongoing randomized trials should be coupled with large demonstration projects to best determine the best way to use HPV testing in routine screening [16,17,21].
- The extremely high negative predictive value for CIN 2,3 (99–100%) noted over time in the 10 year. Portland NCI study provides evidence for increasing the screening interval to 3–5 years for women negative on both cytology and on HPV testing [21].

Primary screening in Europe

- Most organized screening programs recommend that screening should commence at age 25 or 30. Available evidence does not support screening at younger ages [18].
- There is emerging evidence for using HPV as the primary screening test and it is appropriate to now begin large scale demonstration projects using HPV screening as the sole primary screening test. These demonstration projects in conjunction with the ongoing randomized trials will determine the best way to use HPV testing in routine screening [6–8,13–15,18].
- The extremely high negative predictive value (99–100%) of a negative HPV test could allow safe widening of the screening interval to 5 or more years.
- Evaluation of HPV testing in these demonstration projects should be conducted within the confines of organized screening programs and full evaluation of the impact on subsequent CIN3 rates and the incidence of invasive cancer should be undertaken [18].
- European countries without an organized screening system would achieve the greatest benefit in reducing the cervical cancer rate by implementing a comprehensive nationwide call and recall system.
- Implementation of new screening methods and programs must be carefully monitored to ensure that quality is maintained and that the resources are directed to the women in greatest need.
- Screening in young women (<25 years) or too frequently in older women can lead to unnecessary anxiety and morbidity and should be avoided.

Primary screening in developing countries

- In areas where resources are sparse, special campaigns should be mounted to try to ensure that all women aged 30 or more receive at least one screen.
- Sufficient resources to manage and treat all screen positive women are necessary before screening is undertaken.

- The extremely high negative predictive value (99–100%) of a negative HPV test supports a strategy of once or twice in a lifetime screening.
- HPV testing with an affordable rapid HPV test can potentially become the basis for a single visit approach to screening and treatment [20,25].
- Screen and treat with other low cost options, e.g. VIA, may be appropriate in some low-resource settings [25].
- HPV vaccination in some very low resource settings may be the only viable option for cervical cancer prevention, especially if low-cost, simple delivery systems become available.

Triage

General points

- Cervical cancer screening protocols that utilize cervical cytology as the sole primary screen will continue to have Pap interpretations that have an unclear meaning [2,4].
- The majority of these women will be normal, while 6–11% will have CIN 2/3 and approximately 1/1000 will have cervical cancer.
- The high sensitivity and negative predictive value of HPV testing reported for primary screening has been substantiated in the management of women with equivocal Pap diagnoses [2,4,10,23,24].
- HPV testing is efficient and more sensitive than repeat cytology in the management of women with equivocal cytology.
- HPV testing is the preferred management option for women with equivocal cytology derived from a liquid-based Pap sample [2,4,9].
- HPV testing for "test of cure" no sooner than 6 months post-treatment for CIN 2/3 is the most sensitive option for the detection of persistent or recurrent CIN.

Recommendations

- There is overwhelming evidence for the use of HPV testing in the triage of borderline/ASC-US cytology.
- Implementation of HPV testing for borderline/ASCUS cytology triage is recommended in the recently updated European guidelines for Quality Assurance in Cervical Cancer Screening.
- A single HPV test can be performed at 12 months in a variety of post-colposcopy scenarios as it is more sensitive than 2 repeat Paps for the detection of CIN3+.
- Triage of HPV positive/borderline-ASC-US cytology to colposcopy or to cytologic or HPV testing follow-up may be improved by age specific stratification.
- Women with equivocal cytology who are HPV negative can be reassured and recommended to have repeat cytology in 12 months.
- The first use of HPV typing may be in triage once clinical guidelines are developed on the best management of women with HPV 16, 18 and possibly 45.

Directions for further research

- Completion of the ongoing randomized trials in order to evaluate the frequency of high-grade lesions up to and including the next routine screen in women negative for by HPV vs. women negative by cytology.
- Evaluation of cost-effectiveness and clinical utility of HPV testing in screening needs to be completed in multiple international settings.
- Evaluation of biomarkers that will more accurately identify HPV positive women at risk of having or developing CIN3+. This includes HPV typing (especially for HPV 16, 18, 45), HPV type-specific viral load, testing for HPV E6/E7 mRNA and p16.
- Reflex-triage of women with LSIL.
- Continued evaluation of how to best utilize the information we have about HPV to reduce the risk of cervical cancer in developing countries.
- Low-cost and safe treatment options for women positive on HPV testing and/or by visual or other real time methods.
- Exploration of transmission issues and prevention options.
- Evaluation of vaccine acceptability, distribution, funding and administration for each country in preparation for vaccine approval.

Clinical perspectives

In comparison with cytology, HPV testing is highly reproducible, is more easily monitored, provides an objective test outcome and can easily be automated. The lower specificity of HPV testing in younger women is due to a higher prevalence of transient infections. Cytology has a higher PPV than HPV testing, which reduces the costs associated with referral for colposcopy. However, in well-screened populations [14,18], some interval cancers still occur that could potentially be avoided using a more sensitive screening method such as HPV testing.

The higher sensitivity of HPV testing also leads to a higher negative predictive value, suggesting that the screening interval can be safely lengthened if HPV testing is used [6,7,12,14]. The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence that HPV testing can reduce the incidence and mortality from cervical cancer and that it is likely to be *at least as effective* as cytology (IARC 2005) [3]. Basic principles suggest that the most appropriate use of two tests is to perform the most sensitive test first and follow this with the more specific test for those who test positive initially. Tests employing HPV E6/E7 mRNA, p16 or other biomarkers may help distinguish transient from persistent HPV infections, but these still require clinical validation. Recent data support type-specific testing for HPV 16 and 18 as a highly specific marker for risk for CIN 2+.

Appendix A

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