Cervical cancer and human papillomavirus in indigenous Guyanese women

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OBJECTIVE: The purpose of this study was to determine the prevalence of cervical disease, human papillomavirus infection, and human papillomavirus (HPV) genotypes in indigenous villages of Guyana.

STUDY DESIGN: This is a retrospective analysis of a clinical cervical cancer screening and treatment program: 2250 women underwent cytologic screening; 1423 women were concomitantly screened for HPV. HPV genotyping was performed in 45 women with high-grade dysplasia and in 9 women with cervical carcinoma.

RESULTS: We found invasive cervical carcinoma in 0.80% of the women, cervical intraepithelial neoplasia II and III in 5.07% of the women, and a high-risk HPV infection rate in 19.3% of the women, all of which peaked between the ages of 20-30 years. Sixteen genotypes were detected in women with high-grade dysplasia or cancer: HPV 31, 25.0%; HPV 16, 22.7%; HPV 18, 13.6%. The rate of HPV 16 and 18 in cervical cancer was 55.50%.

CONCLUSION: Indigenous Guyanese women have a high rate of cervical cancer and high-grade dysplasia, with an apparent predominance of HPV 16 and18 in invasive cancer and overrepresentation of HPV 31 in high-grade dysplasia.

Key words: DNA, genotype, Guyana, human papillomavirus, neoplasia

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Cervical cancer is the leading cause of cancer-related death among women in developing countries, with the highest incidence and mortality rates among the world's poorest populations.[1,2] According to the Pan American Health Organization,[3] the 2002 incidence of cervical cancer in Guyana was 47.3 per 100,000; the mortality rate was 22.2 per 100,000. In contrast, the 2002 incidence and mortality rates in the United States were 7 and 2.3 per 100,000, respectively. Cervical cancer is the most frequent cancer among Guyanese women; Guyana's Cancer Registry reports a higher prevalence of cervical cancer ($P < .0001$) in indigenous, or Amerindian, women than in any other demographic in Guyana.[4] To date the burden of human papillomavirus (HPV) infection in Guyana has not been reported.[5]

Cytologic screening for cervical cancer decreased the US cervical cancer rate from 14.8 per 100,000 in 1973 to 8.0 per 100,000 in 1999.[6] Womack and Warren[7] report that approximately 60% of women who were diagnosed with cervical cancer in their study either had never been screened or had not been screened in the 5 years preceding diagnosis. Similar findings have been reported by Spence et al[8] and Leyden et al.[9] In Guyana, the only South American country with English as the primary language, the extensive outward migration of trained medical personnel has had a devastating effect on the availability of medical care.[10] Insufficient funding, lack of laboratory infrastructure, and the geographic and logistic barriers to bringing medical care to a largely roadless region have precluded large-scale cytologic cervical cancer screening in Guyana.

This study was conducted to determine the prevalence of cervical disease and HPV among women who live in the indigenous villages of the savannahs and mountainous rainforests of Guyana. All data were derived from a cervical cancer screening and treatment program that was carried out by medical personnel who volunteered their services through Remote Area Medical (RAM) in collaboration with Guyana's Ministries of Health and Amerindian Affairs. A pilot substudy of HPV genotypes was undertaken concomitantly to determine the predominant HPV genotypes that are associated with high-grade neoplasia and invasive cervical cancer.

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RAM is a US-based, nongovernment organization that provides free health care to underserved populations in the United States and globally. RAM has served Guyana's indigenous people since 1992. All RAM physicians are board-certified, and all supplies and services for these missions were donated or funded through grants.

Materials and Methods

Guyana's Minister of Health and the Institutional Review Board of the University of Virginia approved this program. At the program inception, the Minister of Health provided a waiver of written consent for clinical care and data analysis. Parents or legal guardians who requested screening for patients <16 years old provided verbal consent to clinical care. Written informed consent was obtained for genotyping. In October 2008, consent procedures were modified to require written informed consent from all patients who receive clinical care.

From November 2004 through March 2008, 2250 self-selected women who met 2001 and 2006 Consensus Guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP)[11-13] were screened cytologically. Women were informed of screening clinics by the village Medexes (regional health care providers), community health workers, flyers, and community talks that were given by RAM or Peace Corps volunteers. Most women spoke English. Relatives or healthcare workers translated for women who spoke only indigenous languages.

From November 2004 through April 2005, a conventional slide cytologic method was used. Between November 2005 and March 2008, we used the Cytyc ThinPrep liquid-based cytologic method (Cytyc Corporation, Marlborough, MA). Between November 2005 and April 2007, all specimens were screened for HPV with the Digene Hybrid Capture 2 High-risk HPV assay (Digene Corporation, Gaithersburg, MD).

Women with abnormal cytology underwent colposcopy and biopsy, per ASCCP guidelines. Women with high-grade cervical intraepithelial neoplasia (CIN II or III) or with high-grade squamous intraepithelial lesions and unsatisfactory colposcopy results or with high-grade squamous intraepithelial lesions and suspicious lesions on colposcopy were offered loop electrosurgical excision procedure (LEEP). Women with CIN III and positive LEEP margins or for whom LEEP could not be performed because of scarring or adhesions were offered hysterectomy. Women with invasive carcinoma were treated by board-certified gynecologic oncologists. Participants provided written informed consent for all diagnostic and surgical procedures.

LEEP was performed in villages with electricity, running water, and adequate clinical facilities. Procedures that required anesthesia were performed in the regional hospital in Lethem or Georgetown, Guyana.

A substudy analyzed HPV genotypes in 54 women with histologically proven CIN II, CIN III, or carcinoma. Endocervical specimens for genotyping were obtained with Digene collection devices (Digene Corporation) before any other cervical manipulation or sampling.

HPV screening was performed with liquid-based cytology and Digene Hybrid Capture 2 (Digene Corporation). HPV genotype analysis was performed by polymerase chain reaction. All cytologic specimens were prepared and read by certified US cytotechnologists; pathologic specimens were read by board-certified pathologists, using the Bethesda System.

DNA was purified from cervical swab specimens collected in either PreservCyt or Digene liquid-based cytologic fluid with a magnetic bead-based DNA isolation kit (DNA IQ Isolation Kit; Promega Corp, Madison, WI). Purified DNA was amplified with a multiplex polymerase chain reaction kit (QIAplex HPV Genotype Kit; QIAGEN, Germantown, MD) that contained primer pairs that were specific for the following HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 26, 53, 66, 67, 69, 70, 73, 82, 6, 11, 42, and 44. Genotype determination was performed by characterization of fluorescently tagged polymerase chain reaction amplicons that were coupled to genotype-specific fluorescent polystyrene beads with the use of an analyzer (Luminex L100; Luminex Corporation, Austin, TX). The method permits simultaneous detection and characterization of single or multiple HPV types in each clinical specimen.

RAM teams returned to the previously screened villages every 6 months with individual written results of testing. Trained volunteers discussed the results with patients privately and answered all questions. Women who did not come in for their results were provided with a sealed letter, written in English, which was left in the care of the Medex. RAM personnel in Guyana are available to discuss results with patients.

Women with abnormal results who required further evaluation or surgical procedures were notified by a letter that described the result, its interpretation, and the options for management. Letters were delivered to patients or to the Medex by the RAM pilot. Treatment and follow-up evaluation were offered in the nearest village where appropriate facilities were available. Women who required treatments that were not offered in their home village were transported to the designated clinic or hospital either overland or by the RAM air ambulance.

This was a retrospective analysis of the results of clinical testing between 2004 and October 2008, with diagnostic procedures performed in March 2009. All women with an intact cervix and satisfactory cytologic specimens were included in the analysis. For women with >1 test result, the diagnosis for epidemiologic purposes was determined in the following manner: cytologic findings were used for women who had not yet received follow-up diagnostic procedures at the time of data analysis. For women with >1 cytologic result, the highest grade abnormality was recorded. Whenever tissue diagnoses were available, the histologic finding was used in preference to cytologic findings, and the highest grade histologic finding was recorded. We report both high-grade cytologic and histologic findings relative to disease prevalence and HPV status.

HPV screening results were reported as positive or negative. HPV genotypes