

NATURAL HISTORY OF HUMAN PAPILLOMAVIRUS INFECTIONS AND OTHER SEXUALLY TRANSMITTED INFECTIONS IN RWANDA-IMMUNOLOGICAL ASPECTS OF THE UTERINE CERVIX

Akademisk avhandling

Som för avläggande av **Medicine** doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i Hörsal, Arvid Carlsson, Medicinargatan 3, torsdag den 13 december 2018, klockan 9:00

av

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Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

- I. Mukanyangezi MF, Sengpiel V, Manzi O, Tobin, G, Rulisa, S, Bienvenu, E and Giglio D. Screening for human papillomavirus, cervical cytological abnormalities and associated risk factors in HIV-positive and HIV-negative women in Rwanda. *HIV Medicine*. 2018;19(2): 152-66.
- II. Mukanyangezi MF, Rugwizangoga B, Manzi O, Rulisa S, Hellstrand K, Tobin G, Martner A, Bienvenu E and Giglio D. Persistence Rate of Cervical Human Papillomavirus Infections and Abnormal Cytology in Rwanda. Submitted, 2018.
- III. Mukanyangezi MF, Manzi O, Tobin G, Rulisa S, Bienvenu E and Giglio D. Sexual Risk Behaviour in a Cohort of HIV Negative and HIV Positive Rwandan Women. Accepted in *Epidemiology and Infection*. 2018.
- IV. Mukanyangezi MF, Podmolíková L, Tobin G and Giglio D. Radiation Induces Changes in Toll-Like Receptors of the Uterine Cervix of the Rat. Submitted, 2018.
- V. Mukanyangezi MF, Dahlqvist A, Oscarsson N, Winder M, Seeman-Lodding H and Giglio D. Hyperbaric Oxygen Therapy Reverses Changes Induced by Irradiation of the Uterine Cervix of the Rat. Manuscript. 2018

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Abstract

Objective: Cervical cancer stands for the predominant risk of cancer death among Rwandan women. Chronic Human Papillomavirus (HPV) infection constitutes the main risk factor. We here assessed the prevalence and incidence of high-risk (HR)- and low-risk (LR)-HPVs, low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL) and cancer and associated risk factors in 400 HIV- and HIV+ Rwandan women. Whether HPV testing could serve as a screening method for detecting HSIL was analyzed. We also assessed prevalence and curing rates of different sexually transmitted infections (STIs) and sexual behaviour. Advanced cervical cancer is often treated with radiotherapy. In an animal model for radiation cervicitis we wanted to assess how the normal uterine cervix responds to ionization radiation and whether hyperbaric oxygen therapy (HBOT) may reverse these responses.

Methods: Women were interviewed, screened for STIs (baseline and 9 months) and underwent cervical sampling for cytology and a test for 37 HPV strains. Cytological samples were taken again 9, 18 and 24 months later in 100 HIV- and 137 HIV+ women. We explored whether the single nucleotide polymorphism (SNP) rs1297860 in IL28B correlates with susceptibility of HPV infection and persistence and development of SILs. In the preclinical studies, rats underwent cervical irradiation and were either exposed to HBOT or no intervention. Immunological and oxidative responses induced by radiation were assessed and whether HBOT was able to reverse these responses.

Results: HPV16 and HPV52 were the most common HPV strains. The sensitivity was 78% and the specificity 87% to detect HSIL with HPV screening. Chronic and incident HR-HPV infections occurred more frequently in HIV+ women than in HIV- women. HSIL or cancer was diagnosed in 38% of HIV+ women with persistent HR-HPV infections. The C/T and T/T genotypes of the IL28B SNP rs1297860 were more common in the group of women contracting HPV compared with women not contracting HPV. STIs were common in Rwandan women and the use of condoms was not affected by present STIs. TLR5, TRIF, NF- κ B, oxidative stress (8-OHdG) and antioxidant enzymes (SOD-1 and catalase) were up regulated, while cytokines were down-regulated 14 days after cervical irradiation. Changes in 8-OHdG and catalase were normalized after HBOT.

Conclusions: HPVs and STIs are common among Rwandan women. HPV screening may be of particular importance if provided for risk patients such as HIV+ women that develop more often persistent HPV infections and HSIL. Ionization radiation induces oxidative stress and immune responses in the cervix that may be reversed by HBOT.

Keywords: Human papillomavirus, cervical cancer, squamous intraepithelial lesion, screening, IL28B SNP rs1297860, Rwanda, radiotherapy, hyperbaric oxygen therapy