Prevalence of and Risk Factors for Anal Human Papillomavirus Infection Among Young Healthy Women in Costa Rica

Felipe A. Castro,1 Wim Quint,5 Paula Gonzalez,6 Hormuzd A. Katki,1 Rolando Herrero,6,7 Leen-Jan van Doorn,5 Mark Schiffman,1 Linda Struijk,5 Ana Cecilia Rodriguez,3 Corey DelVecchio,4 Douglas R. Lowy,2 Carolina Porras,6 Silvia Jimenez,6 John Schiller,2 Diane Solomon,3 Sholom Wacholder,1 Allan Hildesheim,1 and Aimée R. Kreimer1 for the Costa Rica Vaccine Trial Group

1Division of Cancer Epidemiology and Genetics, 2Center for Cancer Research, and 3Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda; 4Information Management Systems, Rockville, Maryland, USA; 5DDL Diagnostic Laboratory, Voorburg, the Netherlands; 6Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, Costa Rica; and 7Early Detection and Prevention Section, International Agency for Research on Cancer, Lyon, France

Background. Anal cancer is caused by human papillomavirus (HPV), yet little is known about anal HPV infection among healthy young women.

Methods. A total of 2017 sexually active women in the control arm of an HPV-16/18 vaccine trial had a single anal specimen collected by a clinician at the 4-year study visit. Samples were tested for HPV by SPF10 PCR/DEIA/LiPA25, version 1.

Results. A total of 4% of women had HPV-16, 22% had oncogenic HPV, and 31% had any HPV detected in an anal specimen. The prevalence of anal HPV was higher among women who reported anal intercourse, compared with those who did not (43.4% vs 28.4%; \( P < .001 \)). Among women who reported anal intercourse, cervical HPV (adjusted odds ratio [aOR], 5.3 [95% confidence interval {CI}, 3.4–8.2]), number of sex partners (aOR, 2.2 [95% CI, 1.1–4.6] for \( \geq 4 \) partners), and number of anal intercourse partners (aOR, 1.9 [95% CI, 1.1–3.3] for \( \geq 2 \) partners) were independent risk factors for anal HPV detection. Among women who reported no anal intercourse, cervical HPV (aOR, 4.7 [95% CI, 3.7–5.9]), number of sex partners (aOR, 2.4 [95% CI, 1.7–3.4] for \( \geq 4 \) partners), and report of anal fissures (aOR, 2.3 [95% CI, 1.1–4.8]) were associated with an increased odds of anal HPV detection.

Conclusion. Anal HPV is common among young women, even those who report no anal sex, and was associated with cervical HPV infection. Anal fissures in women who report never having had anal intercourse may facilitate HPV exposure.

Clinical Trials Registration. NCT00128661.

Anal cancer is rare, with age-standardized annual incidence rates of 0.2–1.4 cases/100 000. Rates are higher in women and vary by geographical location [1]. During the past 3–4 decades, a significant increase in anal cancer rates has been reported for both sexes in many developed countries [2–4].

Several epidemiological studies suggest that oncogenic human papillomavirus (HPV) infection, a necessary cause of cervical cancer, is the main cause of anal cancer and its precursor lesions [5–9]. A recent meta-analysis [10] of 29 anal cancer studies estimated that HPV DNA was present in 84% of anal cancers worldwide and confirmed previous observations that HPV-16 was the most frequent genotype associated with anal carcinoma (>75% of cases), followed by HPV-18 and HPV-33 (approximately 10% of cases combined).

Research on the natural history of anal HPV infection suggests that sexual behavior is the main risk
factor [11–16]. However, the majority of the research to date has focused on high-risk groups, such as men who have sex with men (MSM) or human immunodeficiency virus–infected male and female subjects. Thus, little is known about anal HPV infection in healthy women. Only one prospective study, which occurred in Hawaii [16], investigated anal HPV infection among healthy women (age range, 18–55 years). The overall prevalence of anal HPV infection was 27%. During follow-up, the vast majority (approximately 90%) of infections cleared by 1 year [17]. The epidemiology of anal HPV infections might vary by age, geographical location, and other characteristics; thus, additional epidemiological studies are warranted to better understand the natural history of anal HPV infection in other general populations. The aim of the present study was to estimate prevalence of individual anal HPV types in young healthy women in Costa Rica and to characterize risk factors for anal HPV infection in this group.

METHODS

Subject Participants and Study Design

Women included in the present evaluation are participants from the control arm of a double-blind, controlled, randomized, phase III study of the efficacy of an HPV-16/18 virus-like particle vaccine in Costa Rica (the Costa Rica Vaccine Trial [CVT]), which has been previously described [18]. Enrolled women from Guanacaste and selected areas of Puntarenas were identified via a census conducted between 2004 and 2005. The main eligibility requirements were as follows: age, 18–25 years (inclusive); good health, determined by history and a physical examination; and willingness to provide written informed consent. The trial was reviewed and approved by human subjects review committees of Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud (INCIENSA), in Costa Rica, and the National Cancer Institute (NCI), in the United States.

A total of 7466 women were recruited for the trial, randomized to receive 3 doses of the HPV vaccine or a control hepatitis A virus vaccine over a 6-month period, and followed annually, with additional visits if clinically indicated [18]. At all study visits, cervical specimens were collected in PreservCyt from sexually experienced women.

At the 4-year annual study visit, women who reported to be sexually active (defined as having had vaginal intercourse) were invited to provide an anal specimen for the evaluation of the HPV vaccine’s efficacy against anal HPV infection. To study the epidemiology of anal HPV infection, analyses in the present study were restricted only to women enrolled in the control arm of the trial.

First, a questionnaire including questions about education, marital status, sexual (including anal intercourse) and reproductive history, use of contraceptives, smoking habits, and family history of cancer was administered. Additionally, among monogamous women, information related to their sex partner, including age, education, circumcision, sexual history, and smoking status, was obtained. Then, a complete medical history was obtained, and a physical examination that included anal specimen collection and a pelvic examination (with cervical specimen collection) were conducted.

Specimen Collection

The anal specimen was collected prior to the pelvic examination by inserting a dry swab 3–4 cm into the anal canal, rotating the swab 1 time, and removing the swab while continuing the rotation, using gentle pressure against the wall of the anal canal. The swab was placed in 1 mL of PreservCyt and frozen immediately in liquid nitrogen.

HPV DNA Testing

Cervical and anal specimens were tested using broad-spectrum polymerase chain reaction (PCR)–based HPV DNA testing at DDL Diagnostic Laboratory in the Netherlands, using SPF10 PCR/DEIA/LiPA25, version 1 (Lab Biomedical Products, Rijswijk, the Netherlands), which is based on amplification of the viral L1 gene using the SPF10 primers. All samples were run through an HPV DNA enzyme immunoassay (DEIA), and the DEIA-positive samples were genotyped by the LiPA line detection system, as described elsewhere [19–21]. All specimens positive for HPV DNA by means of the SPF10 DEIA were additionally tested for the presence of HPV-16 and HPV-18 DNA, using type-specific primers [19, 22].

Statistical Analysis

An anal sample was considered positive for any HPV genotype if it was positive for ≥1 of 25 HPV types. A sample was considered positive for oncogenic HPV if any of 13 oncogenic HPV types (ie, type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68/73) were detected [23], regardless of the presence of nononcogenic HPV. In contrast, a sample was considered positive for a nononcogenic HPV type if only a nononcogenic HPV type (ie, type 6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 70, and 74) was detected in the absence of an oncogenic type. A sample that was SPF10 DEIA-positive, but LiPA25 negative was considered as uncharacterized HPV. For cervical HPV status, a sample was defined as positive for any HPV type if it tested positive for ≥1 of 25 HPV types, regardless of other HPV infections. The distribution of anal HPV was described overall and by the above categorizations.

Determinants for anal HPV infection were evaluated by logistic regression analysis. Variables evaluated in univariate modeling included age, education, marital status, number of pregnancies, age at first sexual intercourse, lifetime number of sex partners, number of sex partners since the last study visit.
RESULTS

Sample Characteristics

Of the 7466 women randomized, 3171 from the control arm attended the 4-year study visit. After exclusion of 188 women who had no history of sexual intercourse and from whom an anal specimen was not collected, 2983 were invited to participate in the present ancillary study. A total of 2112 women (70.8%) provided an anal specimen, and 871 refused. Women who provided an anal specimen were slightly older, less educated, more likely to be currently married, had more pregnancies, and smoked more cigarettes/week than women who refused (data not shown). Women who provided an anal specimen were also younger at sexual debut, reported a greater lifetime number of sex partners, more frequently reported anal intercourse, and less frequently received a diagnosis of irritable bowel syndrome. These 2 groups of women were comparable with respect to smoking status (never/former/current), condom use, and cervical HPV positivity at the 4-year study visit.

Anal HPV Prevalence

After collection of exfoliated cells from the anal canal for HPV DNA testing, samples from 5 women were excluded because the specimen was inadequate and precluded HPV DNA analysis, resulting in 2107 participating women. The overall anal HPV prevalence was 31.6% (95% CI, 29.6–33.6) (Table 1). Oncogenic and nononcogenic HPV types were detected in 22.0% (95% CI, 20.3–23.9) and 17.0% (95% CI, 15.5–18.7) of women, respectively. The most prevalent oncogenic anal HPV type was 51 (4.7% [95% CI, 3.8–5.6]), followed by 52 (4.1% [95% CI, 3.3–5.0]), 16 (4.0% [95% CI, 3.2–5.0]), and 31 (3.1% [95% CI, 2.4–4.0]). The most common nononcogenic types were HPV-53 (4.1% [95% CI, 3.3–5.0]) and HPV-66 (3.5% [95% CI, 2.7–4.3]). All other genotypes were found in <3% of the anal samples. A total of 18.0% of women were infected with a single HPV type, and 13.4% (42.3% of those infected) had at least 2 HPV types. Anal HPV infection was less frequent than cervical HPV infection (31.6% vs 36.5%; P < .0001) (Table 1); concurrent anal and cervical infections were observed in 19.7% of participants (416 of 2107).

HPV Infection Prevalence, by History of Anal Intercourse

Anal HPV prevalence for any type and for most of the oncogenic and nononcogenic types was higher among women with history of anal intercourse (Table 1). The following HPV types were statistically significantly more prevalent among women who reported anal sex: 58, 59, 18, 33, and 16 among oncogenic types and 43, 53, 44, and 70 among nononcogenic types. The percentage of multiple-type infections was significantly higher among women with a history of anal intercourse as compared to those without (21.2% vs 11.2%; P < .0001). Uncharacterized HPV infections were present among both groups (6.6% and 5.3%, respectively).

Risk Factors for Anal HPV Infection

HPV prevalence did not vary by age across our narrow age range. The prevalence of any HPV positivity was 32.8% among women aged 22–23 years, 31.1% among those aged 24–25 years, 29.5% among those aged 26–27 years, and 32.8% among those aged 28–29 years.

In the univariate model, the risk factors associated with any HPV prevalence were the same as those for oncogenic, nononcogenic, and HPV-16 infection (Supplementary Table 1); thus, multivariate risk factor analysis was presented using the outcome “any HPV infection.”
Table 2 shows all independent risk factors for anal HPV infection (any type): lifetime number of sex partners (adjusted OR [aOR], 2.3 [95% CI, 1.7–3.1] for the highest risk category of ≥4 partners), number of anal intercourse partners (aOR, 2.8 [95% CI, 1.7–4.5] for ≥2 partners), and any concurrent cervical HPV infection (measured at the same study visit as anal specimen collection; aOR, 4.8 [95% CI, 3.9–5.9]). Measurements of cervical HPV infection as concurrent (ie, 1-time detection at the same time as anal specimen collection) or persistent (ie, detection 1 year prior to collection of the anal specimen and then again at the study visit when the anal specimen was collected) similarly elevated the odds of anal HPV yet were collinear. This indicates that contemporaneous cervical HPV infection was most important for
increasing the odds of anal infection, regardless of whether the cervical infection was measured at the preceding study visit.

Multivariate analyses stratified by history of anal intercourse were also conducted (Table 3). Among women with and women without a history of anal intercourse, the number of
sex partners and cervical HPV infection each elevated the odds of anal HPV infection; persistent and concurrent cervical HPV infection were similarly associated with anal HPV infection (data not shown). Among women who reported anal sex, those who reported ≥2 lifetime anal sex partners had an increased odds of anal HPV infection (aOR, 1.9 [95% CI, 1.1–3.4]), compared with women who reported only 1 anal sex partner. Women who did not report anal intercourse had an increased odds of anal HPV infection if they reported having anal fissures (aOR, 2.3 [95% CI, 1.1–4.8]).

In an analysis involving 552 monogamous women (data not shown), no associations were present between the number of sex partners of the monogamous subject’s male partner or the woman’s anal HPV status (aOR, 1.0 [95% CI, 0.8–1.3] for number of sex partners as a continuous variable). Only cervical HPV infection was associated with anal HPV infection in this subset of women (aOR, 9.5 [95% CI, 5.8–15.8]).

### DISCUSSION

This study provides information on the epidemiology of anal HPV infection among young, sexually active adult women participating in the control arm of the community-based CVT. Anal HPV infection was relatively common: 4% of women had anal HPV-16 infection, 22% had an oncogenic HPV infection, and 32% had any type of anal HPV detected. The main risk factors for anal HPV infection were (1) high number of lifetime sex partners, (2) cervical HPV infection, and (3) anal sex. Among women who reported anal sex, the odds of anal HPV infection increased as the number of anal sex partners increased. Of interest, among women who reported no anal intercourse, anal HPV infection was still common, and anal fissures were an independent determinant of anal HPV infection.

The observed prevalence of anal HPV infection among women in the Costa Rica study appears to be similar to that in the other large study of anal HPV infection, which involves healthy adult women in Hawaii [16]. Restriction of data from the Hawaii cohort to that for women of the ages included in our study (22–29 years), oncogenic anal HPV prevalence was 21%, and anal HPV16 prevalence was 5% (M. T. Goodman, B. Hernandez, and Y. Shvetsov, personal communication). Given our confirmation of their observed anal HPV prevalence, it seems that the contemporary estimate among generally healthy women for anal HPV-16 infection, the main HPV type implicated in anal cancer, is around 4%–5%. It is important to note that, in our population and, likely, in others, the observed anal HPV prevalence may be somehow inflated, since women who provided an anal specimen were more likely to participate in anal sex practices and to have a higher lifetime number of sexual and anal intercourse partners.

While HPV-16 is responsible for the bulk of anal cancers, it was not the most common type detected among the healthy women. All 25 HPV types tested for in our study were detected as single or multiple infections, in agreement with findings from the Hawaii study [16]. The most prevalent oncogenic types were HPV-51, HPV-52, and HPV-16. Anal infection with certain specific HPV types were more frequently found among women with history of anal intercourse; specifically, HPV types 58, 59, 18, 33, 16, 39, 31, and 51 were at least twice as common among those women, compared with the women who did not report a history of anal intercourse.

Cervical HPV infection was a strong risk factor for anal HPV infection: anal HPV prevalence was significantly higher among women with concurrent cervical infection than among women who were negative for cervical HPV (19.7% vs 11.9%; P < .001). Of interest, the ORs for concurrent cervical HPV detection (4.8) and persistent cervical HPV detection (5.1) were similar. We interpret this to mean that having cervical HPV at the time of anal specimen collection was most

### Table 3. Multivariate Analysis of Determinants for Overall Anal HPV Infection (Any Type), by History of Anal Intercourse, Among 2107 Young Adult Women From Costa Rica

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No History (n = 1655)</th>
<th>History (n = 452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime no. of sex partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.6 (1.1–2.3)</td>
<td>1.7 (1.7–4.0)</td>
</tr>
<tr>
<td>3</td>
<td>1.6 (1.1–2.4)</td>
<td>2.4 (1.1–5.4)</td>
</tr>
<tr>
<td>≥4</td>
<td>2.4 (1.7–3.4)</td>
<td>2.2 (1.1–4.6)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;.0001</td>
<td>.03</td>
</tr>
<tr>
<td>Anal fissures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>2.3 (1.1–4.8)</td>
<td>0.4 (1.1–2.3)</td>
</tr>
<tr>
<td>Lifetime no. of anal intercourse partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>≥2</td>
<td>NA</td>
<td>1.9 (1.1–3.4)</td>
</tr>
<tr>
<td>Age at first anal intercourse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥22 y</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>≤21 y</td>
<td>NA</td>
<td>0.7 (1.4–1.1)</td>
</tr>
<tr>
<td>Cervical HPV status at 4-year study visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>4.7 (3.7–6.0)</td>
<td>5.3 (3.4–8.2)</td>
</tr>
</tbody>
</table>

Statistically significant findings are in bold.

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

\(^a\) Adjusted for all variables included in the table, as well as for education level, marital status, age at first vaginal intercourse, and smoking status.

\(^b\) Includes women who did not having missing values for a related variable above yet had a missing value, refused to respond, or responded “don’t know” for this variable. Categories that have ≤5 cases were collapsed; subjects who tested positive for an uncharacterized HPV type were included in the negative HPV group.
important; having the cervical infection detected prior to that visit and again concurrently did not additionally increase risk of anal HPV detection.

Other risk factors that elevated the odds of anal HPV infection were sexual in nature and included history of anal intercourse and more general sexual exposures (ie, lifetime number of sex partners), factors that have been previously associated with high prevalence of anal HPV infection in women [13, 16] and men [15, 24]. Other routes for introduction of HPV infection in the anal canal have been proposed (ie, autoinoculation or nonpenetrative sexual behaviors) [11, 16, 25]. Our data support this notion: among women who did not report anal sex, anal fissures that could abrade the anal epithelium significantly increased the odds of anal HPV infection.

The advantages of this study include a large sample size that allowed for the analysis of several important risk factors and for stratified analysis based on anal sexual behavior. Although the present study represents the largest group of young adult women tested for anal HPV infection and sampling was based on a population census, women may not be fully representative of the general population because they were participants in a clinical HPV vaccine trial in which several exclusion criteria applied. Additionally, the current lack of longitudinal data meant we could only report on prevalent anal HPV infection and not on incident or persistent anal HPV infection; ongoing serial anal specimen collection will address this limitation in future reports.

Supplementary Data

Supplementary materials are available at The Journal Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Members of the CVT group: Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica: Mario Alfaro (cytopathologist), Manuel Barrantes (field supervisor), M. Concepción Bratti (co-investigator), Fernando Cárdenas (general field supervisor), Bernal Cortés (specimen and repository manager), Albert Espinoza (head, coding and data entry), Yenyor Estrada (pharmacist), Paula González (co-investigator), Diego Guillén (pathologist), Rolando Herrero (co–principal investigator), Silvia E. Jiménez (trial coordinator), Jorge Morales (colposcopist), Luis Villegas (colposcopist), Lidia Ana Morera (head study nurse), Elmer Pérez (field supervisor), Carolina Porras (co-investigator), Ana Cecilia Rodríguez (co-investigator), and Líbia Rivas (clinical coordinator); University of Costa Rica, San José, Costa Rica: Enrique Freer (director, HPV diagnostics laboratory), José Bonilla (head, HPV immunology laboratory), Alfonso García-Piñeres (immunologist), Sandra Silva (head microbiologist, HPV diagnostics laboratory), Ivannia Atmella (microbiologist, immunology laboratory), and Margarita Ramírez (microbiologist, immunology laboratory); NCI, Bethesda, Maryland: Allan Hildesheim (co–principal investigator and NCI co–project officer), Aimée R. Kreimer (investigator), Douglas R. Lowy (HPV virologist), Nora Macklin (trial coordinator), Mark Schiffman (medical monitor and NCI co–project officer), John T. Schiller (HPV virologist), Mark Sherman (QC pathologist), Diane Solomon (medical monitor and QC pathologist), and Sholom Wacholder (statistician); SAIC, NCI-Frederick, Frederick, Maryland: Ligia Pinto (head, HPV immunology laboratory) and Troy Kemp, Women’s and Infants’ Hospital, Providence, Rhode Island: Claire Eklund (QC cytology) and Martha Hutchinson (QC cytology); Georgetown University, Washington, D.C.: Mary Sidawy (histopathologist); and DDL Diagnostic Laboratory, the Netherlands: Wim Quint (virologist, HPV DNA testing), Leen-Jan van Doorn (HPV DNA testing), and Linda Struijk (HPV DNA testing).

Acknowledgments. We extend a special thanks to the women of Guanacaste and Puntarenas, Costa Rica, who gave of themselves in participating in this effort. We also acknowledge the tremendous effort and dedication of the staff in Costa Rica involved in this project, including Bernardo Blanco and his team (census); Ricardo Cerda and Ana Hernández (blood processing); José Miguel González, Osman López, Johnny Matamoros, Manuel Sánchez, Rafael Thompson, and Jorge Umaña (field activity coordinators); Su Yen Araya, Hazel Barquero, Hayleen Campos, Muriel Grijalba, Ana Cristina Monge, Ana Peraza, Diana Robles, Marfa Fernanda Sáenz, Dorita Vargas, and Jessica Vindas (clinic coordinators); Paola Álvarez, Dinia Angulo, Ana Live Arias, Betzaida Barrantes, María Bonilla, Mary José Calvo, Loretto Carvajal, Jessenia Chinchilla, Blanca Cruz, Marianela Herrera, Andrea Interiano, Fabiola Jiménez, Erick Lagos, Viviana Loria, Andrea Messeguer, Rebeca Ocamo, Silvia Padilla, Angie Ramírez, Líbia Rivas, Danila Romero, Byron Romero, Jessenia Ruiz, Daniela Ruiz, Genie Saborio, Sofía Soto, Malena Salas, Adriana Torres, Natalia Ugalde, Ana Cristina Ugalde, Adriana Vallejos, Yesenia Vázquez, and Maricela Villegas (clinicians); Marta Alvarado, Ana Cristina Arroyo, Gloriana Barrantes, Diana Díaz, Marlen Jara, Maureen Matarrita, María Ester Molina, Elida Ordoñez, Gina Sánchez, and Zihara Villegas (nurses); Arianne Castrillo and Vivian Lóvez (education and outreach effort coordinators); Karla Coronado (appointment coordinator); Ricardo Alfaro (quality control coordinator); Charles Sánchez and Livia Romero (document center coordinators); Cristian Montero (quality assurance, regulatory); and Carlos Avila and Eric Alpizar (IT coordinators). Special recognition is also extended to Sofia Elizondo, executive director of Fundación INCINESA, and her staff for their administrative support. In the United States, we thank the individuals from Information Management Services (IMS) who were responsible for the development and maintenance of the data system used in the trial and who served as the data management center for this effort. We specifically acknowledge the invaluable contributions made by Jean Cyr, Julie Buckland, Laurie Rich, Brian Befano, and Dennis Buckman. We acknowledge the contributions made by individuals at Westat who provided project development and/or monitoring support, including Kerry Grace Morrissey, Kirk Milikff, Susan Truitt, Sonia Stozsek, Maribel Gomez, and Isabel Trejos. We acknowledge the assistance provided by Carla Chorley, Troy Moore, Kathi Shea, and Heather Siefers in the establishment of a specimen and vaccine repository for our trial and for their continued assistance with the handling and shipment of specimens. From GSK Biologicals, we acknowledge the contributions of Gary Dubin, Anne Schuind, Frank Struyf, Kelechi Lawrence, Derrick Fu, and Bruce Innis, for their contribution to discussions regarding trial conduct, and Francis Desdy and Catherine Bougeet, for HPV-16/18 antibody testing. We thank members of the data and safety monitoring board charged with protecting the safety and interest of participants in our trial (Steve Self, Chair, Adriana Benavides, Luis Diego Calzada, Ruth Karron, Ritu Nayar, and Nancy Roach), as well as members of the external Scientific HPV Working Group, who have contributed to the success of our efforts over the years (Joanna Cain, Chair, Diane Davey, David DeMets, Francisco Fuster, Ann Gershon, Elizabeth Holby, Silvia Lara, Henriette Raventós, Wasima Rida, Luis Rosero-Bixby, Kristen Suthers, Sarah Thomas, and Raphael Visconti). We thank Annet Westbroek and Yvonne Zomerdiik from DDL, for their help in testing the anal specimens; John Schussler from IMS, for his help with the analysis; and Nora Macklin from the NCI, for her support in preparing the manuscript for submission. We appreciate the data and insights provided for our discussion section by the Investigators of the Hawaii Anal HPV Study, including Marc T. Goodman, Brenda Hernandez, and Yuri Shvetsov.
**Financial support.** The Costa Rica HPV Vaccine Trial is a long-standing collaboration between investigators in Costa Rica and the NCI. The trial is sponsored and funded by the NCI (contract N01-CP-11005), with funding support from the National Institutes of Health Office of Research on Women’s Health, and is conducted with support from the Ministry of Health of Costa Rica. Vaccine was provided for our trial by GSK Biologicals, under a clinical trials agreement with the NCI. GSK Biologicals also provided support for aspects of the trial associated with regulatory submission needs of the company, under FDA BB-IND 7920. Drs Schiller and Lowy report that they are named inventors on US government-owned HPV vaccine patents that are licensed to GSK Biologicals and Merck and for which the NCI receives licensing fees. Drs Schiller and Lowy are entitled to limited royalties as specified by federal law. The NCI and Costa Rica investigators are responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript. The NCI and Costa Rica investigators make final editorial decisions on this and subsequent publications; GSK Biologicals has the right to review and comment.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**