International Journal of Community Medicine and Public Health
Daniel A et al. Int J Community Med Public Health. 2024 Apr;11(4):1717-1719
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20240918

Review Article

Current role of viral biomarkers in cervical carcinogenesis

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Received: 21 January 2024
Revised: 03 March 2024
Accepted: 05 March 2024

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ABSTRACT

Viral biomarkers for cervical cancer screening are valuable in improving timely diagnosis and detection at early stage. The various biomarkers currently there is evidence include high-risk human papillomavirus (hrHPV) deoxyribonucleic acid (DNA) testing, there is place for further research for biomarkers such as hrHPV genotyping hrHPV transcriptional status, and host DNA methylation. Though the evidence is conclusive for hrHPV DNA testing, there is place for further research for biomarkers such as hrHPV genotyping hrHPV transcriptional status, and host DNA methylation. This application of these biomarkers in context of low resource settings has its limitations despite high prevalence of the disease. Improved women participation can be achieved by use of self-samples thereby improving diagnoses rate of the disease and higher cost effectiveness of the screening programme. In due course, biomarkers will be made available in the screening programmes together with self-sampling that will detect hrHPV infections and low-grade squamous intraepithelial lesions (LSIL) before they progress to high-grade squamous intraepithelial lesions (HSIL), and from there to malignancy. This would facilitate prudent timely clinical decisions, reduced patient anxiety, reduction in over referral and unnecessary treatments in women, especially in developing countries.

Keywords: Cervical cancer, Biomarkers, HrHPV

INTRODUCTION

Cervical cancer is estimated as the fourth most frequently occurring cancer worldwide contributing to 6.6% of the total cases of cancer and 7.5% of the total cancer fatalities of women in the year 2018.[1] Currently, cytology pap smear testing and colposcopy are the most common methods for cervical cancer detection.[2] Although screening with cytology has tremendous impact in the reduction of cervical cancer over the last 30 years, there are limitations with its ability to predict progression of disease to cancer. This is related to cytology screening specificity of 98%, but a sensitivity of 51%.[3] Cytology has limited capability to predict the presence of abnormalities in the cervix as well as progression from high-risk human papillomavirus (hrHPV) infections to disease. Considering the high prevalence of disease, it is therefore paramount to predict disease progression. This calls for novel biomarkers for screening and predicting cervical cancer progression. An ideal biomarker must be able to detect the progression of hrHPV infection to disease that can allow pragmatic clinical decision making such as colposcopy referrals, treatment, further cytology testing and discharge to routine screening.[4] Most prevalent viral biomarkers include hrHPV DNA testing, genotyping, viral load, and expression of viral proteins. They are linked to the HPV life cycle and with persistent infection which enhances progression of preinvasive to cervical cancer.[5]

The aim of this review is to summarise the available viral biomarkers and their role at different stages of disease progression.

METHODS

This study was performed based on a comprehensive literature search conducted on the following databases such as PubMed, Medline, Google Scholar and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The following are the list of viral biomarkers discussing their applications and limitations.

hrHPV DNA testing

hrHPV DNA testing is the most prominent biomarker which is currently being utilised as a primary screening of cervical cancer in some countries. The method has high sensitivity and a high negative predictive value, implying that absence of hrHPV DNA means the risk of CIN3 lesions or cervical cancer is low.[6] However, detection of hrHPV DNA can indicate transient infections that may not persist and resulting in cervical cancer. The role of hrHPV DNA testing for triage of ASCUS cytology is determined by ASCUS-LSIL triage study ALTS.[7] Women with initial ASCUS cytology and further hrHPV DNA testing reduces the need for colposcopy referrals. Countries like Turkey, Italy, or The Netherlands, have implemented hrHPV DNA testing as the first-line initial screening program.[8] A systematic review and meta-analysis described that role of hrHPV DNA testing having high sensitivity than cytology six months post-treatment in women with CIN2+ lesions.[9] It is proposed that hrHPV DNA testing could also be included as post treatment test of cure TOC in detecting post treatment lesions.

hrHPV genotyping

The importance of hrHPV genotyping is determined by ATHENA study which showed that the proportion of women who were diagnosed positive for the 14 hrHPV genotypes have increasing grades of CIN lesions across all age groups.[10] According to the ATHENA study, the detection of 12 more hrHPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 in cervical scrapings has a sensitivity of 90.0%, specificity of 70.5%, PPV of 14.0% and NPV of 99.2%. In the presence of a positive HPV16 or 18, immediate referral to colposcopy is warranted, whereas positivity for other HPV genotypes leads to cytology referral.[10] A negative result can preclude development of CIN3+ lesions in next three years and women can be discharged to routine screening. Overall, the current role of this viral biomarker may be as a triage for women following a positive primary screening which includes hrHPV DNA testing and cytology and can allow stratification of women with a higher risk to develop CIN3+ lesions and progression to cervical cancer.[11]

hrHPV transcriptional status

There is a recent significant interest on the use of viral mRNA as a biomarker to understand the infection state as the viral DNA integrates into the host genome and cause upregulation of E6/E7 oncoproteins.[12] The increased levels of E6 and E7 proteins interferes with tumor suppressor genes such as p53 and pRb that control the cell cycle and apoptosis. This results in chromosomal instability and subsequent cancer development.[12] There is supporting literature on the utility of mRNA test when combined with cytology has more clinical relevance than hrHPV DNA screening in women with low-grade lesions.[13] The effectiveness has been evaluated by Stoler et al among women with ASCUS cytology, whereby detection of hrHPV E6/E7 oncogenic mRNA reduces need for colposcopy referrals and overtreatment which has a positive impact on cost savings in the screening programs.[14] A meta-analysis by Macedo et al reports a sensitivity of 93.9% and a specificity of 61.7% for E6/E7 mRNA in predicting CIN2+ lesions.[15]

Viral DNA methylation

Epigenetic alterations like DNA methylation are a host defence cellular mechanism to quiescence invading foreign viral genomes and to inhibit viral replication. HPV DNA methylation are new viral biomarkers as the detection of these epigenetic changes, particularly the early E and late L promoters of HPV can for predict or diagnose cervical cancer in hrHPV-infected women.[16] A study by Kalantari et al revealed that 10% to 12.2% of methylation changes occurring in asymptomatic infection and ASCUS, but in LSIL/CIN1 samples, methylation increased to 13.6%, while in HSIL/CIN2+ lesions to 31.9%, and in cancer to 83.1%.[17] The role of viral DNA methylation may be beneficial for the triage of women with high-grade lesions, therefore, improving referral to colposcopy. However, as the host cellular epigenetic mechanisms respond differently to viral genomic regions and hrHPV genotypes, its utility has limitations and future studies are warranted to evaluate the sensitivity and specificity towards HSIL in future studies.[17]

CONCLUSION

In conclusion, viral biomarkers for cervical cancer screening are valuable in improving timely diagnosis and detection at early stage. Though the evidence is conclusive for hrHPV DNA testing, there is place for further research for biomarkers such as hrHPV genotyping hrHPV transcriptional status, and host DNA methylation. This application of these biomarkers in context of low resource settings has its limitations despite high prevalence of the disease. Improved women participation can be achieved by use of self-samples thereby improving diagnoses rate of the disease and higher cost effectiveness of the screening programme. Lack of homogeneity and validation of studies calls for quality metanalysis for better reproducibility of results. In due course, biomarkers will be made available

in the screening programmes together with self-sampling that will detect hrHPV infections and low-grade intraepithelial lesions LSIL before they progress to high-grade intraepithelial lesions HSIL, and from there to malignancy. This would facilitate prudent timely clinical decisions, reduced patient anxiety, reduction in over referral and unnecessary treatments in women, especially in developing countries.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Daniel A, Daniel S, Nagandla K. Current role of viral biomarkers in cervical carcinogenesis. Int J Community Med Public Health 2024;11:1717-9.