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Cervical HPV natural history among young Western Cape, South African women: The randomized control EVRI Trial

Staci L. Sudenga [a], B. Nelson Torres [a], Matthys H. Botha [b], Michele Zeier [c], Martha E. Abrahamsen [a], Richard H. Glashoff [d], Susan Engelbrecht [d], Maarten F. Schim Van der Loeff [e,f], Louvina E. Van der Laan [b], Siegfried Kipping [b], Douglas Taylor [g], Anna R. Giuliano [a,*]

[a] *Center for Infection Research in Cancer, Moffitt Cancer Center, Tampa, FL, USA*
[b] *Department of Obstetrics and Gynaecology and Unit for Gynaecological Oncology, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa*
[c] *Department of Medicine and Centre for Infectious Diseases, Stellenbosch University, Cape Town, South Africa*
[d] *Division of Medical Virology, Stellenbosch University and NHLS Tygerberg, Cape Town, South Africa*
[e] *Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands*
[f] *Center for Infection and Immunity Amsterdam (CINIMA), Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands*
[g] *FHI 360, Durham, NC, USA*

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Summary *Objective:* The objective of this analysis was to assess human papillomavirus (HPV) infection persistence and incidence 7-months post-enrollment by HPV vaccine study arm (vaccine or placebo).
Methods: HIV-negative, sexually active women aged 16—24 years in the Western Cape, South Africa, were enrolled in the EVRI Trial and were randomized to receive 4-valent HPV vaccine or placebo. Cervical specimens were collected at enrollment and at the 7-month visit and were genotyped for HPV. HPV prevalence, persistence, and incidence were calculated. Prevalence ratios and odds ratios were calculated to assess factors associated with a prevalent and incident HPV infection.

* Corresponding author. Center for Infection Research in Cancer (CIRC), Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, MRC-CANCONT, Tampa, FL 33612, USA. Tel.: +1 813 745 6820; fax: +1 813 745 1328.
E-mail address: Anna.Giuliano@moffitt.org (A.R. Giuliano).

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Results: HPV incidence rates were marginally higher for the placebo group (n = 163) compared to the vaccine group (n = 169). A large proportion of the prevalent high-risk (HR-HPV) HPV types (49%) persisted over the 7-month period in both arms. Prevalent HR-HPV infection was significantly associated with a prevalent gonorrhea infection and detection of Herpes simplex type 2 antibodies. Incident HR-HPV infection was significantly associated with abnormal cervical cytology at enrollment and younger age.
Conclusions: Women living in geographic areas, such as southern Africa, at high-risk for HPV need to receive HPV vaccination at a very young age to maximally prevent infection and subsequent disease.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI), one that can infect multiple anatomic sites in both men and women. Persistent HPV infection is the necessary cause of cervical cancer and causes 90% of anal, 50% of penile, 43% of vulvar, 70% of vaginal, and 33–72% oropharyngeal cancers worldwide.[1,2] Women and men residing in southern African countries have among the highest burden of HPV infection and related cancers worldwide.[3–6]

There are two licensed HPV vaccines that are highly efficacious in preventing 70% of cervical disease among women through protection against HPV16 and HPV18 infections. Recently a 9-valent HPV vaccine was licensed in the United States that increases prevention of cervical disease to 90% through the protection from HPV types 16, 18, 31, 33, 45, 52, and 58.[7] The uptake of the vaccine is of major public health importance, especially in countries that have no or poor cervical cancer screening programs.

Within the context of a Phase II Trial to assess the feasibility of conducting a placebo-controlled randomized HPV vaccine trial to prevent HIV infection, we assessed cervical HPV status at enrollment and 7-months post-enrollment among women at high-risk for HIV.

Materials and methods

Population

Women residing in the Western Cape, South Africa were enrolled from November 2012 to July 2013 in a preparedness study, the **E**fficacy of HPV **V**accine to **R**educe HIV **I**nfection (EVRI) Trial (NCT01489527). A full description of study procedures and conduct of the trial has been published elsewhere.[8] Briefly, women aged 16–24 that were HIV-negative and non-pregnant were enrolled in a Phase II randomized controlled trial of Gardasil (4-valent HPV (4vHPV) vaccine) vs. placebo (saline).

Trial-eligible women were randomized 1:1 to receive 4vHPV or placebo vaccines. All staff and study investigators were blinded to participants' vaccine status. Vaccine was administered at enrollment, month 2, and month 6. Study participants were followed for one month after the last vaccine dose (through month 7). At the 7-month visit, individual unblinding occurred, and women randomized to the placebo group were offered Gardasil vaccine.

This study was conducted in accordance with ethics committee review and approved by the Institutional Review Boards of The University of South Florida and Stellenbosch University. South African policies and ethics approval regarding parental permission for children to take part in research studies were followed.

Study protocol

At each follow-up visit after randomization, urine pregnancy tests and rapid HIV tests were performed. Women with positive pregnancy tests were referred to care and removed from the study. Women with a positive rapid HIV test were retested with two different confirmatory tests. Participants with a confirmed positive HIV test after the enrollment visit were referred to care and remained on trial.[9] However, HIV-positive women (n = 3) post-enrollment were removed from the current analysis as HIV is known to influence HPV natural history.[10] At the enrollment and 7-month visits, sexual history, health, and sociodemographic characteristics were assessed by a tablet-based questionnaire using a computer-assisted self-interview available in English, Xhosa, and Afrikaans.

A speculum exam of the vagina and cervix was conducted and, after collection of specimens, a digital exam was performed. Samples obtained from the vulva/labia and endocervical/ectocervical specimens for HPV detection were obtained at the enrollment and 7-month visits using a pre-wetted Dacron swab placed in an STM collection vial (Digene Hybrid Capture test kit). Specimens for HPV analysis were archived at 4 °C prior to testing. Cervical cytology specimens were obtained at enrollment using the SurePath method. If the Pap cytology results were greater than atypical squamous cells of undetermined significance (ASCUS)/low-grade squamous intraepithelial lesions (LSIL), the participant was referred to the local clinic for a repeat Pap cytology and further clinical management as indicated. If the Pap cytology results were high-grade squamous intraepithelial lesions (HSIL), the participant was referred to the study gynecologist (HB) for colposcopy and clinical management as indicated.

Laboratory analyses

For HPV analyses, DNA was extracted from cervical cell specimens using the Qiagen Media Kit and amplified by polymerase chain reaction (PCR) with the PGMY09/11 L1