EXECUTIVE SUMMARY HPV DNA-BASED SCREENING TEST FOR CERVICAL CANCER

Background

Cancer of the uterine cervix is a leading cause of mortality and morbidity among women worldwide. Current estimates indicate that every year 529,828 women are diagnosed with cervical cancer and 275,128 die from the disease. In 2006, cervical cancer was reported to be the third most common cancer among Malaysian women. The overall age-standardized incident rate (ASR) of cervical cancer in Malaysia was 12.2% per 100,000 populations. Cervical cancer incidence rate increased with age after 30 years and has its peak at ages 60-69 years. Research worldwide has clearly shown that virtually all cervical cancer is caused by human papilloma virus (HPV) infection. The virus is transmitted to the cervix and vaginal tissues primarily by sexual intercourse.

The varying carcinogenicity of these HPV type is partly related to the expression of two oncogenes E6 and E7. The International Agency for Research on Cancer (IARC) has classified 12 HPV types as high risk: type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. Of these, HPV-16 and 18 are most carcinogenic and contribute to over 70% of all cervical cancer cases, between 41%-67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions worldwide.

Screening programs for cervical cancer have been instituted in many countries and are responsible for a substantial fall in the incidence and mortality rates attributed to cervical cancer. Primary cervical cancer screening by cytological examination of cervical cells with a Pap test is considered the most successful cancer screening programme to date. Despite its success, cytology has limitations especially technical limitations regarding sampling and laboratory errors in screening and interpretation. Therefore in recent years, there has been interest for developing new tests with adequate sensitivity and specificity for detecting clinically significant cervical cancer precursors. One such method is Human Papillomavirus Testing via viral DNA detection which is based on the knowledge that infection with HPV is at high risk for development of cervical cancer.

Detection of high risk HPV DNA is considered to be potentially useful in three clinical applications: triage of borderline abnormalities, primary screening in selected age groups, and follow-up of treatment for precancerous or neoplastic lesions.

Technical features

DNA testing for HPV has gained widespread acceptance as an additional cervical cancer screening tool and as follow-up to abnormal changes detected with a Pap smear. There are now several such DNA HPV tests, some of which have been approved for marketing by the FDA, that can detect either the majority of the high-risk types of HPV or specific subtypes, such as HPV-16 and HPV-18.

Policy Question

Should HPV DNA-based test be used in the cervical cancer programme as a primary screening test for cervical cancer in Malaysian women?

Objectives

a) To assess the effectiveness/efficacy, cost effectiveness, social, organizational and legal implications of using HPV DNA-based test as a primary screening test for cervical cancer.
b) To assess the effectiveness of using HPV DNA-based test for triage in primary cervical cancer screening.
c) To assess the role of HPV DNA based test in clinical management and as follow –up to detect treatment failure.

Methods

Literature search was done by two Information Specialists who searched for published articles pertaining to use of HPV DNA-based screening test for cervical cancer. The following electronic databases were searched: MEDLINE via OVID, PubMed, and EBM reviews – Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Databases, EBM reviews – NHS Economic Evaluation Database, EBM Full Text –Cochrane DSR and DARE. The search terms as in Appendix 3 were used either singly or in combination. The search was limited to publication year from 2000-2010. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force.

Results and conclusion

Effectiveness of HPV DNA Based Screening Test for Cervical Cancer

There was good level of evidence to show that HPV DNA-Based testing may be able to decrease the incidence and mortality rates related to invasive cervical cancer. There was good level of evidence to suggest that HPV DNA-Based Screening Test for Cervical Cancer has moderate accuracy if used alone but much higher sensitivity if used in combination with Pap smear. The sensitivity of HPV testing for cervical intraepithelial neoplasia of grade 2 or 3 was 94.6% (95% CI, 84.2 to 100), compared to Pap testing which had a sensitivity of 55.4% (95% CI, 33.6 to 77.2). The sensitivity of both tests used together was 100%, and the specificity was 92.5%. Compared to the other tests, The Hybrid Capture 2 assay showed a sensitivity for CIN2+ of 62% (95% CI 56–68%) and a specificity of 94% (95% CI 92–95%) whereas VIA and VIAM had a sensitivity of 79%, specificity of 85%, while VILI had a sensitivity of about 89%, specificity 85%. Visual inspection is an alternative low-technology screening tests usually done in low resource settings with potential difficulties in implementing cervical cytology-based screening. However a clear understanding of the anatomy, physiology and pathology of the cervix is absolutely essential to understand the basis and to interpret the outcome of screening using VIA, VILI and VIAM.

There was moderate level of evidence to show that HPV-triage using the Hybrid Capture 2 assay was more accurate (significantly higher sensitivity, similar specificity) than repeat cytology to triage women with equivocal Pap smear results. Among women aged 35 or older primary HPV DNA-Based screening with cytology triage is also more specific than conventional screening such as Pap smear which decreases referrals and follow-up tests. False negatives would be reduced, double negative patients could be safely screened at longer intervals (reducing costs)

and patients as being at high risk but not having identifiable cervical cancer could be monitored closely. Compared with cytology, primary screening with HPV DNA-Based test followed by cytological triage and repeat HPV DNA-Based test of HPV DNA– Based positive women with normal cytology increased the sensitivity for CN3+ detection by 30% (95% CI = 9% to 54%), and resulted in a mere 12% increase in the number of screening tests.

There was good to fair level of evidence to suggest that after treatment of cervical lesions, HPV DNA-Based test easily detects (with higher sensitivity and not lower specificity) residual or recurrent CIN than follow-up cytology. Treatment failure expressed in terms of residual or recurrent CIN, occurred on average in 10.2% (95% CI: 6.7–13.8) of treated cases. The sensitivity of HPV DNA-Based test detection in predicting treatment failure ranged from 67% to 100% and was on average 94.4% (95% CI: 90.9–97.9%). There was also good to fair level of evidence on the role of HPV DNA-Based test in post-treatment follow-up of patients after therapeutic excision of the cervix due to positive screening tests. A negative HPV DNA-Based test in the post-treatment period excluded not only the recurring CIN but also the development of persisting cytological atypia (negative predictive value (NPV): 100%) a negative HPV DNA-Based test eliminates the risk of recurrent disease after treatment for CIN. In a positive HPV DNA-Based test, this may indicate a significant risk for the recurrence of persistent cytological atypia and CIN with high sensitivity.

There was fair level of evidence with the assumption that the countries (South Africa, Thailand and Peru) in the studies mentioned represent almost the same resource setting as Malaysia suggesting cost effective options in Malaysia. The studies showed that the ICER was lower than the GDP per capita in Malaysia which was noted to be about USD 5151 in 2008 (According to the International Commission on Macroeconomics and Health guidelines, interventions with an ICER between one and three times gross domestic product (GDP) per capita are considered cost effective). The four strategies derived from four different studies were:

- Using HPV DNA testing every five years as a screening strategy in Colombia (Gamboa A *et al*). The ICER was USD$44 in Colombia.
- A single life time screening with HPV DNA testing coupled with immediate cryotherapy once with positive results of HPV (Goldie S J *et al*). The ICER was **l**ess than $62 in South Africa.
- With at least 1 visit screening with HPV DNA once in a lifetime was the most cost effective strategies (Goldie S J *et al*). The ICER was USD$467 for South Africa, USD $170 for Thailand and USD $152 for Peru.
- Conventional cytology followed by HPV triage for equivocal cytology was the most cost effective strategy (Vijayaraghavan A *et al*). The ICER was USD$409 for South Africa

Beyond the cost issues that arise out of unnecessary testing, another point to consider is the physical discomfort and anxiety that a woman suffers in anticipation of an often unnecessary, invasive procedure. HPV testing may have an adverse psychosocial impact on women who test HPV positive when it is used as a primary screening test alongside conventional cytology. Consideration of the psychosocial consequences of HPV testing is important.

Health care planners who are considering implementing any type of cervical cancer screening must develop clinical protocols that are responsive to the natural history of cervical disease, the diagnostic characteristics of the screening technology, disease prevalence in the target population, and the Malaysian needs and concerns.

As recommended by the Cytopathology Education and Technology Consortium, and endorsed by American Society for Clinical Pathology (ASCP), the American Cancer Society, and several other professional medical societies, HPV DNA-Based testing should be used only for high-risk HPV types and co-testing with the Pap test in women over 30 years of age provides predictive safety for at least three years in women who are negative on both tests.

Recommendation

Based on the above review, HPV DNA-based testing may be incorporated in the cervical screening program. HPV DNA-based testing may be done every five years as a primary screening strategy or combined with Pap test in women over 30 years of age for an interval / frequency of at least three to five years in women who are negative on both tests in the annual screening. Although HPV DNA-based test is expensive (about RM 91.50- RM183 while Pap smear costs about RM 14.16 per test), it has higher sensitivity than Pap smear. For the primary screening strategy, it is suggested that HPV DNA-based testing may be done every five years since the test is expensive for the moment.

Alternatively a single life time screening using HPV DNA-based test was one of the most cost effective strategies carried out in South Africa, Thailand and Peru which Malaysia may emulate. However, local economic evaluation and research should be conducted with due consideration for our Malaysian healthcare systems as well as local costing that will further provide more evidence to support the above strategies.

HPV DNA-based test can be used to triage patients for atypical squamous cells of undetermined significance (ASCUS) in women aged 35 or older, whereby these women will undergo HPV DNA-based testing after conventional cytology. This strategy is recommended since it has been shown that this strategy is less expensive and more effective with higher specificity than screening using repeated cytology alone.

HPV DNA-based testing may be recommended as a follow up screening for post treatment cases since HPV DNA-based test easily detects (with higher sensitivity and not lower specificity) residual or recurrent CIN than follow-up cytology. A negative HPV DNA-based test in the post-treatment period eliminates the risk of recurrent disease after treatment for CIN while a positive HPV DNA-based test, may indicate a significant risk for the recurrence of persistent cytological atypia and CIN with high sensitivity.

A standard guideline needs to be developed for cervical cancer screening and management of abnormal findings if HPV DNA-based testing is adopted as a screening test for cervical cancer screening in Malaysia. Organisational issues such as training, manpower, good referral system, and funding need to be addressed at all levels.