# Abstract

Cervical cancer screening programmes using Papanicolaou (Pap) testing or human papillomavirus (HPV) detection from cervical smears and other invasive biopsy-based assays have been met with limited success in South Africa, which indicates a need to explore other less invasive options for screening. One proposed option is serology testing for overexpression of high-risk human papillomavirus (hrHPV) early 6 or 7 (E6/E7) oncoproteins. The overexpression of E6/E7 oncoproteins corresponds with serological data, showing strong associations with cervical cancer. In conjunction with other suspected infections such as Human immunodeficiency virus (HIV) and other co-factors, these may allow clinicians or screening programmes to identify women who are at high risk of cancerous lesions of the cervix earlier than currently identified. However, in South Africa, data from large lifestyle and serological-based cancer studies in HIV-positive and negative individuals are lacking. This PhD assessed the importance of the HPV-16 and -18 late and early oncoproteins in detecting cervical cancer among adult Black South African women using data from the Johannesburg Cancer Study (JCS). The PhD is made up of three main components of work:

Firstly, we conducted a systematic review and meta-analysis to investigate HPV-antibodies' utility, especially of hrHPV-16/18 E6 and E7 serological markers, in detecting cervical cancer and cervical intraepithelial neoplasia (CIN) 2/3. We identified three articles from 69 reports, all showing low sensitivity but high specificity for detecting cervical cancer. One study used Enzyme-linked Immunosorbent Assay (ELISA), another used a Multiplex immunofluorescent assay, and the last used an immunoenzymatic assay (Slot Blot) to identify HPV seropositivity. Our finding

showed that HPV-16/18 E6 and E7 serological markers have high specificity, but sensitivity is suboptimal for detecting cervical cancer. This study was published in the Journal of Medical Virology in 2022.

Secondly, using data from the JCS, a case-control analysis study was conducted. We assessed HPV types 16/18 L1 E6 and E7 oncoprotein seropositivity and their relation to cervical cancer risk in HIV-positive and HIV-negative Black South African women. In addition, assessment of the utility of HPV-16 and -18 E6 and E7 antibodies in identifying cases of cervical cancer. This was carried out based on the gap identified in the systematic review. The findings from this study showed that HPV-16 E6 and E7 antibody positivity was positively associated with cervical cancer in HIV-positive (Adjusted Odds Ratio (AOR)=33;95% CI:10-107) and HIV-negative women (AOR=97;95% CI:46-203). In HIV-positive women, HPV E6/E7 antibodies had low sensitivity (43.0%) and high specificity (90.6%) for cervical cancer detection. In HIV-negative women, HPV E6/E7 antibodies sensitivity was 70.6%, and specificity was 89.7%. By comparison, conventional Pap smears have a sensitivity of 54% and specificity of 97% in detecting cervical atypical squamous cells of undetermined significance (ASCUS) or worse. The findings from this study would help inform policymakers on the importance of HPV E6 antibodies as a future test for detecting cervical cancer among HIV-positive and HIV-negative women. The study was published in Infectious Agents and Cancer in 2022.

Thirdly, we ranked lifestyle risk factors for cervical cancer among Black women in an urban setting. In decreasing order of priority, cervical cancer was associated with (1) being HIV positive, (2) having lower educational attainment, (3) having higher parity, (4) hormonal contraceptive use,

(5) heavy alcohol consumption, (6) current smoking and (7) rural residence (noting, the JCS was representative of an urban setting. If we repeated the JCS in a rural setting the rankings would come out differently). These findings could inform medical systems on key risk factors to integrate into cervical cancer education literacy programmes. In addition, these findings would help healthcare personnel involved in sensitising women on cervical cancer screening to understand the public-health gains that result from minimising the risk of each factor. The study was published in PLoS One in 2021.

Overall, this PhD research has demonstrated that HPV E6 or E7 antibodies may have a novel role as serological markers for detecting cervical cancer among Black women. Furthermore, a screening strategy that focuses on women at the highest risk (by ranking known cervical cancer co-factors in an urban setting) can be applied as a point-of-care or screening test to address the problem of low turn-out due to the current methods for cervical cancer screening. The critical contribution of this PhD includes: identifying a screening tool that could be used in a place with limited infrastructures and gynaecologists to screen women for cervical cancer. In addition, using the largest dataset in Africa, it has provided the most up-to-date and accurate findings on the accuracy of serological screening for cervical cancer. Furthermore, this PhD identified that HPV-16/18 early oncoprotein markers are less sensitive in HIV-positive women, suggesting other HPV types other than 16 and -18 may be co-responsible. In addition, it identified and ranked cervical cancer risk factors in order of importance in an urban setting. Overall, the findings from this PhD are essential in contributing to cervical cancer prevention and elimination strategies.