Assessment of effectiveness and cost-effectiveness of HPV testing in primary screening for cervical cancer


Introduction

Screening programmes based on cytology have led to a substantial decrease in the incidence of cervical cancer over the past decades, but have been criticised for their low sensitivity and resulting high false negative rates.

Infection with human papillomavirus (HPV) is a necessary precursor of cervical cancer. In June 2006 the first vaccine against HPV was approved by the US Food and Drug Administration for the prevention of cervical cancer. However, vaccination will not replace cervical cancer screening, due to the fact that the vaccine does not protect against all types of high-risk HPV genotypes.

Whether HPV testing can be used to improve cervical cancer screening has been discussed for a number of years now. In 1999, a systematic review concluded that HPV testing could not be recommended for widespread use in screening programmes. Since then, some large studies on HPV testing have been published, and the Hybrid Capture® (HC I) HPV test has been improved and replaced by the HC II and other testing procedures.

Objectives

To compare efficacy and cost-effectiveness of HPV testing and/or cytology in screening for cervical cancer within the German health care setting.

Medical questions

Can existing cervical cancer screening programmes be improved by including HPV testing?

Economic questions

Is there health economic evidence for the cost-effectiveness of the introduction of HPV tests to cervical cancer screening?

Methodology


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We included studies that directly compared the sensitivity and specificity of the HPV test and cytology for detecting precancerous lesions in normal-risk populations. HPV was detected using Hybrid Capture® II or polymerase chain reaction (PCR), and cytology could be either conventional or liquid-based. In addition, a systematic review of the relevant health economic literature was performed to analyze cost-effectiveness in the German setting.

Results

We identified 3188 studies, with 24 of these fulfilling our inclusion criteria, leading to a total of 126988 female participants. One study consisted of three substudies. Hence, we report the results of 26 comparisons of HPV and cytology. The studies were performed in both high- and low-resource settings. HC II was used 18 times, PCR seven times, and one study implemented both tests. Conventional cytology was used 19 times, liquid-based cytology four times, and three studies used both tests.

In 25 of the 26 studies included in our systematic review, the HPV test had greater sensitivity than cytology, whereas cytology had better specificity than HPV testing in 21 studies. Sensitivity for HPV testing was over 90 % in 50 % of the studies, and over 80 % in 80 % of the studies. Sensitivity for conventional cytology was greater than 90 % in only 5 % of the studies, and greater than 80 % in 13 % of the studies. The range and variability of results was considerably larger for cytology than for HPV testing.

15 health economic studies with relevant data were identified. With seven of those a health economic meta-analysis was performed. Due to methodological heterogeneity, the results showed a wide variation. Results of the meta-analysis suggest that in health care settings with already established PAP screening programs, cost-effectiveness strongly depends on screening intervals. In analyses comparing HPV screening to conventional PAP screening with two-yearly intervals, only 25 % of the HPV strategies were found to be cost-effective, whereas in comparison with one-, three-, and five-yearly PAP screening, the percentage of overall cost-effective HPV strategies was 83 %, 55 %, and 92 %, respectively. Results for annual screening intervals are based on the assumption of complete screening compliance, which has to be further evaluated in decision analyses in the future considering the German health care setting.

Discussion

HPV testing in cervical cancer screening is more sensitive, but also less specific than cytology. Including HPV testing in screening programmes might lead to a decrease in the rate of false negatives and to an extension of the annual screening interval which currently is state of the art in Germany. It is possible to use the HPV test alone as the primary test. However, because a large majority of HPV infected women will not develop cervical cancer, doing so may lead to an increase in colposcopic referrals. Therefore, one US guideline recommends HPV testing in combination with liquid-based cytology. A recently published meta-analysis of European and North American studies suggested that HPV testing may be used as the sole primary test with cytology in triage for HPV infected women.

The most appropriate screening interval and the best age to start or stop screening tests remain to be determined. Ongoing trials of HPV tests in cervical cancer screening will hopefully provide answers to these questions over the next couple of years.

Transferring the results to the German context urges the need for a formal health economic decision analysis. One of the major impact factors will be...
the implementation of realistic screening participation and adherence rates. This is of paramount importance, since this implicitly raises screening intervals on an average as well as a patient individual level. Doing so would allow gathering data input for still missing budget impact analyses within the German setting.

Ethical, social, and legal considerations

The vast majority of HPV infected women will never develop cervical cancer. Hence, it is important to inform women with a positive HPV test about their absolute cancer risk to minimise psychological distress. Accompanied by structured educational efforts the diagnosis of a HPV infection showed no significant difference in psychological distress after a rather short period of time compared to cytology alone. A positive aspect in the discussion of the pros and cons regarding HPV testing is the possibility of self-testing, which may increase adherence in cervical cancer screening. Taking this into account there additionally may be a window in addressing non-compliant women for participation in screening programmes in the future.

Conclusion

Considering medical evidence weighing the question whether HPV testing should be implemented into screening routine may not be if but how to do so. Open questions remain in setting the length of optimal screening intervals, the age range in which to screen, and the combination or sequence of existing cytology and HPV testing. Answers to those questions will be gathered in the very near future through large international clinical trials. Cost-effectiveness of implementing HPV testing is likely to exist in the management of borderline or unclear smears in triage treatment as well as in certain scenarios of primary screening within the German health care setting.