

End of project popular science description

Introduction

The natural history of Human papillomavirus (HPV) in sub-Saharan Africa was not yet fully understood. As persistent HPV infection is a necessary factor in development of cervical cancer – a major health problem in sub-Saharan Africa - information about how HIV together with other risk factors interacts with HPV acquisition and HPV persistence/clearance was warranted. Additionally, concern prevails about the quality of cervical cancer preventive strategies in sub-Saharan Africa. Against this background the project aimed to provide a better understanding of the natural history of HPV with a view to HIV status, to measure the impact of a novel and simple screening method based on rapid *CareHPV* testing and to assess how continuity of care among women who are tested HPV positive can be improved. The study was linked up with the existing cervical cancer screening program at Ocean Road Cancer Institute (ORCI) and Kilimanjaro Christian Medical Centre (KCMC); and recruited women who attended screening service or HIV care and treatment. HPV acquisition and persistence/clearance patterns as well as the absolute risk of severe cervical precancerous lesions were determined through a follow up study lasting 28 months. The test performance of rapid *CareHPV* testing, liquid-based cytology and VIA was described and the operating characteristics of the three screening methods was assessed according to HIV status. Finally, the impact of a mobile phone intervention and a patient navigation model was assessed and compared according to the proportion of HPV positive women who returned for follow-up examinations. Additionally, the project implemented a research capacity building component focusing on transfer of knowledge and technology as well as training of PhD students. The activities was carried out as five sub-studies: i) HPV acquisition pattern; ii) HPV persistence/clearance pattern; iii) Test performance of *CareHPV* testing, liquid-based cytology and VIA; iv) Continuity of care among screened positive women and v) research capacity building as well as transfer of knowledge and technology

Results

Four PhD candidates were enrolled into the program and two were registered at Kilimanjaro Christian Medical University College (KCMUco), one at Muhimbili University of Health and Allied Health Science (MUHAS), and one at University of Southern Denmark (SDU). Three PhD candidates have graduated and one will defend her PhD thesis at KCMUco in year 2023. One post-doctoral candidate studied in the project and acquired additional expertise in cervical cancer screening and data analysis. More than 15 nurses and 8 laboratory technologists were trained and skilled to perform HPV-DNA sample collected at the clinic and sample laboratory analysis using *careHPV* machine.

A total of 4043 women participated in the CONCEPT study. About 23.7% of the women had a positive rapid *careHPV* test, 19.2% had positive Hybrid Capture-2 (HC2) test, and 6.4% had a positive Visual Inspection with Acetic Acid (VIA) test. HC2 had the high sensitivity of 92.4%, followed by *careHPV* 89.4% and VIA had the lowest sensitivity of 31.8% but high specificity (94.6%) for detection of High Squamous Intraepithelial Lesion (HSIL+). The positivity and sensitivity of *careHPV*, HC2 and VIA were higher among HIV positive women. We found a good overall agreement 90.5% and concordance ($\kappa=0.66$; 95% CI: 0.56–0.75) between self-collected samples and provider collected samples. Most women preferred self-collection (79.8%). Among 837 *careHPV* positive but VIA negative women at enrolment, 4.2% became VIA positive at follow-up; majority were those who were HIV positive. One-way text message interventions is a type of mobile health (mHealth) that can be implemented in various forms with the aim to improve health-related outcomes. A total of 705 women who had tested positive to a rapid *careHPV*-test during a patient-initiated screening were enrolled for the mHealth and were randomly assigned 1:1 into a one-way text intervention group or control group. The intervention consisted of health educative and reminder text messages. The women were not blinded to the intervention, but the outcome assessors were. Twenty-four percent attended in each group, and

one-way text messages were found to have no effect in improving attendance compared to controls (RR: 1.02; 95% CI: 0.79-1.33). After the trial had finished all non-attendees in the intervention group were traced using various tracing methods, and it was found that attendance could be increased with an additional 24% through phone calls or nurse home-visits and with a further 30% through HPV self-sampling at home-level. A total of 3074 women (80.8%) attended follow-up and the median time between the two examinations was 17.3 months. Among 2253 women, who were HR HPV negative at enrolment, 184 acquired HR HPV during follow-up corresponding to an incidence rate of 54.5 per 1000 person-years. The incidence rate among HIV positive women was 75.2 per 1000 person-years, and 50.9 per 1000 person-years among HIV negative. HR HPV acquisition was higher among HIV positive than HIV negative women. Among the 462 women HR HPV positive at enrollment, 158 had at least one identical type detected at follow-up. The probability of persistence at 18 months after enrollment was 34.2. Stratifying by HIV status, the persistence probability was 42.9% among HIV positive, and 28.0% among HIV negative. Overall, HR HPV persistence was most common for HPV58, 35, 16, 31, and 52. Among HIV positive women it was HPV45, and HPV16, followed by HPV58 and HPV18, and among HIV negative women it was HPV31, HPV33 and HPV58. Risk factors associated with persistence of HR HPV were older age, longer interval between enrollment and follow-up, binge drinking, and HIV status.

Conclusions

In conclusion, HPV DNA testing appears to have good performance in Tanzanian settings in cervical cancer screening, when used in triage with VIA it increases capacity of detecting pre-cancer lesions. We recommend HPV DNA testing to be incorporated in primary cervical cancer screening with special consideration of HIV status in the follow-up visits. Mobile phone messaging (mHealth) program should be approached more cautiously for follow up of cervical cancer screenings follow-up visits and it is important to be linked to self-sampling at home and rapid careHPV testing. Efforts to improve the immune status among HIV positive women may decrease HR HPV acquisition in this population. When taking the HR HPV types acquired in this setting into account, vaccination with the ninevalent HPV vaccine should be considered. HR HPV persistence was common in Tanzania, and most common among HIV positive women with most frequent for HPV 58, 35, 16, 31 and 52 as such ninevalent HPV vaccine should be considered.

Recommendations

Rapid careHPV testing should be used in cervical cancer screening in a triage with VIA. Self-collection of cervical samples for careHPV testing should be established to ensure increased covered of women for screening. Mobile phone messaging (sms) does not increase return for follow-up in cervical cancer screening and thus, other modalities which will ensure increase coverage and retention into care. Improvement of immune status among women with HIV will decrease the acquisition of HR-HPV by strengthening the 90-90-90 strategies for HIV prevention. Ninevalent HPV vaccine should be considered in Tanzanian setting in order to prevent all the HR-HPV subtypes because the current vaccine prevent only two HR-HPV