MaHTAS
Malaysian Health Technology Assessment Section

HPV URINE TEST FOR CERVICAL CANCER SCREENING

Executive Summary

[Adapted from the report by SYFUL AZLIE MD FUZI]

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Background

According to World Health Organization (WHO) and GLOBOCAN 2012, cervical cancer is the fourth most common form of cancer in women worldwide and the fourth leading cause of cancer-related death globally. While more recent data is yet to be published, according to the National Cancer Registry (NCR) Malaysia 2007, cervical cancer was the third most frequent cancer among women and the fifth most common cancer in the entire general population. Since cervical and female genital infection by specific HPV types is highly associated with cervical cancer, those types of HPV infection have received most attention from scientific studies. The International Agency for Research on Cancer (IARC) has classified 15 HPV types as high risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) and 12 as low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108). In particular, HPV16 and HPV18 are known to cause around 70% of cervical cancer cases worldwide. For decades, screening using conventional cytological Pap (Papanicolaou) test or Pap smear has been the most widely used strategy for reducing cervical cancer around the world. Subsequently, the molecular methods to detect the HPV present in infected tissues were introduced. The HPV typing is generally done by liquid hybridization (Hybrid Capture 2) and/or conventional and real-time polymerase chain reaction (PCR), using DNA from cervical scrapes/biopsies. Both screening strategies, however, require a pelvic examination, a procedure that is invasive and uncomfortable for the patient, time consuming for healthcare providers and is unlikely to resolve the problem of poor screening uptake. The use of urine, which is straightforward to collect, is claimed to be valuable for this purpose as exfoliated epithelial cells from the cervix and/or vagina is claimed to normally appear in the urine. In Malaysia, currently all women who are, or who have been sexually active, between the ages of 20 and 65 years, are recommended to undergo Pap smear testing. However, with the significant burden of cervical cancer in Malaysia, and to increase screening uptake as well as the acceptance of the screening procedures, therefore, a Health Technology Assessment (HTA) is required to assess the accuracy, effectiveness, and cost-effectiveness of HPV urine test for cervical cancer screening. This HTA was requested by the Senior Principal Assistant Director of Cancer Unit, Disease Control Division Ministry of Health Malaysia.

Technical Features

Urine would be an appropriate sample for screening large populations as it may increase participation and compliance, since physical scrapes, sometimes unpopular because of the dislike of physical examination or because of religious reasons, are avoided. Efforts have been made to detect the presence of HPV DNA in urine in the most reliable way; using liquid hybridization, and PCR-based methods (using either conventional PCR or real-time PCR).

Policy Question

Should HPV urine test be used as a screening method in the cervical cancer screening programme in Malaysia?

Objective:

i. To determine the diagnostic accuracy of HPV urine test for HPV detection
ii. To determine the benefits of cervical cancer screening using HPV urine test compared with conventional cervical cytological specimen, HPV DNA-based using cervical specimen, combination of conventional cytology and HPV DNA-based using cervical specimen, or no screening, with regards to patient outcomes such as detection rate, mortality rate, survival rate, quality of life (QOL), and quality adjusted life years (QALY) gained

iii. To determine the safety of HPV urine test for HPV detection
iv. To determine the economic impacts of HPV urine test for cervical cancer screening
v. To assess the organizational, ethical, and legal aspects related to cervical cancer screening using HPV urine test

Methods

Studies were identified by searching electronic databases. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present, EBM Reviews - Health Technology Assessment 1st (Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to Feb 2016), EBM Reviews - Cochrane Central Register of Controlled Trials (Jan 2016), EBM Reviews - Database of Abstracts of Reviews of Effects (1st Quarter 2016), EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed. Limitations only for female/women were applied to the search. The last search was run on 4th March 2016. Additional articles were identified from reviewing the references of retrieved articles. Studies were selected based on inclusion and exclusion criteria. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force or NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4(2nd Edition), March 2001 for test accuracy studies.

Results and conclusion:

A total of 114 titles were identified through Ovid interface, PubMed and references of retrieved articles. A total of 43 abstracts were screened using the inclusion and exclusion criteria. After reading, appraising and applying the inclusion and exclusion criteria to 38 full text articles, 13 full text articles comprising of one systematic review and meta-analysis, nine observational studies (cohort and cross-sectional) and three diagnostic accuracy studies were finally included for this review.

Clinical performance (diagnostic accuracy)

There was limited fair level of retrievable evidence to suggest that:

a. In a combination population of symptomatic (78%) and asymptomatic (22%) women, sensitivity and specificity of urine test varies with the types of HPV. Pooled sensitivity and specificity was 87% and 94%, respectively, for urine detection of any HPV. Urine detection of high risk HPV had a pooled sensitivity of 77% and specificity of 88%, while urine detection of HPV 16 and 18 had a pooled sensitivity of 73% and specificity of 98%.
b. In symptomatic population, overall sensitivity and specificity has been quite variable, ranging from 44.8% to 90.5% and 34.8% to 85.0%, respectively. Positive predictive value (PPV) ranged from 37.2% to 86.4% whereas NPV ranged from 75.6% to 89.8%.
c. There was no diagnostic study among asymptomatic women retrieved

HPV detection and genotyping

There was substantial fair level of retrievable evidence to suggest that:

a. Detection of HPV DNA in urine among screened asymptomatic women varies depending on the chosen population. HPV DNA detection ranged from 4.2% to 28.6% in sexually active women, and ranged from 9.2% to 19.2%, particularly in young sexually unexposed girls and healthy tribal girls
b. Detection of HPV DNA in urine was increased among screened symptomatic women ranging from 34.5% to 78.1%
c. HPV type 16 was identified most frequently in both urine and cervical samples

HPV concordance in paired urine and cervical samples

There was substantial fair level of retrievable evidence to suggest that:

a. Overall concordance for HPV positivity and negativity between cervical and urine samples in symptomatic women varied from 69.3% to 90.0% (agreement, κ from 0.41 to 0.80)
b. Type specific concordance rates in the paired samples have been very good for invasive cervical cancer (79.0%)
c. There was no study retrieved on concordance between cervical and urine samples among asymptomatic women

Safety

There was no retrievable evidence on adverse events or complications associated with HPV urine test used for cervical cancer screening.

Cost / cost-effectiveness / economic evaluation

There was no retrievable evidence on the cost-effectiveness of HPV urine test for cervical cancer screening. However, the average cost per HPV-DNA test for cervical specimen using PCR-based method ranged from RM 91.50 to RM 183.00. Hence, it is assumed that the cost for HPV-DNA detection in urine will most probably the same. The average cost per Pap smear test performed in Malaysia is RM 20.12

Organizational, ethical, and legal considerations

There was evidence to suggest that:

a. The detection of HPV DNA and human DNA (hDNA) in urine sample was significantly improved by a DNA conservation buffer (either in-house or commercial). The difference between the untreated and treated urine was highly significant ($p < 0.001$ for the HPV DNA copies and the hDNA copies).
b. A significantly greater number of HPV DNA and hDNA copies were detected in the first void urine fraction compared with the midstream fraction. The difference was highly significant ($p=0.008$).
c. Urine collection method was highly acceptable and preferred compared to physician-collected cervical samples and brush self-collection among participating women ($p < 0.001$)
d. The barriers for screening may be different in different countries because of the different health-care system structure and cultural acceptance
e. For a mass screening programme to be medically and ethically acceptable, the WHO criteria for mass screening programmes have to be met

Recommendation

Based on the review, there was limited retrievable evidence to support its clinical performance of using urine for HPV DNA detection. Studies that related to diagnostic accuracy were only conducted among symptomatic or in combination of symptomatic and asymptomatic population whereas none in asymptomatic. Similarly, most of the study only tested the concordance rates of HPV DNA in paired urine and cervical samples in symptomatic women but none among asymptomatic. Moreover, there was no evidence retrieved related to the effectiveness or benefits of cervical cancer screening using HPV urine test with regards to patient outcomes such as mortality rate, survival rate, QOL, and QALY gained. The highly acceptance of urine-based programme among participating women, may, however, provide some compensation in term of increased participation and compliance.

HPV urine test may have the potential as one of the screening method to be used in the cervical cancer screening. However, in view of the wide range of sensitivity

and specificity in detecting HPV DNA in urine (symptomatic and combination of symptomatic and asymptomatic population) and no diagnostic accuracy study was retrieved among asymptomatic population, hence, currently HPV urine test is not recommended to be used as one of the screening method in the cervical cancer screening programme in Malaysia until there is more evidence on its diagnostic accuracy.